Acknowledgement:
We wish to express sincere appreciation to Adrienne Carmack for her editorial assistance in reading each chapter and advising us. Despite her dual role as a mother and urologist, she was able to find the time to help us once again with the Bladder Cancer Recommendations.

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The tragedy of science: The slaying of a beautiful hypothesis by an ugly fact

Thomas Huxley (1825-1895)


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EVIDENCE – BASED MEDICINE OVERVIEW OF THE MAIN STEPS FOR DEVELOPING AND GRADING GUIDELINE RECOMMENDATIONS.

INTRODUCTION
The International Consultation on Urological Diseases (ICUD) is a non-governmental organization registered with the World Health Organisation (WHO). In the last ten years, Consultations have been organised on BPH, Prostate Cancer, Urinary Stone Disease, Nosocomial Infections, Erectile Dysfunction, and Urinary Incontinence. These consultations have looked at published evidence and produced recommendations at four levels: highly recommended, recommended, optional and not recommended. This method has been useful, but the ICUD believes that there should be more explicit statements of the levels of evidence that generate the subsequent grades of recommendations.

The Agency for Health Care Policy and Research (AHCPR) have used specified evidence levels to justify recommendations for the investigation and treatment of a variety of conditions. The Oxford Centre for Evidence Based Medicine have produced a widely accepted adaptation of the work of AHCPR. (June 5th 2001 http://minerva.minervation.com/cceb/docs/levels.html). The ICUD has examined the Oxford guidelines and discussed with the Oxford group their applicability to the Consultations organised by ICUD. It is highly desirable that the recommendations made by the Consultations follow an accepted grading system supported by explicit levels of evidence.

The ICUD proposes that future consultations should use a modified version of the Oxford system which can be directly ‘mapped’ onto the Oxford system.

1. 1st Step: Define the specific questions or statements that the recommendations are supposed to address.

2. 2nd Step: Analyse and rate (level of evidence) the relevant papers published in the literature.

The analysis of the literature is an important step in preparing recommendations and their guarantee of quality.

2.1 What papers should be included in the analysis?

• Papers published, or accepted for publication in the peer reviewed issues of journals.

• The committee should do its best to search for papers accepted for publication by the peer reviewed journals in the relevant field but not yet published.

• Abstracts published in peer review journals should be identified. If of sufficient interest the author(s) should be asked for full details of methodology and results. The relevant committee members can then ‘peer review’ the data, and if the data confirms the details in the abstract, then that abstract may be included, with an explanatory footnote. This is a complex issue – it may actually increase publication bias as “uninteresting” abstracts commonly do not progress to full publication.

• Papers published in non peer reviewed supplements will not be included.

An exhaustive list should be obtained through:
I. the major databases covering the last ten years (e.g. Medline, Embase, Cochrane Library, Biosis, Science Citation Index)

II. the table of contents of the major journals of urology and other relevant journals, for the last three months, to take into account the possible delay in the indexation of the published papers in the databases.

It is expected that the highly experienced and expert committee members provide additional assurance that no important study would be missed using this review process.

2.2 How papers are analysed?
Papers published in peer reviewed journals have differing quality and level of evidence.

Each committee will rate the included papers according to levels of evidence (see below).

The level (strength) of evidence provided by an individual study depends on the ability of the study design to minimise the possibility of bias and to maximise attribution.

is influenced by:
• the type of study

The hierarchy of study types are:
- Systematic reviews and meta-analysis of randomised controlled trials
- Randomised controlled trials
- Non-randomised cohort studies
- Case control studies
- Case series
- Expert opinion

• how well the study was designed and carried out

Failure to give due attention to key aspects of study methodology increase the risk of bias or confounding factors, and thus reduces the study’s reliability.

The use of standard check lists is recommended to insure that all relevant aspects are considered and that a consistent approach is used in the methodological assessment of the evidence.

The objective of the check list is to give a quality rating for individual studies.

• how well the study was reported

The ICUD has adopted the CONSORT statement and its widely accepted check list. The CONSORT statement and the checklist are available at http://www.consort-statement.org

2.3 How papers are rated?
Papers are rated following a «Level of Evidence scale».

ICUD has modified the Oxford Center for Evidence-Based Medicine levels of evidence.

The levels of evidence scales vary between types of studies (i.e therapy, diagnosis, differential diagnosis/symptom prevalence study).

http://minerva.minervation.com/cceb/docs/levels.html

3. 3rd Step: Synthesis of the evidence

After the selection of the papers and the rating of the level of evidence of each study, the next step is to compile a summary of the individual studies and the overall direction of the evidence in an Evidence Table.

4. 4th Step: Considered judgment (integration of individual clinical expertise)

Having completed a rigorous and objective synthesis of the evidence base, the committee must then make a judgement as to the grade of the recommendation on the basis of this evidence. This requires the exercise of judgement based on clinical experience as well as knowledge of the evidence and the methods used to generate it. Evidence based medicine requires the integration of individual clinical expertise with best
available external clinical evidence from systematic research. Without the former, practice quickly becomes tyrannised
by evidence, for even excellent external evidence may be
inapplicable to, or inappropriate for, an individual patient: with- out current best evidence, practice quickly becomes
out of date. Although it is not practical to lay our “rules” for
exercising judgement, guideline development groups are
asked to consider the evidence in terms of quantity, quality,
and consistency; applicability; generalisability; and clinical
impact.

5. 5th Step: Final Grading
The grading of the recommendation is intended to strike an
appropriate balance between incorporating the complexity of
type and quality of the evidence and maintaining clarity for
guideline users. The recommendations for grading follow the Oxford Centre
for Evidence-Based Medicine. The levels of evidence shown below have again been modified in the light of previous consultations. There are now 4 levels of evidence instead of 5.
The grades of recommendation have not been reduced and a “no recommendation possible” grade has been added.

6. Levels of Evidence and Grades of Recommendation
Therapeutic Interventions
All interventions should be judged by the body of evidence for their efficacy, tolerability, safety, clinical effectiveness and cost effectiveness. It is accepted that at present little data exists on cost effectiveness for most interventions.

6.1 Levels of Evidence
Firstly, it should be stated that any level of evidence may be positive (the therapy works) or negative (the therapy doesn’t work). A level of evidence is given to each individual study.

• Level 1 evidence (incorporates Oxford 1a, 1b) usually involves meta-analysis of trials (RCTs) or a good quality randomised controlled trial, or all or none studies in which no treatment is not an option, for example in vesicovaginal fistula.

• Level 2 evidence (incorporates Oxford 2a, 2b and 2c) includes “low” quality RCT (e.g. < 80% follow up) or meta-analysis (with homogeneity) of good quality prospective ‘cohort studies’. These may include a single group when individuals who develop the condition are compared with others from within the original cohort group. There can be parallel cohorts, where those with the condition in the first group are compared with those in the second group.

• Level 3 evidence (incorporates Oxford 3a, 3b and 4) includes:

good quality retrospective ‘case-control studies’ where a group of patients who have a condition are matched appropriately (e.g. for age, sex etc) with control individuals who do not have the condition.

good quality ‘case series’ where a complete group of patients, all with the same condition/disease/therapeutic intervention, are described, without a comparison control group.

• Level 4 evidence (incorporates Oxford 4) includes expert opinion were the pinion is based not on evidence but on ‘first principles’ (e.g. physiological or anatomical) or bench research. The Delphi process can be used to give ‘expert opinion’ greater authority. In the Delphi process a series of questions are posed to a panel; the answers are collected into a series of ‘options’; the options are serially ranked; if a 75% agreement is reached then a Delphi consensus statement can be made.

6.2 Grades of Recommendation
The ICUD will use the four grades from the Oxford system. As with levels of evidence the grades of evidence may apply either positively (do the procedure) or negatively (don’t do the procedure). Where there is disparity of evidence, for example if there were three well conducted RCT’s indicating that Drug A was superior to placebo, but one RCT whose results show no difference, then there has to be an individual judgement as to the grade of recommendation given and the rationale explained.

• Grade A recommendation usually depends on consistent level 1 evidence and often means that the recommenda-
tion is effectively mandatory and placed within a clinical care
pathway. However, there will be occasions where excellent evidence (level 1) does not lead to a Grade A recommenda-
tion, for example, if the therapy is prohibitively expensive, dangerous or unethical. Grade A recommendation can
follow from Level 2 evidence. However, a Grade A recom-
mendation needs a greater body of evidence if based on anything except Level 1 evidence

• Grade B recommendation usually depends on consistent
level 2 and or 3 studies, or majority evidence’ from RCT’s.

• Grade C recommendation usually depends on level 4 stud-
ies or ‘majority evidence’ from level 2/3 studies or Delfi processed expert opinion.

• Grade D “No recommendation possible” would be used where the evidence is inadequate or conflicting and when expert opinion is delivered without a formal analytical pro-
cess, such as by Delphi.

7. Levels of Evidence and Grades of Recommendation
for Methods of Assessment and Investigation
From initial discussions with the Oxford group it is clear that application of levels of evidence/grades of recommendation for diagnostic techniques is much more complex than for interventions.
The ICUD recommend, that, as a minimum, any test should be subjected to three questions:
1. does the test have good technical performance, for ex-
ample, do three aliquots of the same urine sample give
the same result when subjected to ‘stix’ testing?
2. Does the test have good diagnostic performance, ideally
against a “gold standard” measure?
3. Does the test have good therapeutic performance, that is,
does the use of the test alter clinical management, does
the use of the test improve outcome?
For the third component (therapeutic performance) the same
approach can be used as for section 6.

8. Levels of Evidence and Grades of Recommendation
for Basic Science and Epidemiology Studies
The proposed ICUD system does not easily fit into these
areas of science. Further research needs to be carried out, in
order to develop explicit levels of evidence that can lead
to recommendations as to the soundness of data in these
important aspects of medicine.

CONCLUSION
The ICUD believes that its consultations should follow
the ICUD system of levels of evidence and grades of recommendation, where possible. This system can be
mapped to the Oxford system.
There are aspects to the ICUD system that require further
research and development, particularly diagnostic
performance and cost effectiveness, and also factors
such as patient preference.

P. Abrams, S Khoury, A. Grant 19/1/04
TNM STAGING

T (Primary tumour)
TX Primary tumour cannot be assessed
T0 No evidence of primary tumour
Ta Non-invasive papillary carcinoma
Tis Carcinoma in situ (‘flat tumour’)
T1 Tumour invades subepithelial connective tissue
T2 Tumour invades muscle
T2a Tumour invades superficial muscle (inner half)
T2b Tumour invades deep muscle (outer half)
T3 Tumour invades perivesical tissue:
T3a Microscopically
T3b Macroscopically (extravesical mass)
T4 Tumour invades any of the following: prostate, uterus, vagina, pelvic wall, abdominal wall
T4a Tumour invades prostate, uterus or vagina
T4b Tumour invades pelvic wall or abdominal wall

N (Lymph nodes)
NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in a single lymph node 2 cm or less in greatest dimension
N2 Metastasis in a single lymph node more than 2 cm but not more than 5 cm in greatest dimension, or multiple lymph nodes, none more than 5 cm in greatest dimension
N3 Metastasis in a lymph node more than 5 cm in greatest dimension

M (Distant metastasis)
MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis
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It has been my privilege to chair the recently completed International Consultation on Urologic Diseases (ICUD) Recommendations on Bladder Cancer (BC). After over one year of intense interactive and enthusiastic collaboration with over 100 experts in various aspects of BC the recommendations from the 10 committees were presented at the 2011 European Association of Urology Congress in Vienna on March 18, 2011. Each committee had a chair and co chair and they selected a broad based group of men and women with expertise in bladder cancer. This editorial will provide only some of the highlights of the consultation. The entire proceedings will be found in this book. The comprehensive nature of this text will serve as a superb resource for many years. Of note the first author of each chapter is not necessarily the same as the chair or co chair of the committee.

Bladder cancer is the second most common malignancy of the genitourinary tract. Its protracted course and requirement for frequent monitoring is responsible for the huge costs involved with the care of patients with BC. It has been stated that it is one of the most expensive cancers. It is a heterogeneous neoplasm and even within some categories there are significant differences in behavior among different histologic variants. These nuances are critical to proper management. Unlike prostate cancer the level of awareness for this neoplasm is quite low among not only the public but primary care physicians as well. This is one of the primary problems that leads to a delay in diagnosis which may adversely impact survival in men and women with high grade BC. Thus one of our challenges is to educate the public and members of the medical profession about the association of risk factors such as cigarette smoke and pelvic radiation with the development of bladder cancer as well as the need for prompt investigation of hematuria or persistent irritative bladder symptoms.
COMMITTEE 1: DIAGNOSIS AND STAGING

Committee 1 was charged with reviewing the diagnosis and staging of BC. The co chairs are Ashish Kamat and Paul Hegarty. The sections are replete with valuable information about all aspects of the diagnosis, endoscopic management, and imaging of BC.

The authors stress the importance of prompt investigation of men and women with gross or microscopic hematuria to determine whether a malignancy is the cause of the bleeding. Although the likelihood of identifying cancer as the source of microhematuria is low, upper urinary tract imaging as well as cystoscopy are indicated particularly if there are any risk factors or the individual is over 50. There is no absolute recommendation on the method of imaging the upper urinary tract. In most centers the CT urogram is the most common technique to provide excellent anatomy of the kidneys and ureters as well as the urinary bladder. The excretory urogram (IVP) is gradually going the way of the rotary dial telephone. Nonetheless CT requires intravenous contrast, subjects the patient to significant radiation and is expensive. Urinary cytology should be considered part of the hematuria work up. Urine cytology is specific and sensitive for the detection of high grade BC. Although cytology is not very sensitive for the detection of low grade tumors this is not a reason to shun its use as there is no necessity to detect low grade tumors early. Although cytology and other urine based markers are recommended for the investigation of individuals with hematuria the committee concluded that urinary markers including cytology have not been shown to be helpful in detecting BC in an asymptomatic high risk group, e.g. occupational exposure, smokers. This is largely related to the low prevalence of bladder cancer even in a so called high risk population. Among the various urine based markers the committee indicated that the FISH test is expensive and there are false positive tests. As a result a patient may be subjected to a thorough urologic investigation following a “positive” FISH test yet no urothelial cancer is detected. Its use might be beneficial when there is an atypical cytology reading. Thus the routine use of urinary markers other than cytology have yet to find a place in routine urology practice.

The committee thoroughly reviewed lower urinary tract endoscopy and discussed in detail some of the more recent approaches to enhance endoscopy and endoscopic tumor resection (TURBT). A TURBT is an under estimated surgical procedure and requires skill and judgement. The procedure begins with a thorough history including a review of the patients unique background which includes their overall medical history and their prior history of urothelial cancer. In a discussion of some of the new techniques to enhance endoscopy and TURBT they highlight the fact that residual or new tumors are found in up to 50% of patients at their first post diagnosis follow up or at a reTUR. Many if not most of the tumors identified at a repeat endoscopy/TURBT performed within 4 to 6 weeks of the prior procedure are due to missed or incompletely resected tumor. This fact highlights the difficulty in performing this procedure as the goal is always to remove all evident tumor at the initial TURBT.

Several new methods are nicely described that might improve the urologist’s ability to resect all the tumor, i.e. perform a complete TURBT. These technical innovations include photodynamic diagnostic cystoscopy (PDD), narrow band imaging (NBI), Ramon spectroscopy, and optical coherence tomography. These techniques are designed either to aid in the detection of tumors not seen by standard white light endoscopy or offer the potential to provide in situ tumor staging. I have had experience with PDD and NBI and they do provide added benefit in some patients, particularly in identifying papillary tumors and distinguishing CIS. There are a number of trials demonstrating that PDD can detect more tumors and this leads to a lower recurrence rate presumably as a result of a more complete TURBT. The relative reduction in recurrent tumors was 16% in one prospective randomized multicenter trial. This technique requires the intravesical instillation of a solution containing hexaminolevulinic acid 1 hour before the endoscopy/TURBT. NBI has the advantage of not requiring instillation of any exogenous material. It is initiated by touching a button on the camera or light source which places a filter in the optical system. Papillary tumors in particular are identified by a characteristic blue appearance.

Upon identifying a bladder tumor the urologist must decide upon the depth of resection required to properly stage the tumor. The TURBT provides the tissue i.e. tumor, which is the foundation for the decision making and treatment of bladder cancer. If the endoscopic appearance suggests a possible T1 or T2 tumor (lamina propria or muscularis propria invasion) the resection must contain muscle from the muscularis propria in order to determine the depth of penetration. In the case of an invasive tumor the specimen should be analyzed for lymphovascular invasion as this is an important prognostic factor along with grade and depth of invasion.

I was particularly pleased to note that the authors reiterated that bladder perforation should be discouraged. Many years ago urologists thought it was acceptable to resect through the wall of the bladder in an effort to remove a bladder tumor. The risks clearly outweigh the potential benefit of eradicating a T3 tumor by endoscopic resection.
Committee 2 was devoted to the pathology of BC. The co chairs are M. Amin and Victor Reuter. They collaborated with a virtual who’s who of GU pathologists to write an outstanding chapter. The text is accompanied by superb photomicrographs. The chapter provides an overview of both urothelial (UC) and non urothelial cancers of the bladder. The authors carefully illustrate the differences between dysplasia (not cancer) and carcinoma in situ (CIS). CIS is a flat, high grade cancer confined to the urothelium. Dysplasia may require monitoring while CIS is treated with intravesical therapy, e. g. BCG.

There are many important variants of urothelial cancer (UC) and they have important implications for treatment beyond grade and stage. For example both micropapillary and the nested variant of UC have a distinct histologic appearance and behave in amore aggressive manner than other high grade UCs. The implication is therefore that a diagnosis of nested or micropapillary UC at stage T1 should include a discussion of total cystectomy at the time of diagnosis.

Another tumor type that has important treatment implications is small cell carcinoma (SCC) of the bladder. Like SCC at other sites (lung, prostate) these tumors metastasize early and the initial treatment should be systemic chemotherapy, not cystectomy.

This chapter has a superb section detailing the use of immunohistochemistry which may aid in the diagnosis of different subtypes of bladder cancers. There are some markers which may provide prognostic information as well. Most urologists like myself are not terribly conversant with this area but should attempt to become conversant about the potential role this plays in our ability to decide the best treatment approach. There is also a section on urinary markers including cytology and the chromosome addition/deletion FISH test from the pathologist’s perspective.

The authors detail the necessary information that constitutes an adequate report from the pathologist to the clinician. Although there are many occasions when it would be useful for the urologist or other oncologist to look at the slides with the pathologist this is often not feasible so the report is the primary communication and must contain the critical information the urologist/oncologist requires to make treatment decisions. This includes not only the tumor grade and stage but more precisely the depth of lamina propria invasion, presence of LVI, presence or lack thereof of muscularis propria, and whether there is CIS. In the not too distant future I believe we will have a readily available method to access our patient’s histology on the internet. All pathology reports will be accompanied by the pertinent histology. Viewing histology via the internet should be similar to what most of us currently rely on for viewing images of the upper urinary tract. We would not make a decision to remove a kidney, for example, without reviewing the actual CT/MRI. Why should we not have the same opportunity with biopsy material?

This extensive review of the pathology of bladder cancer will serve as a superb reference for anyone interested in this subject. This is emphasized by the number of references – 761!

Committee 3, authored by S. Shariat et al, details the various molecular markers which might be useful in BC. As it is a heterogeneous neoplasm there are numerous molecular signature patterns which potentially may be immensely helpful for directing treatment. Some of these markers include p53, p21, pRB, and p27 among others. Despite a host of studies that have analyzed the addition or deletion of these and other genes or gene products the information derived from these studies have yet to impact on the decisions we make in the clinic. The authors discuss a number of reasons for this which include the differences in the antibodies used to identify the marker in question and the statistical methodology in specific studies. For those interested in the “state of the art” of this subject this chapter is a terrific resource.

The second part of this chapter reviews the current status of urinary markers for screening, diagnosis, and surveillance of BC. The authors stress the importance of urinary markers and the opportunity they might have to play a larger role in the diagnosis and monitoring of BC. Unfortunately the potential of urinary cytology and other urine based markers has yet to be realized. Although these markers have some efficacy in detecting patients with BC the specificity and sensitivity is such that they have not found wide utilization by most urologists. The discussion of cytology and its lack of sensitivity in low grade BC must be countered with the fact that an early diagnosis of the “benign” acting low grade tumor is not critical however we have abundant evidence that there is a substantial delay in the diagnosis of high grade potentially lethal BC. Thus the authors highlight the potential role of cytology or other markers for the early detection of bladder cancer in a high risk population, i. e. hematuria, smokers, etc.

The authors comment on why most of the urine based markers have not been integrated into a routine work
up for patients with hematuria. This is partly related to the relatively high rate of false positive tests and thus their lack of specificity. In contrast when one has a report of malignant cells identified in a urine cytology the clinician has the obligation to search for a tumor as the chance of a false positive is very low.

Committee 4 concentrated on low grade Ta bladder tumors. The chairs are B. J. Konety and Wim Oosterlinck. Similar to the conclusions noted above as related to cytology and urine based markers these authors make it clear that cytology and urine based markers do not have a role in the monitoring of patients with low grade tumors. The cost and problems with false positives and/or low sensitivity in the context of an already highly sensitive and specific although minimally invasive test to diagnosis and treat these tumors i.e. cystoscopy have relegated these tests to a minor role. The authors emphasize that the risk of a subsequent upper tract tumor following initial diagnosis and treatment of a low grade Ta tumor is low and therefore there is no indication for regular monitoring of the upper tract, e.g. IVP, CT. This recommendation, if followed, will save money as well as lessen the risk of radiation for patients who have LG Ta tumors. Obviously any change in grade, unexplained hematuria or positive cytology would prompt consideration for upper tract imaging.

There are a variety of ways the urologist can manage the patient with a low grade Ta tumor: cold cup resection/fulguration in the operating room, office fulguration, formal TURBT, and initial observation for recurrent very small tumors which appear to be Ta. The goal is to minimize the risks of therapy in a tumor that rarely, if ever, progresses in stage. Because patients with a low grade Ta tumor infrequently develop a high grade BC the committee recommends less vigorous endoscopic surveillance. Thus if the initial three month cystoscopy is negative the next cystoscopy may be at 1 year.

Following the removal of one or more low grade Ta tumor(s) all current guidelines recommend the instillation of at least one dose of intravesical chemotherapy to be instilled into the bladder within hours of the resection. This should not be prescribed if there has been perforation of the bladder. Although this recommendation is consistent among most guideline committees (EAU, AUA, SIU) data from insurance providers in the US indicate it is infrequently practiced. This may in part be related to the obstacles of giving chemotherapy in the postop recovery room. The committee indicated that BCG is not recommended as first line intravesical therapy in low risk patients as the side effect profile is higher than with chemotherapy and the efficacy is equivalent. BCG should be considered for patients who develop a high grade Ta or T1 tumor as well as those who have multiple recurrences despite intravesical chemotherapy.

Committee 5 chaired by Fred Witjes and Max Berger provided recommendations on high grade Ta, CIS, and T1 UC. They indicate that the risk of developing an upper tract tumor over the course of a patient’s life is sufficiently high to warrant periodic upper tract surveillance. Unfortunately there is a paucity of data on how frequently to perform upper tract imaging and importantly whether any schedule identifies a life threatening upper tract UC in a timely fashion. Most guidelines suggest performing an imaging study every 1-3 years following resection of a high grade Ta/T1 but a high grade upper tract urothelial tumor is likely to grow and invade or metastasize within this time frame. If one is really concerned about detecting a high grade upper tract tumor promptly then frequent cytology possibly supplemented by ultrasonography might be a practical and potentially useful alternative.

Cystoscopy is recommended every 3-4 months for BC surveillance following the diagnosis of a high grade UC because there is concern about waiting too long before detecting and treating a high grade recurrence. In contrast to the patient with low grade Ta tumors the risk of recurrence and progression is substantial. Tumors of the urinary bladder which are high grade and Ta are initially treated by complete endoscopic resection which may be facilitated by the use of photodynamic diagnostic techniques using blue light technology. If the surgeon is not confident that he/she has performed a complete resection then a re-resection should be performed within 4 to 6 weeks. Once a complete resection has been assured intravesical BCG should be initiated 2 weeks after the TURBT. The accepted instillation is weekly for six weeks with maintenance therapy for a minimum of one year. There is no data on what is the optimal maintenance schedule although most studies have used the schema initiated by the SOG group. There is evidence that an initial single instillation of chemotherapy provides a longer tumor free interval. The precise role of post TURBT intravesical chemotherapy in these patients is controversial.

Carcinoma in situ is usually multifocal and often seen in conjunction with other tumors in the bladder. Its presence signifies multifocal urothelial cancer.
When identified as the only tumor it is treated with *intravesical BCG*.

Patients with a **high grade T1 tumor(s)** are a particular challenge as the risk of initial under staging and progression is substantial. Some will advocate **cystectomy** at initial diagnosis in patients which have particularly adverse prognostic factors such as multifocal T1 tumor, associated CIS, lymphovascular invasion (LVI) or tumors that cannot be completely resected. There is a strong recommendation that following the resection of a high grade T1 urothelial carcinoma with or without muscularis propria in the specimen a **reTURBt** should be performed to ensure complete removal of all tumor before commencing BCG.

It is important to emphasize that 10 to 20% of patients with an initial high grade T1 UC who are treated by a TURBt followed by BCG ultimately die of metastatic urothelial carcinoma. Thus there should be some consideration and discussion regarding initial cystectomy.

One of the important subjects discussed in this chapter are the definitions of **BCG failure**. Patients who are refractory to BCG never achieve a disease free status with one or two six-week courses of BCG. Patients who have an initial complete response to TURBt followed by BCG and develop another tumor after a year without therapy can be considered for re-treatment with BCG after complete resection of their tumor. Patients who have an initial complete response to TURBt followed by BCG and develop another tumor after a year without therapy can be considered for re-treatment with BCG after complete resection of their tumor. Lastly there are patients who are intolerant of BCG. For patients with high grade urothelial carcinoma that recur promptly despite BCG there are several alternatives but **cystectomy** should be considered the initial option with **alternative intravesical therapies** reserved for those unfit for cystectomy.

Patients who receive BCG after resection of a high grade Ta/T1 tumor and **have not achieved a complete response at three months** are given the alternatives of another 6 weeks of BCG or proceed to cystectomy. Although the authors stress there are insufficient data to direct the timing of abandoning bladder preservation there is a growing consensus that if the tumors are T1 a cystectomy in medically fit patients is appropriate. The chance that the tumor is **understaged** is substantial and delay in removing the bladder can be lethal.

**COMMITTEE 6: MUSCLE-INVASIVE, PRESUMABLY REGIONAL, TUMOR**

Committee 6 chaired by Jason Efstathiou, David Quinn and Arnulf Stenzl aided by 13 urologists, radiation or medical oncologists had the task of reviewing the treatment alternatives for muscle invasive UC (MIBC). This is a wonderful and comprehensive overview of the surgical approaches to MIBC which include **partial and total cystectomy**, and **TURBt alone**. The initial part of the chapter deals with the procedure of **total cystectomy** which in men traditionally includes removal of the **prostate** and in women removal of the **uterus and the anterior vaginal wall**. The precise extent of the procedure may vary depending on the extent of the tumor, patient age, etc. They discuss the variations of this procedure and note there may be occasions when the prostate and uterus and vagina may be spared. The authors caution that the surgeon must weigh any potential quality of life benefit from a less extensive procedure with the risk of leaving an aggressive cancer in situ. A particular example would be the woman who is having a cystectomy for high grade Ta/T1/CIS UC and wishes an orthotopic neobladder. As long as the staging is accurate it may be wise to preserve the anterior vaginal wall and uterus if no prior hysterectomy to act as a support for the pouch.

The literature outlining the extent of the **pelvic lymph node dissection** is detailed. There is substantial data from a number of sources stressing the benefit of extending the node dissection superior to the external iliac vessels and removing lymph nodes along the common iliac vessels and possibly even to the aortic bifurcation. Although removing the lymph nodes superior to the external iliac vessels yields more negative and positive nodes it remains unclear that the additional dissection results in a longer disease free survival. It is clear however that the quality of the cystectomy and node dissection is a factor in the prognosis of patients undergoing this procedure. The percentage of patients with one or more positive lymph nodes is approximately 25% from large RC series and further highlights the aggressive nature of high grade MIBC and the need for some early detection program to improve upon the survival rate from this disease.

The **complication rate** from radical cystectomy ranges from 30 to 50%. There is a long list of medical and surgical problems that can occur after a RC/urinary diversion and some can be addressed with appropriate attention to detail and risk factors. Once again a plea to have these procedures concentrated in centers where there are surgeons and medical and surgical intensivists accustomed to this operation as well as the perioperative care of high risk patients. Thanks to technical improvements to aid the surgeon such as vascular staplers, bipolar cautery devices as well as an improved understanding of pelvic anatomy particularly related to the prostate the blood loss from this surgery has declined. The **perioperative mortality** remains relatively stable and ranges from 1 to 5% depending on a number of factors such as patient comorbidity, age, prior surgery, etc.
Another alternative for the management of muscle invasive bladder cancer is \textit{bladder preservation}. This approach is for selected patients who meet a short list of inclusion criteria which includes a normal upper urinary tract (no hydronephrosis), an adequate bladder capacity, and they must have had a “complete” TURBT. It is preferable they do not have CIS. This program requires the interest and expertise of three disciplines: urology, radiation and medical oncology.

The \textit{treatment plan} calls for an initial complete endoscopic tumor resection followed by 40 Gy radiation therapy with concomitant \textit{cisplatin based chemotherapy}. At this point a \textit{repeat cystoscopy} is required to determine whether there has been a complete response. If not the patient is advised to have their bladder removed. If there has been a complete response the initial treatment is consolidated with additional radiation and chemotherapy with careful endoscopic monitoring. Over the last 20 years the protocol has been changed from a neoadjuvant chemotherapy approach with cisplatin based combination chemotherapy to be followed by radiation therapy and cisplatin to the current approach of \textit{twice a day radiation} and concurrent \textit{cisplatin} and a \textit{taxane}. This is then followed by four cycles of \textit{gemcitabine} and \textit{cisplatin}. The results from this bladder sparing approach in a highly selected group of patients is similar in disease free survival to initial radical cystectomy. A high percentage of the patients have adequate bladder function.

The important subject of \textit{perioperative systemic chemotherapy} is addressed by a group of outstanding medical oncologists. The disease free survival following radical cystectomy has plateaued over the last decade. In order to improve the cure rate we will require either effective systemic therapy or a better method to identify and treat patients with high grade UC before metastases occur. We have systemic chemotherapy that can produce major responses in locally advanced and metastatic UC although complete responses in the latter category are no more than 10%. It is thus a reasonably chemotherapy sensitive tumor with the use of cisplatin based combination chemotherapy. Prospective randomized trials have examined the benefit of \textit{induction (neoadjuvant)} and \textit{adjuvant chemotherapy}. These results are thoroughly reviewed in this chapter. There have been two prospective randomized trials that indicate at least a 5% survival advantage in favor of patients who received induction or neoadjuvant chemotherapy before cystectomy or radiation. Meta analysis of these neoadjuvant trials support the benefit of \textit{cisplatin based combination} chemotherapy as induction treatment. The authors indicate that at this time the four drug combination identified as \textit{MVAC} remains the regimen of choice although in practical terms most oncologists use \textit{gemcitabine and cisplatin}. Randomized studies have shown equivalence between MVAC and GC in metastatic urothelial cancer with less toxicity with the two drug regimen.

One of the important conclusions is that patients are \textit{more likely to receive the intended chemotherapy if given before cystectomy}, i. e. induction rather than as an adjuvant. This is largely related to delays or failure to receive chemotherapy as a result of the frequent complications following this extensive operation. This is a disease of elderly patients and many simply refuse or cannot tolerate our optimal chemotherapy regimen after a cystectomy and diversion. These factors are less operative when considering induction chemotherapy.

This chapter has excellent sections discussing the role of \textit{RC as initial therapy} for several variants of high grade UC. Specifically they discuss the nested variant, micropapillary, and UC with adenocarcinoma and squamous elements. All of these tumors are associated with a poorer prognosis and thus a RC should be seriously considered when they are diagnosed at stage T1.

Another section discusses the role of \textit{monitoring the upper tract} following a diagnosis of MIBC of the bladder. Some of the key points relate to a risk related strategy for monitoring the upper tract since there are no optimal recommendations for imaging the upper tract. No strategy to date has demonstrated that frequent CT or other imaging modality performed at one or two year intervals will detect tumors in a timely fashion. Thus patients with tumor at the ureteral margin or with bladder CIS should have more frequent monitoring. \textit{Cytology} might be a reasonable adjunct to imaging as it can be performed frequently at relatively little cost and does not add the risk of radiation associated with CT scanning.

The committee dealing with muscle invasive bladder cancer also stressed the importance of initial chemotherapy using cisplatin and etoposide for \textit{small cell carcinoma}. Most of these patients have metastatic disease at diagnosis despite negative staging studies and therefore it is a recommendation to \textit{initiate treatment with chemotherapy}. Once a complete response is achieved consolidation is performed with surgery or radiation.

\textbf{COMMITTEE 7: URINARY DIVERSION}

Committee 7 deals with urinary diversion. This committee is chaired by Richard Hautmann and Bjorn Volkmer. The 19 member committee stresses that a radical cystectomy and urinary diversion may be the most difficult operation in urologic surgery. The procedures are often performed in...
elderly patients with significant comorbidity usually related to years of cigarette smoking. The operation, whether by a standard open approach or with laparoscopy, is long and requires that the surgery be performed with attention to detail. At this time most of the urinary diversions are being performed with an open technique even if the RC is performed laparoscopically.

The committee points out that there are few studies which adequately address the complications related to radical cystectomy. An ideal analysis should include operative time, length of stay, estimated blood loss, time to return to work, as well as operative mortality. Few reports detail readmission rates, reoperation rates, time in intensive care, and additional interventional radiologic procedures both in the short-term and long-term. Since there are no randomized studies all recommendations are level III or IV and mostly expert opinion.

This committee surveyed the members of the working group and note that approximately 50% of men and women who have a urinary diversion at these centers of excellence had an orthotopic neobladder, most of the remaining patients had an ileal conduit. A continent diversion to the skin is uncommon. Of interest in population based surveys of the type of diversion only 15% of patients undergo an orthotopic diversion however in centers devoted to the care of these patients up to 70% have an orthotopic neobladder. The committee suggests that a high volume center should perform at least 25 RCs per year. At many centers, including ours, one of us performs the RC and another the diversion. This limits the time in the operating room to under 2 - 3 hours for each and I believe has some benefits.

The committee highlights the fact that the extent of the cancer in the pelvis is not always a barrier to perform an orthotopic neobladder. Positive lymph nodes, for example, should not exclude a patient from a neobladder. There is no consensus on the need for preoperative biopsy of the prostate to determine the acceptability for an orthotopic urinary diversion as the frozen section of the urethral margin will serve as the determining factor of whether an anastomosis can be made to the urethra. Some surgeons like to have information on the status of the prostatic urethra in hand to discuss the type of diversion. I rely on the intraoperative frozen section.

Nerve sparing can be utilized depending on the extent of the tumor and will allow preservation of erectile function in some young men who undergo a total cystoprostatectomy. The committee indicates that preserving the seminal vesicles and the nerves surrounding them may be beneficial in preserving more nerves involved in erectile function and continence. There is no age cut off for a neobladder. Many patients more than 70 years old wish to avoid an abdominal stoma. The motivation of the patient is the most important factor in the decision to perform a bladder substitute. The urethral anastomotic stricture rate is low. With procedures performed at centers of excellence the stricture or stenosis at the uretero-ileal junction is less than 5%. Orthotopic diversion in women is becoming increasingly utilized and the motivation of the patient is critical. One would hesitate to perform a neobladder if the carcinoma invades the bladder neck or vaginal wall.

The authors discuss the role of renal function both in deciding the type of diversion and the need to monitor renal function after the diversion. In order to perform an orthotopic diversion the patient must have a creatinine clearance of >50 cc/min. Few patients have a decline in renal function following a diversion. One should monitor the upper tract with periodic creatinine levels as well as by renal ultrasound. Early diagnosis of stricture at the ureteroileal anastomosis is important.

The authors have an excellent section discussing perioperative complications of urinary diversion. They stress some practical points such as the preservation of the anterior vaginal wall, when possible, and the use of an omental interposition flap to decrease the chance of a urethral vaginal fistula.

**COMMITTEE 8: UROTHELIAL CARCINOMA OF THE PROSTATE**

Committee 8, authored by Juan Palou, David Wood, and four other urologists reviewed the topic of urothelial carcinoma of the prostate. Many years ago this was thought to be a rare entity. With improvements in endoscopy and TURBT along with intravesical therapy urothelial carcinoma of the prostate is more frequent. With control of tumors in the bladder we have changed the natural history of UC of the lower urinary tract. The urologist managing patients with high grade Ta/T1/CIS of the bladder must always consider the status of the prostatic urethra and guard against a non visible area of high grade cancer in the prostate. A positive urinary cytology in the absence of a visible source in the bladder requires a biopsy of the prostatic urethra, which should be a TUR resection biopsy.

It is important to accurately stage the extent of high grade urothelial carcinoma of the prostatic urethra. The stages are: carcinoma in situ (CIS), involvement of the prostatic ducts, and invasion of the prostatic stroma. The latter portends a particularly adverse prognostic factor. The 5 year survival is 60% if there is no stromal invasion and 30% if there is. Stromal invasion can either occur by direct extension of a muscle invasive tumor from the bladder or by growth.
from the prostate urothelium down the ducts into the stroma. When stromal invasion occurs by extension from the bladder the survival is particularly poor despite cystoprostatectomy.

Treatment for **CIS of the prostate** is **endoscopic resection followed by BCG**. High grade tumor after an initial course of BCG should prompt consideration for a **RC. Tumor in the ducts** can be initially treated similarly although some advocate cystoprostatectomy at initial diagnosis of ductal involvement. The prognosis for patients with stromal invasion is poor despite a cystoprostatectomy. Induction chemotherapy should be considered in such cases.

**Papillary low-grade tumors** of the prostate have a good prognosis and can be managed with **endoscopic resection** with or without intravesical chemotherapy.

### COMMITTEE 9: CHEMOTHERAPY

Committee 9 is authored by Cora Sternberg with the help of 9 outstanding medical oncologists and one urologist. Their chapter discusses the role of systemic chemotherapy for advanced BC. There are several prospective, randomized trials which have examined the activity of systemic chemotherapy using the four drug combination referred to as **MVAC** or the **combination of cisplatin and gemcitabine**. An important 400 patient prospective, randomized trial compared these two regimens and demonstrated equivalent efficacy and less toxicity with the two drug combination. Thus although some oncologists feel that in the “healthy” patient MVAC might be superior the majority of oncologists use the two drug regimen for the majority of patients for first line chemotherapy in locally advanced or metastatic UC. The committee also discussed the role of high-dose MVAC with **G-CSF rescue**.

The authors discuss the common problem of **cisplatin ineligible patients**. Cisplatin is the most active single agent for UC however many patients with advanced urothelial cancer are elderly and/or have reduced renal or cardiac function. Forty per cent of patients are ineligible to receive cisplatin due to renal impairment. Most studies which have given chemotherapy in these patients have used **carboplatin** in place of cisplatin. One of the problems of evaluating these reports is the variability in the definition of unfit patients. The traditional **exclusion criteria** are a performance status less than 60% and a creatinine clearance less than 30 ML per minute. Patients also require a cardiac ejection fraction better than 40% in order to receive cisplatin.

The chapter discusses the many agents that have been used for patients who have progressed despite first line chemotherapy. Unlike other cancers in which there are effective **second and third line programs** there is a lack of effective salvage therapy in UC.

### CHAPTER 10: NON-UROTHELIAL CARCINOMA OF THE URINARY BLADDER

Chapter 10 authored by Bruce Kava, Alex Colquhoun, Jack Baniel et al reviews non-urothelial carcinoma of the urinary bladder. This category includes **squamous cell, adenocarcinoma**, and **small cell carcinoma** of the urinary bladder. Other very rare histologic types are also mentioned. There is a paucity of information based upon any randomized trial to determine the optimal approach for the first two of these tumor types. Since there is **no effective systemic therapy** for squamous cell or adenocarcinoma there is a consensus that the best option for the majority of these tumors is **RC**.

**Squamous cell carcinoma** is relatively infrequent outside of Egypt or other countries in which schistosomiasis is endemic. Squamous cell carcinoma of the bladder may be caused by chronic inflammation of the bladder. Patients with an indwelling catheter, bladder calculi, spinal cord injured patients who have a neurogenic bladder are at an increased risk for squamous cell carcinoma of the bladder. The local failure rate for squamous cell carcinoma appears to be higher than for UC of the bladder.

**Adenocarcinoma** of the bladder has several subtypes which include **urachal and non urachal tumors**. The former are usually treated by extensive partial cystectomy ensuring negative margins at frozen section.

Despite apparent local control the incidence of local and systemic failure is high. Unfortunately there is **no effective adjuvant chemotherapy** although in some instances radiation might be considered.

**Small cell carcinoma** has been discussed in part in the sections on pathology and MIBC. The key here is to make the diagnosis after the initial diagnostic TURBT. After thorough staging the initial treatment is **cisplatin and etoposide** systemic chemotherapy. The initial response is usually excellent. Following chemotherapy there are no data driven recommendations on whether the optimal approach is RC, radiation, or observation. I have treated patients using each of these with success.
BLADDER CANCER

EDITORS

MARK S. SOLOWAY AND SAAD KHOURY,
Committee 1

Screening, Diagnosis, and Evaluation

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Peter E. Clark, Judson D. Davies, Jinhai Fan, Jason R. Gee,
Nicholas J. Hegarty, Paul K. Hegarty, Murugesan Manoharan,
Tim S. O’Brian, Amit Patel, Sudhir Rawal, Rafael Sanchez-Salas
Robert S. Svatek, William Turner

A. SCREENING AND DIAGNOSIS: EVALUATION OF PATIENTS WITH HEMATURIA

I. SCREENING

The object of screening is to identify disease at an earlier stage when it is more amenable to treatment. An evaluation of the quality of studies concluded that there were no randomized controlled trials or high-quality controlled observational studies comparing screening to not screening for bladder cancer [Chou 2010]. No study was identified that randomized screen-detected cancers to treatment versus non-treatment. Thus the recommendations on screening remain unchanged from the 2006 ICUD guidelines.

II. PRESENTATION

Hematuria, typically painless, is the cardinal presenting symptom of noninvasive bladder cancer. In patients with CIS, hematuria may be accompanied by irritative voiding symptoms. The incidence of bladder cancer is 17-18.9% in patients presenting with macroscopic hematuria and 4.8-6% in patients presenting with microscopic hematuria [level of evidence 2; Edwards et al, 2006, Datta et al, 2002, Mishriki et al, 2008]. The prevalence of asymptomatic hematuria ranges from 0.19% to 21% depending on the population being studied, and prevalence appears to increase with age [Rodgers et al, 2006]. The prevalence of microscopic hematuria is 23% in men over 60 years of age, and in men older than 60 years with microscopic hematuria, the risk of bladder cancer on subsequent investigation is 5% [level of evidence 2; Britton et al, 1989]. It is unknown if early detection of bladder cancer following investigation of asymptomatic microscopic hematuria leads to an improved outcome. Findings on physical examination are unremarkable in patients with noninvasive bladder cancer.

III. INVESTIGATION

Cystoscopy is the cornerstone investigation in patients with suspected bladder cancer. Flexible cystoscopy can be performed in the office with local anesthetic lubricant. The office-based procedure can be omitted in patients in whom bladder cancer has already been identified on imaging and who proceed directly to transurethral resection.

In patients with hematuria, imaging is an important part of the evaluation; imaging is used primarily to visualize the upper urinary tract as cystoscopy allows inspection of the lower urinary tract. The incidence of upper urinary tract malignancy among patients undergoing evaluation because of hematuria is 0.2-0.7% [level of evidence 2; Khadra et al, 2000, Edwards et al, 2006]. Options for imaging are ultrasonography, IVU, CT urography, MRI, or a combination of these. Ultrasonography and IVU appear to be equally sensitive in diagnosing upper tract disease [level of evidence 2; Khadra et al, 2000]. Using CT as the gold standard, ultrasonography has a positive predictive value of 100% in detecting renal cancer [level of evidence 2; Datta et al, 2002]. Improvements in the technical quality of ultrasonography have resulted in improved performance of this imaging modality in detecting bladder cancer; reported sensitivities are 63-98%, and reported specificity is 99% [level of evidence 2; Datta et al, 2002]. Thus, diagnostic flexible cystoscopy can be omitted in cases in which ultrasonography reveals bladder cancer. CT
Urine cytology is not a laboratory test; rather, it is a pathologist's interpretation of the morphologic features of urothelial cells. The combination of urine cytology and cystoscopy has been the gold standard for the diagnosis and surveillance of bladder cancer.

Cytology is a simple, noninvasive, cost-effective procedure and the combination of urine cytology and cystoscopy is superior to cystoscopy alone in the detection of high-grade flat lesions—i.e., CIS and dysplasia; in the detection of high-grade urothelial carcinomas; and in the detection of upper urinary tract malignancy (level of evidence 2; Chlapoutakis et al, 2010). The disadvantages of CT urography are relatively high radiation dose, need for intravenous contrast medium, limited availability, and relatively high cost.

Edwards et al (2010) tested a protocol in which patients with hematuria underwent flexible cystoscopy, ultrasonography, and plain radiography as first-line procedures and IVU if there were abnormal findings on first-line procedures or there was persistent hematuria in a patient over 40 years of age. With a medium follow-up time of 4 years, the risk of missing a tumor with this protocol in a patient with microscopic hematuria was less than 1%. For macroscopic hematuria, the risk of missing a tumor was 2% for men over 30 years of age and women over 50 years of age, and the risk increased a further 1% for each decade over 50 years of age for both sexes (level of evidence 2). These so-called “missed tumors” probably represent new tumors or tumors not visible on initial cystoscopy (level of evidence 3; Messing et al, 2005).

IV. URINE CYTOLOGY

Urine cytology has reported sensitivities of 88-100% and specificities of 93-100% in diagnosing urothelial carcinoma. A meta-analysis of 5 studies of CT urography yielded a pooled sensitivity of 96% and a pooled specificity of 99% in diagnosing upper urinary tract malignancy (level of evidence 2; Chlapoutakis et al, 2010). The disadvantages of CT urography are relatively high radiation dose, need for intravenous contrast medium, limited availability, and relatively high cost.

The role of urine cytology in the diagnosis of bladder cancer has been universally accepted and extensively analyzed. However, a critical review of the literature reveals a paucity of randomized controlled trials of urine cytology. Most of the earlier studies concentrated on the sensitivity, specificity, and positive predictive value. A pooled analysis of 36 studies reported a sensitivity of 44% and a specificity of 96% for urine cytology (Mowatt et al, 2010). Once urinary biomarkers were introduced, the focus of research shifted to comparison of cytology and biomarkers and subsequently to the utility of biomarkers as an adjunct to cytology. In a meta-analysis comparing fluorescence in situ hybridization (FISH) and cytology, even though the sensitivity and specificity of FISH were superior to those of urine cytology, the sensitivity of FISH was lower than that of cytology for higher-stage tumors (Yang et al, 2009).

The American Urological Association best practice policy recommends voided urine cytology for all patients with risk factors for urothelial carcinoma. For patients with asymptomatic microscopic hematuria without risk factors for urothelial carcinoma, either urine cytology or cystoscopy can be used (Grossfeld et al, 2001).

Because of its high specificity and sensitivity in the detection of pTis disease, urine cytology fulfills the requirements for an adjunct to cystoscopy in the surveillance of patients with pTa-T1 bladder urothelial carcinoma (Babjuk et al, 2008). A multicenter study performed in the United States to compare the performance of cytology, the ImmunoCyt tumor marker test, and the combination of cytology and ImmunoCyt in patients monitored for recurrence of bladder cancer showed that ImmunoCyt enhanced the sensitivity of cytology (Messing et al, 2005). About 50-70% of patients with superficial bladder cancer develop recurrence within 5 years, and 25% eventually develop invasive disease. Lifelong surveillance is therefore mandatory in the management of non muscle invasive cancer (Fritsche et al, 2010). Urine cytology remains the gold standard for surveillance of patients with non muscle invasive cancer.
V. URINARY BIOMARKERS

Urinary biomarkers for the diagnosis of bladder cancer have been evaluated extensively, but to date, there have been relatively few completed randomized trials. Glas et al (2003) performed a meta-analysis of 42 case series (n=5,706) that compared urine cytology versus urinary biomarkers—including NMP22, telomerase, BTA, BTA-Trak, and BTA-Stat—in the diagnosis of primary bladder cancer. None of the urinary biomarkers exhibited sensitivity that would justify the use of biomarker measurement as a substitute for cystoscopy. Furthermore, when all studies were combined, urine cytology had a specificity of 94%, which was higher than the specificity of any of the biomarker tests evaluated. Twenty-two of the 42 studies included in the meta-analysis used a case-control design, which can be associated with bias [Glas et al, 2003]. In a more recent, cross-sectional study involving 668 patients, Grossman et al (2006) found that the sensitivity of the NMP22 test as a point-of-care test for the detection of recurrent bladder cancer was 49.5%, versus only 12.2% for urine cytology. While these results cannot justify the use of NMP22 in lieu of cystoscopy, the addition of the NMP22 assay did improve sensitivity compared with cystoscopy alone (99% vs. 91%), whereas the addition of voided urine cytology did not significantly increase the sensitivity compared with cystoscopy alone (94% vs. 91%) [Grossman et al, 2006].

Results for urinary biomarker tests vary widely. For instance, for NMP22, the sensitivity has been found in cohort studies to be as low as 44% [Chahal et al, 2001] and as high as 91% [Miyanaga et al, 1999]. The specificity of NMP22 in the Chahal et al and Miyanaga et al studies was 91% and 76%, respectively, and in another series, the specificity was only 40% [Tritschler et al, 2007]. Significant variability has also been noted for other urinary biomarkers, including BTA (sensitivity of 28% [Johnston et al, 1997] versus 80% [Leyh et al, 1997]); telomerase (specificity of 24% [Cassel et al, 2001] versus 100% [Kinoshita et al, 1997]); and cytokeratin 8/18 (UBC) (sensitivity of 12.1% [Babjuk et al, 2008] versus 70.5% [Hakenberg et al, 2004]).

Results for FISH appear more consistent. In a recent meta-analysis of 14 studies involving 2,477 FISH tests, for all studies combined, the sensitivity of FISH was 72% (69-75%), and the specificity was 83% (82-85%). In comparison, for all studies combined, the sensitivity of cytology was 42% (38-45%), and the specificity was 96% (95-97%). However, when cases of non muscle invasive cancer were excluded from the analysis, only a marginal difference was noted in the performance of FISH and cytology [Hajdinjak, 2008].

Other recent studies regarding FISH in the diagnosis of bladder cancer call into question the role of this assay in clinical practice. In a study by Ferra et al (2009), patients with suspicious findings on urine cytology were also evaluated by FISH. When findings on cystoscopy and biopsy were used as the gold standard, the sensitivity of FISH was 68.3% and the specificity was 39.7%, indicating that in patients with suspicious findings on urine cytology and negative findings on cystoscopy, positive findings on FISH could not justify aggressive evaluation [Ferra et al, 2009]. Youssef et al (2010) performed a review of 142 patients undergoing cystoscopic surveillance and confirmed that a cancer diagnosis in patients with negative findings on both cystoscopy and cytology was rare (1/111 patients). Furthermore, cancer in patients with equivocal or positive findings on cystoscopy was relatively common, such that the authors concluded that FISH was not useful in these cases either and that a cost analysis should be done before adoption of widespread use of FISH in patients with negative findings on urine cytology [Youssef et al, 2010].

Combinations of urinary biomarkers have also been explored. In a study by Horstmann et al (2009), 221 patients undergoing cystoscopic surveillance for non-muscle-invasive bladder cancer were evaluated with urine cytology, NMP22 testing, FISH, and ImmunoCyt. Sensitivity was increased to over 90% and negative predictive value was increased to over 80% with combinations of 2 or 3 biomarkers, although specificity was reduced to an average of 44% with 2 biomarkers and 35% with 3 biomarkers [Horstmann 2009].

Currently, there is no consensus regarding the use of urinary biomarkers for the diagnosis of bladder cancer. While results of many carefully conducted clinical studies have been reported, randomized clinical trials are needed to determine the appropriate use of urinary biomarkers in diagnosis and surveillance of bladder cancer.

REFERENCES


B. ENDOSCOPIC EXAMINATION OF THE LOWER URINARY TRACT

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One of the cornerstones of the diagnosis and management of urothelial carcinoma is cystoscopic examination of the lower urinary tract. In this section, we will provide an overview of white light cystoscopy (WLC); the techniques of lower urinary tract endoscopy; and newer optical technologies that can enhance endoscopy, including fluorescence cystoscopy, narrow band imaging (NBI), Raman spectroscopy (RS), and optical coherence tomography (OCT). The evidence presented in this section is level 3 unless stated otherwise, and all recommendations presented in this section are grade C unless stated otherwise.

I. WHITE LIGHT CYSTOSCOPY

White light endoscopic examination of both the urethra and the bladder (white light cystoscopy; WLC) remains the gold standard for screening and diagnosis for multiple diseases of the lower urinary tract, including urothelial carcinoma. Cystoscopy not only permits visualization of the bladder urothelium but also affords access to the ureteral orifices to facilitate assessment and treatment of the upper urinary tract.

Cystoscopy can be performed utilizing either rigid or flexible endoscopes, depending on the clinical circumstances. The standard caliber measurement for all endoscopes is based on the French (Fr) scale, in which 1 Fr equals 1/3 mm (for example, a 12-Fr endoscope has a diameter of 4 mm). Endoscopes from 8-12 Fr are typically used for pediatric patients, and endoscopes from 16-28 Fr are typically used for adult patients.

1. RIGID CYSTOSCOPY

For screening and diagnostic work, most often sheaths of 20-22 Fr are used for adult patients, and smaller sizes are used for pediatric patients. For suspected urethral neoplasms, a 0-degree lens is useful. For examination of the prostatic urethra, the bladder trigone, and the bladder wall except the part immediately adjacent to the bladder neck, a 30-degree lens is generally used. For more acute or difficult angles, particularly at the anterior bladder neck, a 70-degree or 90-degree lens may be employed, although in such cases, use of adjunctive implements, such as catheters or biopsy forceps, is typically not possible without specialized deflecting bridge adaptors.

The large bore of rigid cystoscopes typically allows for excellent irrigation flow and visualization, even when there is mildly to moderately bloody urine or debris, and provides a port that can accommodate a variety of instruments. However, because of their large size and rigid nature, rigid cystoscopes typically cannot be used effectively in the office; most often, particularly in men, rigid cystoscopes are used in an operating room with the patient under general or some form of regional anesthesia. In addition, for a rigid cystoscope to be used effectively, the patient must be placed in a dorsal lithotomy position, and in the occasional patient this may pose difficulties.

2. FLEXIBLE CYSTOSCOPY

Rigid cystoscopy was the standard of care in urology for many years, but starting in the early 1970s, the advent of better fiberoptic technologies permitted the development of flexible instruments that could be used more easily than rigid cystoscopes in the office. The first published report of use of a flexible “fibercystoscope” for examination of the bladder neck was by Tsuchida and Sugawara in 1973. This report was followed over a decade later, in 1984, by the development of the first commercial flexible instrument built specifically for cystoscopy. Since that time, the use of flexible fiberoptic cystoscopy has grown rapidly, and flexible cystoscopy is now a standard method for diagnosis and surveillance of a variety of lower urinary tract disorders, including urothelial carcinoma. The fact that flexible cystoscopy can generally be performed without anesthesia has led to widespread acceptance of this procedure; it is now the most common office-based procedure performed by urologists in developed countries such as the United States. Over time, manufacturers have developed improved optics that permit smaller-caliber scopes while maintaining high image quality, and the development of a working channel allowed for the use of flexible instruments. This, coupled with the advent of active deflection, has permitted a range of office-based procedures that can potentially be done without the need for general anesthesia. In addition to decreased discomfort, the other advantage of flexible cystoscopy is the use of active deflection to improve visualization of the anterior bladder neck.

Despite their advantages and widespread use, flexible cystoscopes have some disadvantages compared to rigid endoscopes, such as the small irrigation port and lack of a separate working sheath, which limits the ability to irrigate and use instruments simultaneously. Typically only the smallest of tumors can be ablated or biopsied using only flexible endoscopy. Finally, flexible endoscopes are typically more costly and more prone to damage than rigid endoscopes if not handled properly, including during cleaning and sterilization between cases.

The flexible fiberoptic cystoscopes commonly in
First introduced by French researchers in 1956,[2] video cameras as an adjunct to endoscopy were first introduced by French researchers in 1956,[2] and this concept has led to improved ergonomics, improved safety through avoidance of contact with body fluids, enhanced patient and resident education, and improved documentation of findings and sharing of information among physicians through the use of digital cameras and recording devices.[3] One study showed that male patients who were able to monitor their cystoscopy by watching the procedure on a video monitor experienced up to 40% less pain and discomfort during endoscopy compared to patients who did not watch their procedure on a video monitor.[4]

Perhaps the biggest recent advance in WLC has been the development of digital endoscopy. With this method, light from the generating source still travels through the traditional fiberoptic imaging bundle. However, the image is no longer carried back along fiberoptic bundles to the eye piece. Instead, there is a digital sensor at the very tip of the endoscope that is based on a charge-coupled device and complementary metal oxide semiconductor chips. The image is acquired through the digital sensor through millions of photodiodes that convert the photons of light into an electric current that is subsequently transformed into voltage, then amplified and converted to a digital format.[2] The semiconductor chips transfer the information to a receiver that presents the image on a monitor and/or stores it digitally.

Digital endoscopy offers the promise of improved optical resolution, contrast, and color differentiation and may be more durable than traditional flexible endoscopy. Ex vivo studies have suggested that distal endoscopes are superior to more traditional fiberoptic cystoscopes in terms of resolution, contrast discrimination, and red color differentiation.[5]

4. CONCLUSION

WLC, whether performed in the office utilizing flexible instruments or performed in the operating room using rigid instruments, is the standard approach to diagnosis and management of lower urinary tract disease, including urothelial carcinoma, and is the gold standard against which other approaches must be compared.

II. FLUORESCENCE CYSTOSCOPY

1. PHOTODYNAMIC DIAGNOSIS OF BLADDER TUMORS

Non-muscle-invasive bladder cancer is associated with a significant risk of recurrence; thus, lifelong patient surveillance is required. Recurrence of non-muscle-invasive bladder cancer has been postulated to result either from failure to identify abnormal mucosal areas or from incomplete resection under conventional WLC. After WLC and resection, reported rates of residual or recurrent disease at follow-up WLC can be as high as 55%.[9-11] Fluorescence cystoscopy (photodynamic diagnosis; PDD) can improve the visualization of bladder tumors compared to standard WLC. Improved visualization has led in turn to reduced rates of residual tumor at first-check cystoscopy and in some series to reduced rates of recurrence.[9-11]

However, many of the studies to date on PDD have shortcomings, including inclusion in the studies of both patients with newly presenting and patients with recurrent tumors; failure to use the best current
standard of care—for example, transurethral resection plus immediate single instillation of intravesical mitomycin C—in the control arm of studies; use of surrogate endpoints such as histology rather than the more clinically relevant endpoint of recurrence; and, in older studies, use of the photosensitizer 5-aminolevulinate (5-ALA) rather than the currently licensed product hexylaminolevulinate (Hexvix, Cysview; see the next section).

**a) Principle of PDD**

PDD relies on an endogenous or exogenous photosensitizer that causes abnormal cells to fluoresce under a specific wavelength of light. Currently, the most frequently used exogenous photosensitizers are derived from the heme biosynthetic pathway. Nonactive molecules are converted in a series of enzymatic reactions to the active fluorescent molecule protoporphyrin IX (PPIX), which under normal conditions is then rapidly converted to heme. This metabolic reaction takes place in all nucleated cells.

The starting point of the heme biosynthetic pathway is 5-ALA. Administration of exogenous 5-ALA causes rapid rises in the levels of PPIX. Fluorescence microscopy following administration of 5-ALA has shown tumor selectivity of PPIX accumulation, which is at least 5 times as great in tumors as in normal urothelium.[1] Significant differences in heme metabolism have been demonstrated between tumor and normal cells, and these differences promote the selective accumulation of PPIX.[1] Higher concentrations of intracellular 5-ALA are from the reduced diffusion barrier to the absorption of exogenous 5-ALA. This is in part due to fewer intercellular tight junctions and recruitment of transmembrane channel proteins, which provide active transport of 5-ALA into the cytoplasm.[2]

Fluorescence of PPIX is achieved by the presence of pyrole rings, which have photo-optical properties and fluoresce when excited by light of certain wavelengths. PPIX absorbs light at around 400 nm (violet blue) and emits fluorescence at 635 nm (red).

At the molecular level, a photon of light interacts with the electron shell of a single PPIX molecule, causing excitation. Fluorescence is emitted as the electron returns to its ground state. When tissues with high levels of PPIX are illuminated by a blue light, they fluoresce red (Figure 1).

**b) Practical Considerations**

Fluorescence cystoscopy uses a normal rigid cystoscope combined with an excitation light source called a D-light. The D-light consists of a short-arc xenon lamp and an integrated observation filter to filter out all but the fluorescence emission wavelength that is of interest and enough excitation blue light back-scattered to suppress nonspecific red fluorescence. Urine fluoresces yellow-green under fluorescence ("blue light") cystoscopy; therefore, the bladder should be emptied before blue light illumination.

Lowering of the intensity of the bright blue light to the tone of fluorescence results in images 10 times darker than those produced by WLC. As a result of the darker image, the video photography is done at 15 rather than 50 frames per second, and the cystoscope needs to be moved slowly to reduce strobe effect. It is recommended that the bulk of tumor resection be carried out under WLC with blue light reserved for checking the resection margins.

The intensity of PPIX fluorescence diminishes with time, a process referred to as photobleaching. Illumination causes the degradation of the tetrapyrole ring of PPIX and return of the delocalized electrons to ground state and a reduction in fluorescence. This effect is greatest at the blue-light wavelength but also occurs under white-light conditions, although at a less rapid rate. Reducing the viewing distance between the cystoscope and the urothelium also increases the rate of photobleaching. Fluorescence is greatly reduced when the viewing distance is halved.[3]

Artifact fluorescence is defined as an increase in fluorescence intensity not due to tumor. False
fluorescence is usually a less-bright pink color and less discrete than the fluorescence in tumor cells and occurs at sites of thickened urothelium. Folds of the urothelium will cause such artifact, and therefore the bladder should be sufficiently full to minimize folds. Other common sites where artifact fluorescence is seen are along blood vessels, on the trigone, and around the ureteric orifices. Squamous metaplasia at the bladder neck and the trigone produces nonspecific fluorescence, which is used as a control to confirm the adequate absorption of the fluorophore when there is no fluorescence elsewhere in the bladder. The viewing angle between the cystoscope and the bladder can also give rise to false fluorescence due to increasing the thickness of the urothelium with tangential viewing angles. This problem can be overcome by using a range of cystoscopes to distinguish pathological from tangential fluorescence.

**RECOMMENDATIONS FOR USE OF PDD**

PDD is currently recommended for treatment of patients with newly presenting non-muscle-invasive bladder tumors; examination of patients with positive findings on voided urine cytology but negative findings on WLC; treatment of multifocal recurrent bladder tumors; and teaching of urological surgeons in training. Each of these situations is discussed below.

### 2. EVALUATION AND TREATMENT OF PATIENTS WITH NEWLY PRESENTING NON-MUSCLE-INVASIVE BLADDER TUMORS (GRADE C)

The advantage of WLC plus PDD over WLC alone in the visualization and staging of bladder tumors is widely recognized.[12-17] The tumor detection rate is 73-96% with WLC alone, compared to 90-96% with WLC plus PDD.[12-17] PDD is particularly helpful in the detection of carcinoma in situ (CIS); rates of detection are 23-68% with WLC alone, compared to 91-97% with WLC plus PDD. While PDD improves sensitivity in the diagnosis of non-muscle-invasive bladder tumors, there remain issues surrounding its specificity. Early studies suggested a slightly higher false-positive rate of 3-8%[13-15] due to nonspecific inflammation that can occur after treatment of a urinary tract infection, after TURBT, or after intravesical therapy with bacillus Calmette-Guérin (BCG). It is therefore recommended that PDD be delayed for 9-12 weeks after any activity that could result in bladder inflammation.[18] Intravesical mitomycin C is not associated with a higher false-positive rate.[19]

PDD may also be able to improve the quality of resection compared to WLC. Geavlete et al reported at repeat TURBT 6 weeks after initial resection that residual tumor was found in 31% of patients who underwent WLC resection and 11% of those who underwent PDD resection.[20] If validated, these results would indicate improved visualization of the tumor with PDD and thus more complete resection.

Improved detection and resection of bladder tumors with PDD has been reported to improve recurrence-free survival compared to WLC. Stenzl et al performed a multicenter randomized controlled trial and over a 9-month follow-up period found that the tumor recurrence rate was lower in the PDD group (47%; 128 of 271) than in the white light group (56%; 157 of 280) (p=0.026); the relative reduction in the recurrence rate was 16%.[21] Trials with a longer follow-up duration but using 5-ALA have shown that the reduction in recurrence extends up to 8 years of follow-up.

### 3. EXAMINATION OF PATIENTS WITH POSITIVE FINDINGS ON VOIDED URINE CYTOLOGY BUT NEGATIVE FINDINGS ON WLC (GRADE C)

PDD has been shown to detect new bladder tumors in approximately 30% of patients with positive findings on urine cytology and negative findings on urinary tract investigations.[23] This rate can rise to approximately 66% in patients previously treated for bladder cancer. Patients with negative findings on PDD and normalized cytology usually have a clear urinary tract for at least 2 years.[14] If findings on cytology remain positive, an abnormality is likely to be detected within 1 year. Improved detection of bladder lesions can reduce the need for bilateral ureterorenoscopy and stents and their associated morbidity. Tritschler et al evaluated the use of fluorescence endoscopy and found that the sensitivity and specificity of bladder wash cytology was greater with fluorescence cystoscopy than with white light endoscopy. However, 3.4% of tumors were diagnosed by bladder wash cytology only, and most of these were high-grade tumors.[Tritschler et al, 2010].

### 4. TREATMENT OF MULTIFOCAL RECURRENT BLADDER TUMORS (GRADE C)

Patients with multifocal bladder tumors are at high risk for the development of recurrence. Holmang et al reported that 88% of patients with 3 or more tumors experienced recurrence within 5 years after diagnosis.[24] Ray et al showed that PDD detected additional disease in 8 (57%) of 14 patients with already confirmed recurrence.[18] Four patients in whom additional disease was detected were found to have CIS, and thus had treatment with BCG initiated. Only the results from a phase II trial as to whether PDD in patients with multifocal disease affects recurrence rates on follow-up, the results of phase III trials are awaited.
5. Teaching Urological Surgeons in Training (Grade D)

PDD offers endoscopists better visualization of tumors and their resection margins, thereby facilitating improved transurethral resection of bladder tumor (TURBT) technique. Thus, PDD is a useful tool for teaching urological surgeons in training.

6. Additional Considerations

Whether early repeat cystoscopy is required after initial tumor resection with PDD is not yet known. PDD cystoscopy could potentially help rationalize the use of early resection, optimize case selection, improve outpatient management modalities, and permit more precise tumor resection. PDD is not currently recommended in patients for whom cystectomy is indicated or in the outpatient setting with flexible cystoscopes. Although PDD flexible cystoscopy has been shown to be feasible and as effective as PDD rigid cystoscopy [25], the need for a second cystoscopy under a general anesthetic for biopsy has not made this approach cost-effective.

Conclusions

Non-muscle-invasive bladder cancer is associated with a significant risk of recurrence; thus, lifelong patient surveillance is required. PDD can improve detection of disease, especially CIS; improve completeness of resection; and, most importantly, reduce rates of recurrence of non-muscle-invasive bladder cancer. Improved initial resection, such as with PDD, has been suggested to improve recurrence rates after intravesical chemotherapy, but this needs to be further evaluated in clinical trials.

III. New Optical Imaging Techniques for Bladder Cancer Diagnosis

Cystoscopy and cytology are considered to be the current gold standard for detection and follow-up of non-muscle-invasive bladder cancer. However, these techniques have a low sensitivity and other limitations. First, CIS may easily be missed by standard WLC. Second, no information on histopathologic information is provided during WLC, which often makes discrimination between inflammatory lesions and CIS difficult because both can appear as mucosal red spots. Finally, estimates of grade or stage of bladder cancer made during cystoscopy are often not accurate even when they are made by an experienced urologist [26]. New optical imaging modalities for bladder cancer diagnosis have been developed to overcome the limitations of cystoscopy and cytology. These new techniques include PDD, NBI, RS, and OCT. We herein present our review of these new techniques for detecting bladder cancer (except for PDD, which was discussed earlier in the chapter) and speculate regarding their potential future applications.

1. Narrow Band Imaging

a) Principle of NBI

For NBI, modified optical filters are used in the light source of a video endoscope system to narrow the bandwidth of spectral transmittance. NBI enhances the differences in penetration depth between wavelengths. Light penetration depth within tissue is highly dependent on wavelength: shorter wavelengths produce only superficial penetration and longer wavelengths produce deeper penetration. Blue light, therefore, penetrates superficially, while red light penetrates deeply [27]. NBI narrows the bandwidth of light output from the endoscope system to between 415 nm and 540 nm. The relative intensities of blue and green light are increased, while the intensity of red light is decreased to a minimum. This narrow bandwidth of green and blue light is strongly absorbed by hemoglobin, so NBI enhances visibility of surface capillaries and blood vessels in the submucosa without the use of dyes (Figure 2). Systems that have integrated NBI and WLC are already commercially available. With the
push of a button, the NBI mode is activated by mechanical insertion of a narrow-band filter in front of the white light source.

b) NBI Cystoscopy for Detection of Non-muscle-invasive Bladder Cancer

NBI cystoscopy is easy for surgeons to adopt and has a high sensitivity for detecting small papillary and otherwise undetectable cancers, especially CIS. NBI was initially shown to be useful in gastrointestinal disease, particularly for detection of adenomas at colonoscopy and for follow-up of Barrett's esophagus [30]. The first report of NBI in bladder cancer was published by Bryan et al in 2008 [31]. These authors performed WLC and subsequent NBI flexible cystoscopy to detect bladder cancer in 29 patients with recurrent non-muscle-invasive bladder cancer [31]. NBI flexible cystoscopy provided much better visualization of bladder cancer than did conventional flexible WLC. NBI cystoscopy revealed 15 additional tumors (in 12 patients) not detected by WLC. However, these additional tumors were not confirmed histopathologically because all tumors were treated by diathermy ablation following cystoscopic examination. With NBI cystoscopy, the vasculature appears dark green or black against the almost white normal urothelium, whereas with WLC, tumors appear red in a background of normal pink urothelium (Figure 3).

Sensitivity and specificity rates for NBI cystoscopy and WLC in patients with non-muscle-invasive bladder cancer and CIS are presented in Table 1. Herr et al described a series of 427 patients who underwent follow-up with WLC and NBI cystoscopy, 103 of whom had tumor recurrence [32]. Ninety patients (sensitivity 87%) had their disease diagnosed by WLC, and the other 13 (sensitivity 100%) had their disease detected only by NBI cystoscopy, including 8 patients with CIS, 4 patients with Ta disease, and 1 patient with T1 disease. NBI cystoscopy performed better than WLC in demarcating margins of CIS lesions from surrounding normal-appearing mucosa. In another series, Tatsugami et al performed WLC and then NBI cystoscopy in 104 consecutive patients [27]. In 39 (26.9%) of 161 sites suspicious for tumor, bladder tumors were identified only by NBI. These tumors were CIS in 25 patients, Ta tumors in 12 patients, and T1 tumors in 2 patients. In this entire series, 14 of 30 patients with CIS had their disease detected only by NBI. However, the aforementioned studies might be flawed owing to observer bias since WLC and NBI cystoscopy were performed by the same urologist. To avoid observer bias, Cauberg et al conducted a trial in which WLC and NBI cystoscopy were performed by different surgeons in 95 patients [33]. Seventy-eight patients had histopathologically confirmed non-muscle-invasive bladder cancer. NBI identified additional tumors in 28 of those 78 patients. In contrast, WLC identified additional tumors in only 3 of those 78 patients.

Possible limitations of the currently published studies are their monocentric nature and the possible observer bias since WLC and NBI were performed sequentially and observed by the same urologist. Ye et al conducted a study designed to compare the rate of detection of non-muscle-invasive bladder cancer by NBI cystoscopy versus WLC in a multicenter setting with a randomized sequence of the 2 procedures. One hundred three consecutive patients from 4 academic centers in China were included in this prospective, multicenter, phase III trial presented in abstract form in 2010 [34]. Eighty-seven patients had confirmed bladder tumors. In 29 of these 87 patients, tumors were detected by NBI cystoscopy only, and in 4 patients, tumors were identified by WLC only. The mean number of detected tumors per patient was 1.45 with WLC and 1.85 with NBI cystoscopy.

c) NBI Cystoscopy for Detection of Residual Cancer after Treatment

Two trials to detect residual cancer by NBI cystoscopy were conducted in patients with high-risk non-muscle-invasive bladder cancer. In a series of 47 patients, all patients were examined with WLC and NBI cystoscopy and underwent a second TURBT procedure approximately 1 month after an initial TURBT. Overall, 16 of 47 patients were discovered to have residual or recurrent cancer, including 6 patients with high-grade cancers detected only by NBI [35]. In another series, 61 patients were evaluated with both WLC and NBI cystoscopy 3 months after beginning induction therapy with BCG. NBI correctly identified 21 of 22 cases of residual cancer [36].

d) NBI Cystoscopy as a Follow-Up Tool

Another trial compared the usefulness of WLC and NBI cystoscopy as follow-up tools. Patients were followed up with WLC for 3 years and with NBI cystoscopy for the next 3 years. The trial revealed fewer tumor recurrences, smaller numbers of recurrent tumors, and a longer recurrence-free survival time with NBI cystoscopy. Small solitary papillary tumors and clusters of papillary tumors were more efficiently treated with NBI cystoscopy than with WLC [37]. However, only patients with frequently recurrent tumors were included in this study. Hence, the authors were unable to discriminate the natural history of disease from an influence of NBI cystoscopy on outcomes. With longer follow-up periods, tumors generally recur less frequently [38]. More investigation appears to be indicated to confirm this trial’s conclusions.

e) WLC versus NBI Cystoscopy for TURBT

NBI technology is available for rigid cystoscopy and bladder tumor resection. One feasibility report of TURBT performed with NBI cystoscopy indicated shorter operative times, shorter time to catheter
Figure 3. Examples of the differences between tumors visualized with WLC (left) and NBI cystoscopy (right). (Photos were cited from “Case study of NBI (Specific Wavelength Light) Vol.1” which was published by Olympus medical systems Corporation.)
removal, and shorter time to hospital discharge with NBI cystoscopy than with WLC, although the differences were not statistically significant [39]. The authors speculated that use of NBI cystoscopy for TURBT would substantially reduce the recurrence rate of bladder tumors. However, the observer in this trial was allowed to take a “second look” with the alternative form of imaging, which may have introduced a bias.

f) Learning Curve for NBI Cystoscopy
Herr et al demonstrated that both experienced and relatively inexperienced urologists quickly learned NBI cystoscopy as a supplement to WLC [40]. That is, use of NBI cystoscopy to detect and characterize bladder tumors is not associated with a steep learning curve. Bryan et al confirmed these findings [41].

g) NBI Cystoscopy Controversies
By permitting better visualization of the margins of non-muscle-invasive papillary and flat bladder lesions, NBI cystoscopy facilitates more thorough excision of tumor. Fluorescence cystoscopy (PDD) using 5-ALA or its hexyl ester has been recognized to improve the detection of non-muscle-invasive papillary and flat bladder lesions compared to WLC and to reduce the recurrence rate of non-muscle-invasive bladder cancer [17]. However, whether the better visualization and high sensitivity associated with NBI cystoscopy compared to WLC likewise translate into lower tumor recurrence rates cannot be confirmed. Prospective randomized trials with long-term follow-up are ongoing to compare the efficacy of TURBT performed with WLC and with NBI cystoscopy [39]. Results of these trials are eagerly awaited.

Because NBI cystoscopy detects ulcers of bladder mucosa and areas of angiogenesis more readily than does WLC, the value of NBI cystoscopy in the diagnosis of interstitial cystitis/painful bladder syndrome is apparent [42]. One notable deficiency of NBI cystoscopy for bladder cancer detection is its low specificity (high false-positive rate), which leads to unnecessary resection of noncancerous tissue. Intravesical agents (immunotherapy or chemotherapy), cystitis, and hematuria may be associated with inflammatory mucosal appearances mimicking urothelial tumors (see Figure 3). In view of its low specificity (60-85%), use of NBI in combination with other modalities such as urine cytology, RS, or OCT that allow histopathologic diagnosis may well be advised.

2. RAMAN SPECTROSCOPY

a) Principle of RS
Raman spectroscopy measures molecular components of tissue both qualitatively and quantitatively. Photons interact with laser light to contribute to or derive energy from a tissue's intramolecular bonds. The result is a change in the bonds' vibrational state and emission of a different wavelength of scattered light [43]. Each molecule has unique vibrational energy levels and corresponding wavelength shifts. When a tissue is exposed to laser light, altered wavelengths from different molecules combine to form the Raman spectrum, which depends on the molecular composition of the tissue being investigated. Using RS, a pseudocolor map of examined tissue is created. Tissue areas with similar molecular composition, and therefore with similar spectra, are depicted in the same color. Such images are comparable to histopathology and images of stained tissues. Molecular composition changes if pathologic transformations occur. Thus, RS can provide an objective prediction of the pathologic diagnosis [26].

b) RS for Detection of Non-muscle-invasive Bladder Cancer
Several trials were performed to compare the diagnostic accuracy of RS and histology in ex vivo bladder samples. A study of 15 tumor and nontumor bladder tissue samples demonstrated that RS had a sensitivity of 92% and a specificity of 94% in the diagnosis of bladder cancer [44]. In another series, of 75 bladder tissue samples, Crow et al showed that RS could differentiate normal, inflammatory, and malignant tissue with a sensitivity of 90-95% and a specificity of 95-98% [46]. Discrimination between grade 1 or 2 and grade 3 malignant samples was achieved with sensitivity and specificity of greater than 93%. The ability to discriminate between CIS,
inflammation, and the changes associated with intravesical therapy, all of which can appear as red spots in the bladder mucosa, is an important finding. Draga et al were the first to perform RS in vivo [47]. The microfiber optic probes were utilized endoscopically through a working channel. These authors found that RS distinguished normal bladder from cancer with a sensitivity of 85% and a specificity of 79%. Combining the new diagnostic modalities of RS and 5-ALA, Grimbergen et al showed that applying 5-ALA affected the Raman spectra of bladder tissues [48]. Whether combining fluorescence with RS could improve its diagnostic capability is unknown.

Shapiro et al used RS to detect tumor epithelial cells in urine samples and in a broader sense to diagnose cancer in isolated cell samples [49]. Baseline spectral features were obtained from bladder cancer tissue for high-grade (T2), low-grade (Ta), CIS, and normal bladder tissue (Figure 4). The signal obtained from epithelial cells in urine samples correctly diagnosed bladder cancer with a sensitivity of 96% (100% of the high-grade tumors) and a specificity of 90% (Figure 5). Furthermore, the authors delineated the thresholds for normal tissue, low-grade tumors, and high-grade tumors, which makes the use of RS for bladder cancer diagnosis feasible.

c) Future of RS for Detection of Bladder Cancer

To date, only a few small-scale clinical trials have been conducted of RS for detection of non-muscle-invasive bladder cancer. Small, flexible fiberoptic probes compatible with the working channel of a rigid or flexible cystoscope have been developed [45]. In other fields of medicine, findings have been reported for use of RS to check intraoperative margins during partial mastectomy and for use of RS to characterize atherosclerotic plaques during vascular surgery. In bladder cancer, RS must be targeted at visually suspicious lesions or lesions identified by other methods, such as PDD or NBI cystoscopy. The potential advantage of RS is its ability to provide a noninvasive, real-time, and objective prediction of the pathologic diagnosis [46]. Application of RS to urine samples presents an exciting approach to the diagnosis of bladder cancer, one with sensitivity and specificity similar to that of cystoscopy. Maybe one day RS can be used instead of urine cytology as the preliminary screening study for bladder cancer. Further investigations are needed to verify the performance of RS in urine samples and also in other cellular systems to determine the applicability of RS to other malignancies.

3. OPTICAL COHERENCE TOMOGRAPHY

a) Principle of OCT

OCT produces high-resolution, cross-sectional images of tissue. OCT is similar to B-mode ultrasound imaging except that OCT measures reflected infrared light rather than acoustic waves. The intensity of back-reflected light from structures within tissue is displayed as a function of depth [52]. Because of its high resolution (approximately 10 micrometers), superior dynamic range (approximate

Figure 4. Raman spectrum obtained from high-grade urothelial carcinoma (UC; dashed) tissue, low-grade UC tissue (dotted), and normal tissue (solid). The 1584-cm-1 wave is higher in high-grade tumors but is also present in low-grade tissue (The figure was cited from Shapiro A 49).
140 dB), and optimal depth of penetration (up to 2-3 mm), OCT is potentially useful for noninvasive screening for superficial lesions in bladder mucosa [53]. The 3 anatomic layers of the normal bladder wall (the urothelium, lamina propria, and muscularis propria) can be clearly distinguished from one another with OCT. This is possible because of the different scattering properties of each distinct layer [52].

**b) OCT for Detection of Bladder Cancer**

OCT allows noninvasive acquisition of real-time, high-resolution images of the bladder and provides information about the depth of tumor growth. As of this writing, results of 5 studies on the diagnostic accuracy of OCT have been published [54-58]. Goh et al and Sengottayan et al found similar results: OCT in the diagnosis of muscle-invasive bladder cancer had a sensitivity of 100% and a specificity of 90% [59]; 97.5% and 78.6%, respectively, for PDD; and 97.5% and 97.9%, respectively for PDD combined with OCT (Figure 6 and 7). Thus, combining PDD with targeted OCT increased specificity substantially. To enhance the accuracy of detection of CIS, Ren et al used 3-dimensional OCT [60]. Sensitivity and specificity were 56.5% and 61.5%, respectively, with 2-dimensional OCT and 95.7% and 92.3%, respectively, with 3-dimensional OCT.

**c) Limitations of OCT**

Some authors point out that most false-positive findings on OCT are caused by inflammatory lesions of the bladder. Whether or not previous intravesical instillations or radiotherapy, both of which can cause inflammation, influence the accuracy of OCT is unknown. In addition, OCT may have limited reliability in the measurements of muscle-invasive tumors because of insufficient imaging depth. Furthermore, OCT is not ideal for screening the entire bladder because, in the absence of visually suspect lesions, OCT must be used in combination with other diagnostic methods (e.g., NBI or PDD) to identify the region of interest [26].

In contrast to ultrasonography, OCT can be
Figure 6. (a) Optical coherence tomography image of normal bladder wall: urothelium (U), lamina propria (LP), and muscularis layer (MP); (b) OCT probe placed on the bladder wall, as seen during cystoscopy (The figure was cited from Schmidbauer J [59]).

Figure 7. Pathologic findings on optical coherence tomography imaging: (a)dysplasia; (b) carcinoma in situ; (c)papillary Ta lesion; (d)T1 lesion; (e)muscle-invasive urothelial cell carcinoma (The figure was cited from Schmidbauer J [59]).
performed at other sites within the urinary tract through optical fibers without the need for a distal transducer or transducing medium [52]. The interpretation of OCT scans requires some training and is operator dependent. To address this problem, Lingley-Papadopoulos et al presented an automated algorithm that uses texture analysis to discriminate bladder cancer in OCT images [61]. In differentiating benign from malignant tissue, this algorithm had a sensitivity of 92% and a specificity of 62%.

4. SUMMARY

Compared to WLC, NBI, the newest optical diagnostic technique, permits an improved evaluation of non-muscle-invasive bladder cancer, particularly at the margins of non-muscle-invasive papillary and flat bladder lesions. Furthermore, NBI cystoscopy significantly enhances tumor detection compared with WLC. NBI cystoscopy plus WLC appears to be superior to WLC alone, and NBI cystoscopy is an easy-to-handle complement to WLC. However, whether NBI cystoscopy alone is as good as WLC alone has yet to be established in larger series. No trials have confirmed the superiority of TURBT performed with NBI cystoscopy to TURBT performed with WLC after long-term follow-up. However, ongoing trials might generate more robust data concerning these applications of NBI. In future studies comparing NBI cystoscopy and WLC, we should avoid the observation bias introduced by permitting a “second look.”

PDD has been applied extensively to enhance the rate of detection of non-muscle-invasive bladder cancer. However, PDD is costly and time-consuming: 5-ALA is expensive, and the time between instillation of 5-ALA and fluorescence endoscopy is at least 1 hour. To date, PDD has been shown to have sensitivity and specificity similar to that of NBI in the detection of non-muscle-invasive bladder cancer. It is difficult to compare these 2 modalities because of different protocols, and no 3-arm study is yet available. Nevertheless, 3-arm studies for direct comparison of NBI cystoscopy versus PDD versus WLC in terms of tumor detection rates, false-positivity rates, recurrence rates, mortality rates, and cost would be helpful. However, because of the different principles underlying NBI cystoscopy and PDD, the additional tumors identified by them may not be the same ones.

RS and OCT are 2 new optical diagnostic modalities. Both of these involve access to the bladder obtained through the working channel of a cystoscope and are used to predict histopathologic diagnosis objectively and in real time. RS can measure the molecular components of tissue in a qualitative and quantitative way, while OCT can produce high-resolution, cross-sectional images of tissue comparable to histopathology images. Both techniques have been performed in vivo and have shown impressive preliminary results. RS may be utilized to detect tumor epithelial cells in urine samples, which may represent a new approach for preliminarily screening of patients who present with hematuria. However, more research must be conducted to assess the advantages of these new techniques.

Since RS and OCT have a limited field of view, screening the entire bladder with either of these techniques would be excessively time-consuming. On the other hand, while NBI cystoscopy and PDD allow the operator to quickly assess the entire bladder wall, these techniques suffer from low specificity. Therefore, a strategy in which RS or OCT measurements are targeted at visually suspicious lesions or lesions identified by PDD and/or NBI cystoscopy may overcome the drawbacks of the various modalities to increase both the sensitivity and the specificity of bladder cancer detection. Encouragingly, the first steps with this approach have been taken, and promising preliminary data indicate that RS and/or OCT combined with PDD and/or NBI likely will lead to better characterization of non-muscle-invasive bladder cancer. We speculate that RS for detection of tumor epithelial cells in urine samples might be the alternative to cytology for preliminarily screening patients with hematuria or a history of non-muscle-invasive bladder cancer. NBI cystoscopy or PDD combined with either RS or OCT could produce more sensitive and specific detection, more complete endoscopic resection, and lower recurrence rates for non-muscle-invasive bladder cancer. However, whether the combinations predict a better prognosis and fewer inspections by cystoscopy is unknown. Also, we must consider the efficacy of inspection against the cost. More research has to be conducted before these techniques can be implemented in the management of non-muscle-invasive bladder cancer.

REFERENCES

22. Babjuk, M., Soukup, V., Petrik, R. et al.: 5-aminolaevulinic acid-induced fluorescence cystoscopy during transurethral resection reduces the risk of recurrence in stage Ta/T1 bladder cancer. BJU Int, 96: 798, 2005
the bladder, extravesical spread, and pelvic lymph node status whereas ultrasonography may not. Magnetic resonance urography is similarly effective.

2. LABORATORY INVESTIGATIONS

Only basic laboratory investigations are required prior to TURBT. Urine should be cultured, and infections should be treated. In patients with infections, it is unclear if a subsequent negative culture is required before TURBT. A complete blood cell count and measurement of electrolytes and creatinine are also required as anemia or elevated creatinine or potassium levels may have implications for anesthesia. A coagulation profile should be obtained if indicated. (Level 4)

3. MEDICAL CLEARANCE AND ANESTHESIA REVIEW

Bladder cancer is usually a disease of the elderly, and hence preoperative medical clearance or anesthesia review is beneficial and may lead to a lower rate of cancellation at the time of surgery. Patients should be evaluated at a preanesthesia clinic for any issues pertaining to the airway and respiratory and circulatory systems, for medications, and for anemia and diabetes. Referral for further cardiac or respiratory evaluation can then be initiated as needed.

The major components of the clinical evaluation are the history, physical examination, and electrocardiography, the goal of which is to identify any coronary artery disease, previous myocardial infarction, angina pectoris, or other serious cardiac disorders like heart failure or disorders requiring pacemakers. It should be determined whether the patient has chronic obstructive or restrictive pulmonary disease, diabetes mellitus, peripheral vascular disease, or another major comorbid condition and whether the patient has previously undergone major vascular, thoracic, or abdominal surgery. Renal dysfunction is common in elderly patients, and creatinine level, potassium level, and estimated glomerular filtration rate are useful in calculating the dose of antibiotics as well as anesthetic agents, particularly muscle relaxants. (Level 4)

A thorough medication history is critical. Antiplatelet agents may be discontinued 7-10 days prior to surgery. Warfarin should be discontinued and the international normalized ratio (INR) should be checked on the day of surgery. While the INR is subtherapeutic, low-molecular-weight heparin may be required. Spinal or epidural anesthesia should not be performed if the INR is greater than 1.5. Beta-blockers should not be discontinued before TURBT; however, alpha blockers may need to be documented as they may result in marked hypotension during regional anesthesia. Diuretics may cause hypokalemia, which can alter the effect of muscle relaxants. (Level 4)

Diabetic patients need to have their medications reviewed and need to be given instructions regarding the use of oral hypoglycemics and insulin while fasting prior to TURBT.

Finally, patients need to be evaluated to ensure that they are able to tolerate the surgical position. Particular care is needed in placing patients with hip and knee replacements in the lithotomy position. Previous spinal surgery may make it difficult to use spinal or epidural anesthesia.

II. TECHNIQUE

1. ANESTHESIA

For TURBT, the goal of anesthesia is to enable safe resection of the bladder tumor with appropriate analgesia and relaxation. General or regional anesthesia or a combination of the two can be used. Regional anesthesia in the form of spinal or epidural blockade is effective. It also provides the advantage of a conscious patient, which means that any intraperitoneal bladder perforation can be identified by abdominal or shoulder-tip pain.

General anesthesia with or without paralysis can also be used. The obturator reflex can be a technical challenge during TURBT, and full relaxation is recommended when tumors on the lateral bladder walls are resected. Alternatively, transvesical obturator nerve block can be performed using lidocaine. (Level 1B)

2. ANTIBIOTIC PROPHYLAXIS

The goal of antibiotic prophylaxis is to prevent infectious complications from TURBT. As stated earlier, a preoperative urine culture should be performed, and any infection should be treated preoperatively. However, antibiotic prophylaxis is still recommended at the time of surgery. Oral agents with good bioavailability can be given several hours prior to TURBT, but common practice is to administer an intravenous antibiotic at the time of anesthesia to ensure that peak plasma concentrations have been achieved at the time of instrumentation. (Level 4)

There is a paucity of data on the role of antibiotics in TURBT; however, without prophylaxis, the risk of subsequent urinary tract infection may be as high as 39%. Two randomized trials have been performed comparing antibiotic prophylaxis to placebo following TURBT. MacDermott et al found a significantly reduced rate of bacteriuria in patients who received antibiotics compared to patients who did not receive antimicrobials. Most of the data
on antibiotic use in genitourinary surgery is related to transurethral resection of the prostate (TURP), in which the benefits of antibiotic prophylaxis are clear. Systematic reviews by Berry and Barratt and by Qiang et al demonstrated that prophylactic antibiotics reduced the incidence of bacteriuria and sepsis following TURP. Hence, it is recommended that prior to TURBT, urine should be sterilized if possible, and prophylactic antibiotics should be administered. There is no evidence to support prolonged use of antibiotics after TURBT in the absence of specific indications like persistent bacteriuria from calculi or anatomic abnormalities.

3. INDICATIONS FOR HOSPITAL ADMISSION

Following TURBT, the majority of patients can be discharged home with a Foley catheter, which can be removed 1-2 days after the procedure. Indications for admission to the hospital with continuous bladder irrigation are very large resections, significant hematuria, and bladder perforation.

4. SURGICAL TECHNIQUE

TURBT in conjunction with cystoscopy and examination under anesthesia serves both a diagnostic and a therapeutic purpose. The diagnostic purpose of TURBT is to obtain a specimen sufficient to permit proper estimation of the natural history of the tumor, which is currently based largely on stage, grade, histological subtype, and the presence of lymphovascular invasion. The therapeutic purpose of TURBT is to remove all tumor and provide the best milieu for intravesical therapy to be most effective.

The surgical technique of TURBT is largely based on surgeon experience. The description herein expands on the review provided by Committee 1 of the First International Consultation on Bladder Tumors [17].

The appropriate anesthesia to use during TURBT is individualized according to the patient and to surgeon and anesthesiologist preference. General anesthesia with endotracheal intubation or a laryngeal mask airway, spinal anesthesia, or epidural anesthesia may be appropriate. Resection of tumors along the lateral wall may elicit an obturator nerve reflex[17]. For such procedures, neuromuscular blockade is recommended; the use of an obturator nerve block is optional and is unnecessary in the majority of patients (Level 4).

The patient is positioned in a dorsal lithotomy position with the buttocks at the edge of the table and all pressure points padded. Special care should be taken to pad the lateral proximal fibula to avoid foot drop due to neurapraxia of the common peroneal nerve. An examination under anesthesia prior to tumor resection is optional. An examination under anesthesia should always be performed, however, after tumor resection (see the section Examination Under Anesthesia below).

The cystoscope is inserted, and the entire urethra is examined. It is possible to obtain a urine sample by barbotage immediately after the scope is inserted into the bladder using gentle irrigation with normal saline through a catheter, the cystoscope sheath, or the resectoscope sheath. However, it is recommended that urine be collected after complete inspection of the bladder because during barbotage the bladder wall can be drawn against the sheath, causing urothelial trauma that may mimic the appearance of CIS.

The bladder should be examined with both a 30-degree and a 70-degree lens. Visualization of the anterior bladder neck may be enhanced by using a 120-degree scope or by using retroflexion with a flexible cystoscope. The dome and anterior bladder are examined by applying gentle suprapubic pressure to move the bladder mucosa down and closer to the lens. It is critical to maintain optimal bladder distention during cystoscopy and TURBT. Underdistention prevents complete examination of the mucosal surface and can result in inadvertent bladder perforation during TURBT. Overdistention, on the other hand, can result in thinning of the bladder mucosa, increasing the likelihood of bladder perforation and inducing mucosal hemorrhage. Cystoscopic findings recommended to be reported are listed in Table 2.

The smallest resectoscope necessary should be introduced in an atraumatic fashion. Continuous irrigation is usually recommended to improve visualization and prevention overdistention of the bladder. Delicate movements of the sheath should be used, along with delicate movement of the loop itself to adjust the depth of resection.

There are 2 basic approaches to performing TURBT: staged resection and en bloc resection. Both are described below.

a) Staged Resection

Staged TURBT is done in several phases (Level 3). First, the most superficial portion of the tumor protruding into the bladder is resected, and the surgeon starts medially and works laterally if possible. Next, the next layer of tissue is resected in a similar fashion. Layers of tissue are resected in this manner until the base of the tumor is reached. Finally, the base of the tumor is resected. For resection of the base of the tumor, some authors recommend starting just adjacent to the bladder tumor to include normal adjacent mucosa to help guide the depth of the subsequent resection, progressing towards the tumor and towards the adjacent normal mucosa on the other side. Other authors advocate removing the bulk of the tumor base first and then performing a third phase in which the tissue surrounding the tumor base is removed. The resected tissue may be sent together for collective analysis, or tissue from...
each stage may be sent separately for a differential analysis[17-19].

**b) En Bloc Resection**

En bloc resection may be used for small tumors, generally those less than 3 cm in greatest dimension[20-22] (Level 3). Reported advantages of en bloc resection include more accurate pathologic assessment because of decreased cautery artifact, avoidance of tumor fragmentation, and preservation of the spatial orientation of the tumor relative to the bladder wall. There have been no comparative studies of en bloc TURBT versus staged TURBT.

c) Hemostasis

Following resection, it is important to achieve hemostasis. Hemostasis may be achieved by selective cautery of obviously bleeding vessels, to avoid unnecessary bladder contracture due to excessive cautery. An alternative approach is to cauterize the entire base of the resection site to prevent subsequent bleeding. Cautery near the ureteral orifices should be avoided if possible to avoid ureteral stricturing[23-25].

d) Examination under Anesthesia

Examination under anesthesia should be performed following resection of the bladder tumor. The objective of the examination under anesthesia is to properly stage the disease and to help guide appropriate therapy. A properly performed examination under anesthesia includes a bimanual examination following drainage of the bladder and without a catheter in place so that the bladder is completely empty. One hand is placed in the suprapubic region, and 1 or 2 fingers of the other hand are placed into the anus (males) or vagina (females)[17]. The hand on the abdomen displaces structures, and the posterior finger or fingers are used to note the anatomic features. The bladder, prostate, and other pelvic structures are palpated between the 2 hands[17]. If clinical stage T3 disease (palpable mass on examination under anesthesia) is present, this should be recorded, along with an estimate of the 3-dimensional size of the mass. If a mass or the bladder is fixed, the location of the fixation should be noted (Table 2). Involvement of adjacent organs should be assessed. In addition, the prostate should be examined.

**Table 2. Recommended documentation at the time of TURBT**

<table>
<thead>
<tr>
<th>Cystoscopy</th>
<th>Examples or comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of tumors</td>
<td>2</td>
</tr>
<tr>
<td>Description of gross tumor architecture</td>
<td>Flat papillary or sessile</td>
</tr>
<tr>
<td>Size (cm)*</td>
<td>3-4cm</td>
</tr>
<tr>
<td>Tumor location(s)</td>
<td>1 –Right lateral wall</td>
</tr>
<tr>
<td></td>
<td>2- trigone</td>
</tr>
<tr>
<td>Suspected depth of invasion</td>
<td>Appears Non-invasive</td>
</tr>
<tr>
<td>Adjacent mucosa (trabeculated, normal)</td>
<td>Normal adjacent mucosa</td>
</tr>
<tr>
<td>Presence of diverticula</td>
<td>No diverticula seen</td>
</tr>
<tr>
<td>Ureteral orifices</td>
<td>Normal location, clear efflux of urine</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TURBT</strong></td>
<td></td>
</tr>
<tr>
<td>Approximate Depth of resection</td>
<td>Superficial, into muscle, into perivesical fat depth of resection</td>
</tr>
<tr>
<td>Completeness of resection</td>
<td>Complete resection of tumor</td>
</tr>
<tr>
<td>Ureteral orifice(s)</td>
<td>Resected or intact ureteral orifice</td>
</tr>
<tr>
<td>Complications</td>
<td>No complications</td>
</tr>
<tr>
<td><strong>EUA (following resection)</strong></td>
<td></td>
</tr>
<tr>
<td>Prostate</td>
<td>Smooth, symmetric, no nodules, 40grams</td>
</tr>
<tr>
<td>Bladder</td>
<td>Freely mobile</td>
</tr>
<tr>
<td>Bladder mass (estimate 3 dimensions when present)</td>
<td>3cm x 3cm x 4cm (mobile)</td>
</tr>
</tbody>
</table>

* Use loop (1cm) as reference
III. TURBT IN SPECIFIC CIRCUMSTANCES

1. DIFFUSE CIS

For patients with diffuse bladder lesions and/or suspected diffuse CIS, excessive bladder biopsies and cautery are not recommended. TURBT is not therapeutic for most cases of CIS, and there is clinical evidence indicating that the appropriate treatment of diffuse CIS is intravesical therapy[26] (Level 1).

2. TUMORS AT THE URETERAL ORIFICE

Cautery should be used sparingly near the ureteral orifice. When cutting current is used to remove tumors at or near the ureteral orifice, ureteral stenosis is uncommon (Level 3). A ureteral stent may be used to prevent temporary obstruction due to postoperative edema, but whether ureteral stents prevent ureteral stenosis is unknown [17] (Level 3). A functional study, such as IVU or a renal scan, is generally recommended 3-6 weeks after resection over the ureteral orifice[27] (Level 4). Resection of the ureteral orifice may lead to vesicoureteral reflux, which may increase the risk of upper tract recurrence (Level 3). Therefore, more frequent surveillance may be needed in patients with reflux (Level 3).

3. TUMORS ON THE ANTERIOR SURFACE AND LATERAL WALL

The anterior surface of the bladder is one of the most challenging locations for TURBT. Resection of tumors on the anterior surface can be made easier by applying counterpressure to the bladder in the suprapubic region[17] (Level 4). Resection of tumors on the lateral wall may stimulate the obturator nerve and result in a sudden adduction of the leg and subsequent bladder perforation. Maneuvers to decrease the risk of eliciting an obturator nerve reflex include use of neuromuscular blockade, use of obturator block, avoiding overdistention of the bladder, using intermittent cutting current, and lowering the resection current (Level 4).

4. TUMORS IN BLADDER DIVERTICULA

Diverticula of the bladder lack the muscularis propria, and thus diagnosis and treatment of tumors in diverticula is challenging. The lack of a muscular component precludes proper assessment for muscle invasion. On the other hand, deep biopsies of bladder tumors in diverticula should be avoided because of the high risk of perforation due to a thin bladder wall. No prospective comparative trials have been published on different therapeutic approaches for diverticular tumors. However, general guidelines are as follows: For large or high-grade tumors arising from diverticula, a diverticulectomy, partial cystectomy, or radical cystectomy should be considered (Level 4). Small, low-grade lesions can be managed with careful resection or fulguration (Level 4). In addition, intravesical therapy should be considered, especially if the completeness of excision is in doubt (Level 4).

5. MUSCLE-INVASIVE TUMORS

When a muscle-invasive tumor is suspected, the depth of resection largely depends on the clinical context. In general, sufficient tissue should be resected to reveal whether or not tumor is present in the muscularis propria. Intraoperative frozen tissue assessment may be used to ensure that sufficient muscle is available for proper evaluation. In addition, proper staging of muscle-invasive bladder cancer requires an examination under anesthesia performed following complete transurethral resection of intravesical tumor[33]. Among patients treated with neoadjuvant chemotherapy, patients with pathologic T0 disease on radical cystectomy performed after systemic chemotherapy have a significantly better prognosis than patients with residual intravesical disease[34]. However, it is unclear if the completeness of TURBT influences the response to neoadjuvant chemotherapy. In general, it is advised that as much tumor be removed as is safe to decrease the local tumor burden and possibly optimize the response to chemotherapy prior to radical cystectomy (Level 5). For patients who are deemed not candidates for or who refuse a radical cystectomy, TURBT should be as thorough as possible to provide the patient with the best opportunity for cancer control. In such cases, re-resection to include deep tissue, sometimes into the perivesical fat, may be warranted[20] (Level 3).

6. REPEAT TURBT

Current management guidelines for bladder cancer are based on the depth of invasion, and therefore it is critical that the urologist obtain the most accurate staging assessment. Several cohort series indicate that the depth of tumor invasion is often underestimated on an initial TURBT. Herr reported on 150 patients with bladder cancer who underwent a repeat TURBT; 28 (29%) of the 96 patients with non-muscle-invasive bladder tumors were reclassified as having muscle-invasive disease at repeat biopsy. In addition, of the 23 patients with T1 lesions without muscle in the specimen on primary resection, 49% had their disease reclassified as T2 at the second TURBT. However, the patients in that series represented a unique population—they were all referred to a tertiary care center, and the completeness of the primary TURBT in that setting may have been limited because of the expectation of subsequent referral to the tertiary care center. Nevertheless, others have reported similar findings. Dutta et al reported understaging in 64% of patients with T1 disease when muscle was not present in the specimen versus 30% of patients with T1 disease.
when muscle was present (Level 3)[36]. Zurkirchen et al reported that 37% of patients with T1 bladder tumors at initial diagnosis had persistent tumor on repeat resection[35]. Grimm et al reported finding residual tumor in 22% of patients, including 53% of those with bladder tumors initially diagnosed as T1 (Level 3)[36]. Brauers et al reported that 24% of patients with non-muscle-invasive bladder cancer had their disease reclassified as T2 or CIS on repeat TURBT (Level 3)[37]. A prospective cohort evaluation by Schips et al revealed residual disease in at least 50% of patients at repeat TURBT, and patients with multifocality and high-grade disease were more likely to have persistent disease at repeat resection[38]. Klän et al [39] identified residual tumor at repeat TURBT in 20 (43.5%) of 46 patients and noted that patients who underwent a staged resection (see the section Staged Resection above) had a lower incidence of tumor at repeat TURBT. Recently, Shen et al reported results of a large observational study that included 125 patients with non-muscle-invasive disease who underwent a repeat TURBT[40]. Of the 125 patients, 43 (34.4%) had residual tumor on repeat TURBT, and the presence of muscle tissue in the initial TURBT specimen was significantly associated with a decreased likelihood of having residual disease (Level 3)[40].

Recently, a prospective, randomized trial was conducted to address the value of repeat TURBT in patients undergoing intravesical therapy with mitomycin C. Divrik et al randomly assigned patients with newly diagnosed T1 bladder cancer to a second TURBT with adjuvant intravesical mitomycin C (74 patients) or adjuvant mitomycin C following the initial resection without repeat TURBT (68 patients). Patients with CIS, incomplete resection, or muscle-invasive disease were excluded from the study. At a mean follow-up time of 31.5 months, the authors observed a significantly higher recurrence rate in the group that did not undergo a second TURBT (63.2%) than in the group that did undergo a second TURBT (25.7%). In addition, the progression rates were higher in the group that did not undergo a second TURBT (11.8% vs. 4.05%; p=0.097). In summary, this trial provides evidence that a second TURBT decreases recurrence rates for patients with T1 bladder cancer (Level 2)[41].

7. RANDOM BLADDER BIOPSIES DURING ROUTINE TURBT
Random bladder biopsies are performed to identify the presence of CIS or dysplasia, which may not be discernible by gross inspection but could alter management recommendations. Unlike site-selected biopsies, random bladder biopsies are performed in completely normal appearing urothelium. The role of random bladder biopsies during routine TURBT has not been resolved—here is a lack of convincing evidence either for or against routine random bladder biopsies.

The percentage of patients with tumor on random bladder biopsies ranges from 1.5-14.5%[42-45]. In a European Organisation for Research and Treatment of Cancer study, 393 patients with solitary Ta and T1 tumors underwent a biopsy of normal-appearing mucosa, and CIS was detected in 1.5%[44]. Taguchi et al reported that CIS was detected in 12 (14.5%) of 83 patients who underwent random bladder biopsies [45]. Fujimoto et al performed random bladder biopsies in 100 consecutive patients with non muscle invasive cancer, and in 8 of them, biopsy revealed additional tumor[43]. May et al [46], in a large series, reported finding urothelial tumor on random bladder biopsies in 12.4% of patients, including 4% of those with CIS (Level 3). Moreover, these authors reported that random bladder biopsy findings influenced the management in 7% of patients (Level 3)[46].

The risk of tumor implantation and subsequent tumor recurrence due to random bladder biopsy is controversial. Levi et al reported that bladder biopsy using a cold-cup biopsy grasper increased the risk of tumor recurrence in the presence of CIS[47]. Mufti and Singh [42], on the other hand, did not find tumor implantation to be a risk factor for subsequent tumor development.

A consensus opinion is that routine random bladder biopsies do not change the clinical treatment in most cases and are generally not recommended (Level 5). Random bladder biopsies are recommended in cases of discordance between urine cytology findings and the gross appearance of the bladder mucosa and in bladder mapping prior to consideration of a partial cystectomy. Finally, although there is little evidence to support recommendations regarding the location and number of random bladder biopsies, it is common practice to obtain 5 biopsy specimens, of the lateral walls, trigone, posterior bladder, and dome.

IV. SAMPLE TRANSPORT AND PATHOLOGIC PROCESSING: OR HOW BEST TO HELP YOUR PATHOLOGIST GIVE YOU THE MOST USEFUL PATHOLOGY REPORT
The pathologic evaluation of bladder tumor specimens acquired by TURBT differs markedly from the usual pathologic evaluation of tumor specimens. This is due in large part to the nature of the procedure, which cuts the bladder tumor into multiple fragments with electrocautery. The pathologist receives a specimen without any anatomic orientation, has to process multiple fragments of the specimen, and has to deal with potentially extensive cautery artifacts. The pathologist’s interpretation of this specimen will guide decisions about subsequent treatment—repeat TURBT, observation, intravesical therapy, or
radical cystectomy or radiotherapy. The most critical information gained from pathologic interpretation of TURBT specimens is information about whether there is invasion of the lamina propria or muscularis propria. Detection of lamina propria invasion usually leads to re-resection and intravesical therapy, if not immediate cystectomy, and detection of muscularis propria invasion leads to radical cystectomy, sometimes preceded by neoadjuvant chemotherapy. It is imperative that TURBT specimens be handled and processed optimally to help the pathologist make the most accurate assessment.

1. TISSUE ACQUISITION

The specimen delivered to the pathologist by the urologist depends on the type of resection. Bladder biopsies are often performed to evaluate suspicious-appearing areas of bladder mucosa or performed randomly to rule out CIS. Bladder biopsies are typically performed with cold-cup biopsy forceps and include mucosal tissue with a varying depth of subepithelial tissue, sometimes including muscularis propria. The specimens are small and friable. They must be minimally handled to prevent distortion[48-50]. Specimens are generally placed immediately on nonadherent gauze (e.g., Telfa, Kendall) and transferred directly into formalin (level 4). Orientation on nonadherent gauze facilitates the identification of early invasion[51]. Cautery artifacts are not an important issue in cold-cup biopsy specimens, but denudation of mucosa is a significant risk. Denudation is seen commonly with CIS, and hence a denuded biopsy specimen is concerning but nondiagnostic.

TURBT of a unifocal tumor is the most common clinical scenario. If the tumor is small, removal with cold cup biopsy is often preferable to resection with a cautery loop to minimize the cautery artifact. If the tumor is larger, the final specimen will be a collection of tissue chips, each measuring approximately 6 mm in diameter. These will have varying length and depth and will be derived from different portions of the tumor (superficial, middle, and base with interface to bladder wall). Larger tumors should be sent as 2 separate samples: 1 from the bulk of the tumor and 1 from the tumor base[50] (level 4). This enables the pathologist to make the most accurate assessment possible of whether there is invasion into the lamina propria or muscularis propria and decreases the likelihood that such invasion could be missed because of sampling errors.

TURBT of multifocal tumor requires some additional considerations. To map the bladder adequately, each tumor should be sent as a separate specimen. This practice requires that the surgeon document pictorially the location of the tumors in the bladder in the written operative note. The base of each larger tumor should be sent as a separate specimen to allow optimal assessment of depth of invasion. Separate evaluation of each tumor should facilitate detection of lamina propria invasion in any 1 tumor, reveal whether the surgeon should perform repeat resection of specific tumor beds because of inadequate depth of resection on initial TURBT, and reveal whether the presence of lamina propria invasion requires second resection (level 4).

When repeat TURBT is required for more certain staging of high-grade and/or T1 bladder tumors, the surgeon should resect the resection bed 4-6 weeks after initial TURBT. Specimens from repeat TURBT are generally flat and are sent to the pathologist as a single specimen per tumor site, without a separate sample from the tumor base. Interpretation of specimens from repeat TURBT can be complicated by inflammatory changes due to the preceding resection.

Laser TURBT is a novel procedure that has not found widespread application. In principle, use of laser energy for resection does not change the handling and processing of tissue specimens[54]. The principal limitation of laser TURBT is the potential for tissue alteration and destruction that prevents adequate pathologic investigation[55].

En bloc TURBT is a novel approach that is designed to allow better pathologic evaluation of tumors. Like laser TURBT, however, en bloc TURBT is not widely practiced. With en bloc TURBT, the surgeon uses a flat loop electrode, laser, or knife to resect tumors up to 3 cm in diameter as a single specimen. This gives the pathologist more accurate anatomic orientation and potentially enables better assessment of depth of invasion.

2. URINE CYTOLOGY

Urine samples sent for cytologic evaluation also require special handling and processing [58]. Cytologic evaluation of a urine specimen involves a certain degree of subjectivity. Interpretation errors will occur if specimens are collected, handled, and processed incorrectly[59]. Optimal diagnosis can only be obtained by following best practices.

Urine for cytologic analysis can be voided, obtained during catheterization, or taken at the time of instrumentation. The quantity of cellular material and the quality of the specimen are best for instrumented specimens, intermediate for specimens obtained during catheterization, and worst for voided specimens[60-62].

Instrumented urine samples can be obtained by barbotage, which involves irrigating in and out to release more cells and thereby enhance the diagnostic quality of the specimen. It is important to use normal saline, and not water or glycine for barbotage, in order to preserve cellular morphology.
It is equally critical to obtain specimens prior to instillation of contrast dye or any other agents. Ideally, the cystoscope is inserted into the bladder, and barbotage is performed with saline through the cystoscope (level 4). As is the case for cytology in general, these maneuvers are best for detecting high-grade carcinoma, and both the sensitivity and specificity are low for low-grade lesions. The pathologist must be wary of the risk of overdiagnosing low-grade urothelial neoplasms, especially in the case of instrumented urine specimens. These samples often contain benign cellular clumps that can resemble urothelial carcinoma but usually have more defined borders and a more densely staining cytoplasmic collar[63-65].

A urine specimen for cytology should not be taken from the first voided urine of the day. The premise for this recommendation is that the first voided urine of the day has likely dwelled in the bladder for a relatively long time and will have poorly preserved cellular architecture. A common recommendation is to have the patient empty the bladder in the morning and collect the next specimen after 2-3 hours of adequate hydration (level 4).

The ideal urine specimen volume is poorly defined, but 25 mL can be considered a minimal volume. A larger volume may come at the expense of longer dwell time in the bladder, which can be detrimental. It is not advisable to collect urine for a defined period of time, such as 12 or 24 hours, because this leads to poor specimen quality due to specimen storage (level 4).

There are no well-defined timelines for processing urine for cytologic examination, but it is clear that the degree of cellular deterioration increases with time. The diagnostic accuracy therefore increases with the expediency of specimen processing. The time from specimen collection to processing should not exceed 8 hours [58] (level 4). Urine is best examined as a fresh specimen for cytology but, if expeditious examination of a fresh specimen is not feasible, the specimen can be preserved with various solutions, including 70% ethyl alcohol (2:1 dilution by volume), polyethylene glycol, or the solution in kits used for liquid-based Papanicolaou testing (level 3).

Techniques for processing urine specimens for cytologic analysis in the laboratory vary. Conventional methods include using filters, cytocentrifugation (cytospin), or concentrated smears. Newer techniques include various commercial kits using liquid-based methods: ThinPrep (Hologic, Inc., Bedford, Massachusetts); SurePath (Becton Dickinson Company, Franklin Lakes, New Jersey); Millipore filter preparations (Millipore Corporation, Billerica, Massachusetts); AutoCyte PREP (BD Diagnostics–Tripath, Burlington, NC); Shandon Cytospin (Thermo Electron, Waltham, MA); nitrocellulose membrane filtration (Magna MCE nitrocellulose filter, BioBlock Scientific, Illkirch, France); and Monoprep (Monogen, Lincolnshire, IL)[66]. These methods deliver a more uniform, single-layer preparation with more cells, better preserved morphology, and less background debris[66-69] (level 3). Urine samples are placed immediately into proprietary fixatives, which provide immediate and superior preservation.

Recently, immunocytochemistry for vimentin (but not high-molecular-weight cytokeratin) has been reported to better differentiate reactive renal tubular cells from low-grade urothelial carcinoma cells in voided urine. Thus this technique eliminates one specific confounding factor in the evaluation of urine cytology.

3. CLINICAL INFORMATION

Adequate clinical information allows the pathologist to initiate any specific tests required to guide clinical management and to avoid unnecessary investigations[72]. Clinical information may accelerate the diagnostic process. For example, the pathologist may request additional immunohistochemical analyses based on clinical data. Conversely, the written pathology report is the principal line of communication from the pathologist back to the treating clinician, and this report can be tailored to the clinical need, thereby enhancing communication. The essential clinical information is highlighted in Table 3.

Table 3: Recommended essential clinical information for pathologic specimen submission

<table>
<thead>
<tr>
<th>Tumor characteristics:</th>
<th>Clinical history:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flat</td>
<td>Prior bladder tumors (grade/stage/histology/location)</td>
</tr>
<tr>
<td>Papillary</td>
<td>Prior intravesical chemotherapy/immunotherapy</td>
</tr>
<tr>
<td>Nodular</td>
<td>Prior systemic chemotherapy</td>
</tr>
<tr>
<td>Ulcerated</td>
<td>Prior radiation therapy to the bladder/pelvis</td>
</tr>
<tr>
<td>Location in the bladder</td>
<td>Prior instrumentation</td>
</tr>
<tr>
<td></td>
<td>History of stones, infection, other urologic conditions</td>
</tr>
<tr>
<td></td>
<td>Prior non-bladder malignancy (type and location)</td>
</tr>
</tbody>
</table>
Documentation of the site of tissue acquisition is essential for pathologic identification and evaluation. In the context of TURBT, the primary information required is whether the specimen was taken from the bladder or the urethra. Within the bladder, documentation of the location from which tissue was obtained may be important for mapping of tumors—for example, should there be a need for re-resection of 1 or more sites. Location on the dome may be relevant for diagnosing urachal carcinoma.

The pathologist should also be given information about the patient’s relevant medical history. A prior history of kidney stones or urinary tract infection may affect the interpretation of bladder biopsies. A prior history of BCG instillation may aid in the diagnosis of granulomatous changes. Use of photodynamic agents such as hexaminolevulinate at the time of TURBT does not appear to affect the pathologic specimen.

For cytopathology requisitions, it must be noted whether a patient has an intact bladder or has undergone prior urinary diversion. Inflammatory changes associated with urinary diversion may lead the cytopathologist to be concerned about atypia if the prior urinary diversion is not mentioned. Previous BCG therapy and previous stone disease are also relevant as both can cause artifact.

4. PATHOLOGIC PROCESSING

a) Tissue Fixation

In the operating room, all tissue must be placed immediately in 10% neutral buffered formalin in a 10:1 ratio by volume of fixative to tissue to ensure adequate fixation. Filling a specimen cup with tumor chips without adequate fixative will lead to poor fixation and increased tissue degradation. Alternatively, 4% paraformaldehyde may be used instead of neutral buffered formalin. In fact, 4% paraformaldehyde may even be a superior fixative for immunohistochemistry as it tends to decrease background staining. However, it must be freshly made just before use. The duration of fixation can be 12-24 hours for TURBT specimens since each tissue fragment tends to be small (level 4).

In the pathology laboratory, it is important to avoid overfilling the specimen cassettes, as this is more likely to lead to undersampling of some tissue fragments (level 4).

b) Specimen Examination

Every sample sent from the operating room should be processed individually and reported separately. Expert pathologists recommend that all tissue fragments from any TURBT sample be processed. The degree to which these samples are sectioned and analyzed is, however, not clearly established, and practice in this area is not uniform. Undersampling may lead to understaging because of missed focal invasion into the lamina propria or muscularis propria. The presence of muscularis propria in the specimen is considered a measure of quality control[79], and it is therefore important to obtain a biopsy sample that includes muscularis propria. If not all chips are sampled, the pathology report should indicate what proportion of the chips was sampled[49] (level 4).

The College of American Pathologists has developed a “Protocol for the Examination of Specimens from Patients with Carcinoma of the Urinary Bladder” (http://www.cap.org/apps/docs/committees/cancer/cancer_protocols/2009/UrinaryBladder_09protocol.pdf) [80]. The panel drawing up this protocol was made up primarily of United States contributors but also included some members from other countries. This document focuses mostly on standard reporting for TURBT specimens but also includes recommendations for tissue processing.

The College of American Pathologists protocol calls for examination of 1 microscopic section for every 1 cm of tumor diameter up to 10 sections. If this evaluation reveals that tumor invades into muscle, sampling can be considered adequate. If, however, there is evidence of invasion into the lamina propria but not muscle, further sampling is necessary to exclude muscularis propria invasion. Similarly, if there is no evidence of invasion on the initial analysis, more tissue must be sampled. Depending on the size of the tumor, it may be necessary to examine the entire specimen (level 4).

The European Society of Uropathology and the Uropathology Working Group have also described standardized methods for handling and reporting bladder tumor specimens. Their report stems from a Uropathology Workshop held in Sesto Fiorentino, Italy, in 2003 and represents a statement of expert opinion. The standardized methods outlined in the report incorporate recommendations made by the College of American Pathologists and the Association of Directors of Anatomic Pathology and are in line with the recommendations for tissue sampling described above. In addition, the European Society of Uropathology and the Uropathology Working Group emphasize that the number, size (aggregate dimensions), and weight of each sample must be recorded (level 4).

Assessment of lamina propria invasion is one of the most significant challenges in bladder pathology. There is a high degree of interobserver variability in the assessment of lamina propria invasion, and the clinical relevance of such assessment is substantial, as patients with T1 lesions are considered at high risk for recurrence and progression when bladder preservation is attempted. The status of the lamina propria can determine the need for repeat resection and intravesical BCG or, in patients who have had prior treatments, the need for cystectomy.
One of the most significant obstacles to accurate assessment of invasion is poor orientation of the specimen due to the piecemeal fashion in which it is delivered to the pathologist and tangential sectioning. There is a risk that papillary tumors can be sectioned in such a way that isolated clusters of noninvasive tumor cells are visualized with surrounded stroma, giving the appearance of invasion. The pathologist must deduce from smooth and regular contours that this is an artifact of sectioning, while irregular contours with haphazard arrangement favor true invasion. If necessary, re-embedding and further sectioning can be helpful[50].

Accurate identification of the presence of muscularis propria in the TURBT specimen is essential for accurate staging and determination of the appropriate subsequent clinical management [81]. As mentioned above, the presence of muscularis propria in the TURBT specimen is also evolving as an important quality indicator of the TURBT itself[79].

The pathologist must be careful to distinguish muscularis mucosa from muscularis propria and sometimes even myofibroblasts in desmoplastic stromal reaction associated with the carcinoma. Muscularis mucosa consists of thin muscle bundles in the lamina propria that are classically described as being arranged in a single interrupted, dispersed, or continuous layer[82]. In practice, however, the distinction may be less obvious, especially if the muscularis mucosa is hyperplastic, and immunohistochemical staining with anti-smooth-muscle-specific actin[53] or smoothelin can help in selected cases (level 3). Smoothelin is a marker of terminally differentiated smooth muscle cells and has recently been shown to stain muscularis propria with relative specificity. Smoothelin stains muscularis mucosa either weakly or not at all and does not stain myofibroblasts in desmoplastic stroma.

After routine hematoxylin-eosin staining, immunohistochemical analysis of tissue samples with uncertain histology may be necessary to confirm or rule out the diagnosis of urothelial carcinoma. The most common distinction that needs to be made is the distinction between urothelial carcinoma and high-grade prostate cancer [86]. Urothelial carcinoma typically stains positive for uroplakin III, thrombomodulin, cytokeratin 7, and cytokeratin 20. Negative immunostaining for prostate-specific antigen and prostatic acid phosphatase is an important indicator of urothelial carcinoma as opposed to prostate cancer (level 3).

Lymphovascular invasion (LVI) is an established biomarker used for risk stratification in cystectomy specimens[88-90] as well as in TURBT samples [91] and hence LVI is often used clinically in bladder cancer care decision-making. It is therefore relevant for the pathologist to inspect the sections for LVI and comment correspondingly in the report (level 3). Strict criteria would demand specific immunohistochemical staining with endothelial markers such as factor-VIII-related antigen, CD31, or CD34[48]. In some cases, staining will not resolve the problem of differentiating lymphatic from artifactual space entrapment by tumor cells. Retraction artifact is also prominent in the “micropapillary variant” of urothelial carcinoma which has been well described by Kamat et al.

Cautery artifact can be one of the principal factors limiting pathologic analysis of TURBT specimens. Cautery can cause severe morphologic distortion that prevents adequate interpretation. Lopez-Beltran et al suggest 2 methods to help overcome cautery artifact[51]: deeper sections can uncover regions of tissue that are better preserved, and immunohistochemistry with anti-cytokeratin antibodies can delineate tumor tissue. If adequate interpretation is not possible despite these methods, that fact needs to be documented in the pathology report.

5. PATHOLOGY REPORTING

Careful harvesting, handling, and processing of TURBT specimens is ultimately of little benefit if the findings are not reported clearly[92-94]. The presence of key findings such as focal invasion or concomitant CIS can be missed by the treating physician if these findings are not clearly documented in the pathology report[92]. The goal of the pathologic investigation and the final report is to provide the urologist or other treating physician with the most accurate information possible so that he or she can make the most appropriate management decisions for the patient from whom the specimen was obtained[95]. An important component of pathology reporting is specific documentation of known risk factors for disease recurrence and progression as well as predictive factors for response to therapy.

The College of American Pathologists’ “Protocol for the Examination of Specimens from Patients with Carcinoma of the Urinary Bladder” includes a component on the optimal reporting of pathologic findings in bladder tumor specimens (http://www.cap.org/apps/docs/committees/cancer/cancer_protocols/2009/UrinaryBladder_09protocol.pdf). This protocol was first published in 1996[96] and was updated in 2003[80]. These standards were subsequently adopted by the Commission on Cancer of the American College of Surgeons as a mandated checklist in its Cancer Program Standards for Approved Cancer Programs (2004). The checklist is reproduced with permission in Figure 8 (level 4).

The Association of Directors of Anatomic Pathology has generated a Final Anatomic Diagnosis Checklist for Urinary Bladder Neoplasms, but these guidelines are for cystectomy specimens only.

It is important that the pathologist state not only what is present in, but also what is absent from, the TURBT specimen. It is vital, for example, to state the...
Surgical Pathology Cancer Case Summary (Checklist)

Protocol web posting date: October 2009

URINARY BLADDER: Biopsy and Transurethral Resection of Bladder Tumor (TURBT)

Note: Use of checklist for biopsy specimens is optional

Select a single response unless otherwise indicated.

* Procedure (Note A)
  * __ Biopsy
  * ___ TURBT
  * ___ Other (specify): ____________________________
  * ___ Not specified

Histologic Type (Note B)
  ___ Urothelial (transitional cell) carcinoma
  ___ Urothelial (transitional cell) carcinoma with squamous differentiation
  ___ Urothelial (transitional cell) carcinoma with glandular differentiation
  ___ Urothelial (transitional cell) carcinoma with variant histology (specify): __________________________
  ___ Squamous cell carcinoma, typical
  ___ Squamous cell carcinoma, variant histology (specify): __________________________
  ___ Adenocarcinoma, typical
  ___ Adenocarcinoma, variant histology (specify): __________________________
  ___ Small cell carcinoma
  ___ Undifferentiated carcinoma (specify): __________________________
  ___ Mixed cell type (specify): __________________________
  ___ Other (specify): __________________________
  ___ Carcinoma, type cannot be determined

Associated Epithelial Lesions (select all that apply) (Note C)
  ___ None identified
  ___ Urothelial (transitional cell) papilloma (World Health Organization [WHO] 2004/International Society of Urologic Pathology [ISUP])
  ___ Urothelial (transitional cell) papilloma, inverted type
  ___ Papillary urothelial (transitional cell) neoplasm, low malignant potential (WHO 2004/ISUP)
  ___ Cannot be determined

Histologic Grade (Note C)
  ___ Not applicable
  ___ Cannot be determined

* Data elements with asterisks are not required. However, these elements may be clinically important but are not yet validated or routinely used in patient management.

Figure 8. Checklist for pathologic reporting
Urothelial Carcinoma (WHO 2004/ISUP)
   ___ Low-grade
   ___ High-grade
   ___ Other (specify): ______________________________

Adenocarcinoma and Squamous Cell Carcinoma
   ___ GX: Cannot be assessed
   ___ G1: Well differentiated
   ___ G2: Moderately differentiated
   ___ G3: Poorly differentiated
   ___ Other (specify): ______________________________

* Tumor Configuration (select all that apply)
   * ___ Papillary
   * ___ Solid/nodule
   * ___ Flat
   * ___ Ulcerated
   * ___ Indeterminate
   * ___ Other (specify): ______________________________

Adequacy of Material for Determining Muscularis Propria Invasion (Note D)
   ___ Muscularis propria (detrusor muscle) not identified
   ___ Muscularis propria (detrusor muscle) present
   ___ Presence of muscularis propria indeterminate

Lymph-Vascular Invasion (Note E)
   ___ Not identified
   ___ Present
   ___ Indeterminate

Microscopic Extent of Tumor (Note F) (select all that apply)
   ___ Cannot be assessed
   ___ Noninvasive papillary carcinoma
   ___ Flat carcinoma in situ
   ___ Tumor invades subepithelial connective tissue (lamina propria)
   ___ Tumor invades muscularis propria (detrusor muscle)
   ___ Urothelial carcinoma in situ involving prostatic urethra in prostatic chips sampled by TURBT
   ___ Urothelial carcinoma in situ involving prostatic ducts and acini in prostatic chips sampled by TURBT
   ___ Urothelial carcinoma invasive into prostatic stroma in prostatic chips sampled by TURBT
abnormal absence of LVI or the absence of muscularis propria if the pathologist has examined the specimen carefully and not identified these features. In patients with urothelial malignancy, a report of “denuded biopsy” (most probably related to CIS) is significantly different from one stating that “no tumor is seen” [52]. Tumor in fat should not be interpreted as perivesical fat invasion, because the bladder wall can contain fat.

Just as the pathologic requisition is an important document for communicating the clinical scenario to the pathologist, the pathology report is the principal means by which the pathologist communicates back to the urologist and to subsequent treating physicians. In complex cases, face-to-face communication between the pathologist and the urologist can be essential for accurately conveying the findings. Such communication can involve the surgeon’s delivering the specimen to the pathologist with specific details on orientation of the specimen or the pathologist’s demonstrating the pathology under the microscope to the urologist. A more intimate working relationship is likely to enhance patient care[95]. Nuances are conveyed better on the telephone or in person than in the pathologic report.

When there is diagnostic uncertainty, the pathologist should make this clear but still provide a likely diagnosis. The opinion of additional pathologists or a reference pathologist may be helpful. Finally, the pathology report should not include management recommendations because many possible clinical parameters could make these recommendations inappropriate[95].

REFERENCES

D. IMAGING AND BLADDER CANCER

I. METHODS

Medline, Embase, the Cochrane Library, Biosis, and Science Citation Index were searched using the terms bladder cancer, IVU, US, CT, MRI, and PET. In addition, a direct search was done of the last 3 months’ issues of the major urology and radiology journals.

Overall, 3,586 articles were retrieved. The decision was made to limit the review to articles published within the last 10 years, which left 1,814 articles. From these articles, case reports, articles that pertained to benign disease, and articles that did not refer to bladder cancer per se were excluded. A total of 186 articles remained.

These 186 articles were then analyzed as to the level and quality of evidence and recommendations made according to the International Consultation on Urological Diseases guideline [Abrams 2010]. All evidence quoted is Level 3 unless otherwise stated.

II. VIRTUAL CYSTOSCOPY

Both the American Urological Association and the European Association of Urology recommend WLC as the gold standard for the assessment of suspected bladder tumors [Babjuk 2008, Hall 2007]. However, discomfort or pain is reported by more than one-third of people undergoing flexible cystoscopy [Van der Aa 2007]. In an effort to reduce discomfort while providing information equivalent to or perhaps superior to the information provided by flexible cystoscopy, virtual cystoscopy was developed. Initially, CT virtual cystoscopy was described; subsequently, MRI virtual cystoscopy was described. The place of virtual cystoscopy in the diagnostic pathway is discussed elsewhere in this document. Virtual cystoscopy has reported sensitivities and specificities of the order of 90-95%. A meta-analysis of 26 virtual cystoscopy studies involving 3,084 patients concluded that CT virtual cystoscopy has higher diagnostic value than MRI virtual cystoscopy or ultrasonography [Qu 2010]. However, the risks associated with exposure to radiation limits the use of repeated CT virtual cystoscopy in bladder cancer surveillance.

RECOMMENDATION

It is difficult to assess the role of virtual cystoscopy in clinical practice. Certainly catheterless forms of virtual cystoscopy may allow patients to avoid the discomfort associated with standard cystoscopy. Cystoscopy does, however, offer the advantages of being able to detect tumors of all sizes, being able to detect areas of mucosal irregularity or CIS, and allowing biopsy or definitive treatment to be performed. The broad availability of cystoscopy and familiarity with its use mean that it remains the gold standard. Grade C

III. CT IN LOCALIZED BLADDER CANCER STAGING

Cross-sectional imaging has a very real role in assessing the local extent of bladder cancer. The National Comprehensive Cancer Network guidelines for Bladder Cancer [Version 1. 2011] state that if the cystoscopic appearance of a tumor is solid, is high grade, or suggests invasion into muscle, a CT scan of the abdomen and pelvis is recommended before TURBT [Level 4]. CT can be used on its own or in combination with positron emission tomography scanning in the detection of both local and distant disease. The reported sensitivity of CT for detecting and staging bladder cancer ranges from 62-91%, and the reported specificity ranges from 63-95% [Baltaci 2008, Blanco Diez 2003, Jaume 2003, Kim 2004, Koplay 2010]. Studies with multidetector CT showed sensitivity of 89-91% and specificity of 92-95% [Kim 2004, Koplay 2010]. Protocols for CT for localized bladder cancer staging vary, as do CT machines themselves. It has been suggested that acquisition 60 seconds after the administration of contrast yields the best results [Kim 2004]. In staging patients who have undergone TURBT, delaying the scan until at least 1 week after surgery facilitates interpretation of images and reduces the number of false-positive results associated with postoperative inflammatory changes [Kim 2004].

RECOMMENDATIONS

CT cannot reliably differentiate non-muscle-invasive bladder cancer from T2 disease. Thus, TURBT with inclusion of muscle layer remains the preferred diagnostic option. Grade C

CT and in particular multidetector CT is of use in detecting extravesical spread. Grade B

CT should be delayed for at least 7 days in patients who have undergone TURBT. Grade B
IV. MRI IN LOCALIZED BLADDER CANCER STAGING

MRI is performed using T1-weighted, T2-weighted imaging, with or without gadolinium enhancement and diffusion weighting. Studies with diffusion-weighted MRI show that this method can detect 98-100% of bladder tumors [El-Assmy 2009, Matsuki 2007]. Staging sensitivity ranges from 68-80% and specificity ranges from 90-93% [Tillou 2008, Watanabe 2009]. Overall, MRI is probably not more sensitive in defining the T classification than is TURBT, but in cases in which there is discordance between findings, close follow-up with early second-look surgery is advised because as many as 60% of cases may be understaged on initial TURBT [Tillou 2008]. There is some evidence that MRI can predict tumor grade [Takeuchi 2009] and other biological processes such as angiogenesis [Tuncbilek 2009]. Comparative studies suggest that MRI is superior to CT in preoperative staging of bladder cancer, detecting 78-90% of tumors compared to 67-85% with CT [Akmanjit 2003, Fernandez Mena 2001]. MRI also has the advantage of considerably less artifact in patients with hip prostheses [Charnley 2005].

RECOMMENDATIONS

Diffusion-weighted MRI has poor sensitivity in differentiating between Ta, T1, and T2 bladder tumors. Grade B

Diffusion-weighted MRI is, however, very useful in the detection of T3 and T4 disease. Grade B

V. DETECTION OF NODAL DISEASE AND METASTASIS

1. CT AND MRI

Lymph node metastases in bladder cancer are detected by CT with a sensitivity of 31-50% and specificity of 68-100% [Baltaci 2008, Lodde 2010, Picchio 2006]. While MRI can detect more lymph nodes overall than CT and is in particular better than CT in the detection of nodes smaller than 5 mm [Saokar 2010], the ability of MRI to identify tumor in normal-sized or slightly enlarged nodes is poor. Efforts to image tumor in normal-sized nodes with ultrasmall superparamagnetic iron oxide particles have met with mixed results. These particles are taken up by macrophages, which allows the architecture of individual, even normal-sized, nodes to be identified. Areas not taking up ultrasmall superparamagnetic iron oxide particles are presumed to contain metastases. After early studies reported very encouraging results with this technique, including sensitivity of 94% and specificity of 95% [Deserno 2004], other studies have shown little difference compared to contrast-enhanced MRI [Thoeny 2009, Harisinghani 2005].

2. PET SCANNING

A number of tracers have been explored in positron emission tomography (PET) scanning for bladder cancer, including 11C-methionine [Ahstrom 1996] and 11C-choline [Picchio 2006, de Jong 2002]. The utility of PET for local staging of bladder cancer has been similar to that of CT; the utility of PET in evaluation for lymph node metastases has been superior to that of CT. 18F-fluorodeoxyglucose (FDG) is the contrast agent most widely studied in PET imaging for bladder cancer. Excretion of FDG in the urine can lead to misdiagnosis: focal FDG accumulation may mimic tumor uptake of FDG, whereas diffuse FDG activity may obscure an FDG-avid pelvic lesion. Repeated bladder irrigation and retrograde filling and prone-position imaging are useful techniques to ascertain the nature of any observed FDG accumulation [Anjos 2007, Lin 2009]. Diuretic protocols have been described that can significantly lower bladder FDG activity and potentially improve image quality [Nijjar 2010]. Studies using FDG-PET/CT in patients with muscle-invasive bladder carcinoma cancer show a sensitivity of 57-81% and a specificity of 88-100% in the detection of pelvic lymph node metastases [Apolo 2010, Drieskens 2005, Lodde 2010, Kibel 2010]. Similar results are seen in the assessment of recurrent disease [Jadvar 2008].

While comparative studies generally indicate superiority of PET scanning over CT and MRI in the detection of lymph node metastases [Apolo 2010, Lodde 2010], at least 1 study has reported equivalence of PET and CT [Swinnen 2009].

RECOMMENDATIONS

CT, MRI, and PET scanning are all of use in the detection of lymph node metastasis. Grade B

Of the 3 modalities, PET scanning appears to have the greatest accuracy. Grade C

Experience with ultrasmall superparamagnetic iron oxide particles is not broad enough to recommend their routine use. Grade D

VI. IMAGING AFTER BLADDER CANCER TREATMENT

CT after TURBT has a sensitivity of 89% and a specificity of 95% for the detection of extravesical spread [Kim 2004]. PET has accuracy similar to
that of CT in detecting residual bladder cancer after TURBT and outperforms CT in detecting lymph node enlargement [Picchio 2006].

MRI can differentiate between responders and nonresponders to chemotherapy with a sensitivity of 91% and specificity of 93% [Schrier 2006]. In patients receiving chemotherapy and radiotherapy prior to surgery, MRI has 57% sensitivity and 92% specificity in predicting the final histology, and diffusion-weighted MRI demonstrates significantly greater accuracy than T1- and T2-weighted MRI [Yoshida 2010].

Chemotherapy results in reduced cellular activity in viable cancer cells. Thus, the sensitivity of PET for the detection of metastatic disease drops from 77% in untreated patients to 50% in patients treated with chemotherapy [Liu 2006].

VII. GENERAL COMMENTS

There is a paucity of randomized controlled trials of imaging for bladder cancer, which is somewhat surprising as bladder cancer would seem to lend itself to such studies. Many of the studies that have been published were underpowered and quote differences in outcomes that are frequently based on trends rather than proven differences. The only meta-analysis identified in the search was that by Qu et al. The ICUD has suggested that different considerations should be applied in the assessment of diagnostic and investigative tools. One of the tests that they have suggested is to ask whether the tool has an effect in clinical practice. By this test, virtual cystoscopy is disappointing while virtual cystoscopy has been the subject of numerous articles over the last decade, few centers have adopted this technique into routine clinical practice.

REFERENCES

SUMMARY OF THE RECOMMENDATIONS

1. SCREENING AND DIAGNOSIS:
   a. Currently, the available evidence indicates that bladder cancer screening is not helpful in improving survival. Further studies to evaluate the utility of bladder cancer screening are warranted (Grade C).
   b. Bladder cancer screening should probably be confined to patients at high risk for bladder cancer (Grade C).
   c. Screening in high-risk patients should consist of yearly cytopathologic examination of urine (urine cytology) and dipstick urinalysis to evaluate for hematuria (Grade C).
   d. There is no correlation between the number of red blood cells per high-power field seen on urine microscopy and the diagnosis of bladder cancer (Grade B).
   e. Nearly all patients with bladder cancer diagnosed on cystoscopy have some form of microscopic or macroscopic hematuria. Hence, patients with microscopic or macroscopic hematuria require further evaluation, such as with flexible cystoscopy (Grade D).
   f. Microscopic hematuria in patients with bladder cancer varies in intensity and is intermittent; hence, lack of hematuria on a single urinalysis does not exclude bladder cancer (Grade C).
   g. In patients with irritative voiding symptoms such as dysuria, frequency, and urgency, bladder cancer, particularly carcinoma in situ (CIS), must be ruled out (Grade C).
   h. For patients with asymptomatic microscopic hematuria without risk factors for urothelial carcinoma, urine cytology or cystoscopy can be used (Grade B).
   i. For initial work-up of patients with hematuria, imaging of the upper tracts must be performed (Grade B).

2. CYSTOSCOPY AND URINARY MARKERS
   a. Cystoscopy alone is the most cost effective method to detect recurrence of bladder cancer. Among urinary markers, urine cytology is the gold standard for surveillance of patients with non muscle invasive cancer (Grade B).
   b. Cytopathologists should use uniform nomenclature (Grade C).
   c. Bladder wash cytology provides a better diagnostic yield than voided urine cytology (Grade B).
When cystoscopy is performed, thorough cystoscopy with minimal manipulation should be performed, the residual urine should be collected, and then a formal bladder lavage should be performed. Both the residual urine and the bladder lavage specimen should be sent for cytology (Grade D).

e. In the follow-up of patients with urothelial neoplasms, urine cytology is most useful for diagnosis of high-grade tumor recurrence (Grade B). Urine cytology is especially valuable for differentiating high-grade urothelial carcinomas from low-grade urothelial neoplasms (Grade B).

f. There is no consensus on the application of urinary markers in the diagnosis of bladder cancer (Grade D).

g. The role of urinary markers – in particular FISH (fluorescence in situ hybridization) – appears to be most useful in the setting of a negative cystoscopy and atypical cytology. (Grade C).

3. NEWER MODALITIES FOR ENDOSCOPY

a. White light cystoscopy (WLC) is the gold standard for evaluation of the lower urinary tract (Grade B).

b. Fluorescence cystoscopy improves the rate of detection of carcinoma in situ (CIS) (Grade B). Fluorescence-guided transurethral resection of bladder tumor (TURBT) decreases the likelihood of leaving behind residual tumor (Grade B).

c. Fluorescence cystoscopy can be used in the examination of patients with positive findings on voided urine cytology but negative findings on WLC (Grade C).

4. IMAGING

a. For initial work-up of patients with hematuria, imaging of the upper tracts must be performed (Grade B).

b. While computed tomography (CT) urography is becoming the de facto standard imaging modality for patients with bladder cancer, intravenous urography (IVU), CT of the abdomen and pelvis, ultrasound, and magnetic resonance imaging (MRI) are options (Grade C).

c. Imaging for staging should be obtained prior to TURBT or delayed for 1-2 weeks after TURBT to avoid artifacts (Grade C).

d. Abdominal and pelvic imaging (MRI or CT) is not accurate for staging of primary bladder tumors but may be useful for confirming or ruling out metastatic disease (Grade B).

e. For patients with invasive bladder tumors, evaluation for metastatic disease should include chest radiography, liver function tests, and alkaline phosphatase measurement (Grade C).

f. Bone scan is not necessary in all cases but should be performed in patients with bone pain or elevated alkaline phosphatase concentration (Grade B).

5. TECHNIQUE OF TURBT

a. At present, there is insufficient information to support the recommendation of a specific technique for TURBT (Grade D).

b. Patients undergoing TURBT should be given appropriate prophylactic antibiotics (Grade B).

c. The shape, size, and location of the tumor should be documented explicitly as these details provide important prognostic information (Grade C).

d. The appearance of the base of the tumor, whether sessile or pedunculated, should be documented as the appearance often predicts the invasiveness of the tumor (Grade C).

e. Separate tumor base and margin biopsies should be performed during TURBT (Grade C).

f. During TURBT, complete tumor resection should be attempted except in patients with diffuse CIS (Grade C).

g. CIS may manifest as velvety erythematous patches. Endoscopists should specifically look for such changes, and all suspicious lesions should be biopsied (Grade C).

h. During TURBT, bladder perforation should be avoided (Grade C).

i. When the ureteral orifice is resected, cutting current should be used; coagulation of the ureteral orifice should be avoided. Three to 6 weeks after resection of the ureteral orifice, a functional study should be obtained to check for stenosis (Grade C).

j. Aggressive resection of a tumor in a bladder diverticulum can lead to perforation. Low-grade, noninvasive tumors in a bladder diverticulum may be treated with transurethral resection or fulguration with or without intravesical therapy (Grade C).

k. A second TURBT should be performed in all patients with a high-grade Ta lesion or any T1 lesion (Grade B). The optimal timing of repeat TURBT is within 1-4 weeks after the first resection (Grade C).
I. Routine random bladder biopsies are not recommended (Grade C). Patients with positive findings on urine cytology and normal findings on cystoscopy should undergo random bladder biopsies (Grade B). Patients undergoing partial cystectomy should undergo random bladder biopsies (Grade C).

m. Routine prostatic urethral biopsy is not recommended at initial evaluation. Prostatic urethral biopsy is indicated in cases of multifocal urothelial carcinoma of the bladder, CIS, and visible abnormalities of the prostatic urothelium (Grade B).

n. Prostatic urethral biopsy should be performed using electrocautery loop resection including the 5 o’clock and 7 o’clock positions of the verumontanum (Grade B).
Committee 2

Pathology Consensus Guidelines by the Pathology of Bladder Cancer Work Group

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Pathology Consensus Guidelines by the Pathology of Bladder Cancer Work Group

MAHUL B. AMIN, VICTOR E. REUTER, JONATHAN I. EPSTEIN, DAVID J. GRIGNON, DONNA E. HANSEL, OSCAR LIN, JESSE K. MCKENNEY, RODOLFO MONTIRONI, GLADELL P. PANER, MARK SOLOWAY, AND MEMBERS OF THE PATHOLOGY OF BLADDER CANCER WORK GROUP

INTRODUCTION

There have been several forums in the last two decades in which an international consensus dialogue pertaining to the pathology of the bladder cancer have been conducted and promulgated. In this document we provide new consensus guidelines built on past such endeavors, supported by comprehensive literature review of the recent literature where possible, and based on the best practices of an expert group of 38 international urologic pathologists from 13 countries. While strong evidence is commonly lacking to make many of the recommendations herein, the proposals made are in the interest to move the field forward, acknowledging where data is lacking, but at the same time providing consensus guidelines to our clinician colleagues to provide optimal patient care. It is hoped that when the guidelines made here are based on the absence of a high level of evidence in the literature, they will prompt future studies using these guidelines as a common platform of nomenclature and the state of understanding of the pathology of bladder cancer as it pertains to contemporary patient care in the year 2011. Where possible, levels of evidence and grades of recommendation (Table 1) are provided. It must be noted, however, that the criteria for levels and grades of recommendation are primarily promulgated for clinical studies and have been used by our Pathology of Bladder Cancer Work Group as a framework to support their guidelines.

In this international consultation, we focus on a select important unique aspects and provide an update on: 1) the knowledge of the histoanatomy of the bladder as it pertains to the diagnosis and staging of bladder cancer, 2) the prognostic significance of histologic grading by the WHO (2004)/ISUP system, its contributions, shortfalls and opportunities for refinement, 3) the information needed from the clinicians by the pathologist in order to provide optimal pathologic reporting of bladder cancer, 4) on nomenclature for inverted lesions of the bladder, 5) the histologic types of bladder cancer and the variants of urothelial cancer, some relatively recently described, with a focus on definition for diagnosis and their implied clinico-pathologic significance, 6) role of immunohistochemistry and molecular studies in contemporary routine practice diagnosis, prognostication or prediction of bladder cancer, 7) the reporting of bladder cancer in transurethral resection of bladder tumors (TURBT) and cystectomy specimens, and 8) recommended nomenclature for urine cytology and role of ancillary testing in urine specimens.

Table 1. Levels of evidence and grades of recommendation*

<table>
<thead>
<tr>
<th>Levels of Evidence</th>
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<tr>
<td>Level 1: Metanalysis of randomized trials of a good quality randomized trial</td>
<td>Grade A: Usually consistent level 1 evidence</td>
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<td>Level 2: Low quality randomized trial or metanalysis of good quality prospective cohort studies</td>
<td>Grade B: Consistent level 2 or 3 evidence or “majority evidence” from randomized trials</td>
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<td>Level 3: Good quality retrospective case control studies or case series</td>
<td>Grade C: Level 4 evidence, “majority evidence” from level 2-3 studies, expert opinion</td>
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<td>Level 4: Expert opinion based on “first principles” or bench research, not on evidence</td>
<td>Grade D: No recommendation possible because of inadequate or conflicting evidence</td>
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*Adapted from Evidence-based medicine: Overview of the main steps for developing and grading guideline recommendations, by P Abrams, A Grant, and S Khoury, d nuary 2004
A. URINARY BLADDER
HISTOANATOMY AND IMPACT ON
CANCER DIAGNOSIS AND STAGING

I. EPITHELIAL CHANGES

1. UROTHELIAL DENUDATION

Prior instrumentation and prior intravesical therapy are frequent contributors to denudation at cystoscopy or in bladder specimens. Urothelial carcinoma in situ (CIS) is also often associated with prominent cellular discohesion and exfoliation of neoplastic cells in the urine. The presence of extensive denudation in bladder biopsy samples has been shown to be associated with CIS on prior or subsequent bladder biopsies[1]. (Figure 1) Tissue specimens obtained by hot wire loop may show urothelial denudation which can be attributed mainly to thermal effects of the procedure, and can be seen even in low risk patients for CIS. In contrast, substantially denuded biopsy samples obtained by cold cup biopsy are in most cases related to CIS. Levi et al [1] showed that 31% of patients with denudation on cold cup biopsy developed CIS within 24 months, and that CIS was seen in 75% and 29% of patients with and without history of CIS, respectively. This demonstrates a higher risk for subsequent CIS in denuded biopsy samples in the setting of both cold cup procedure and with prior CIS (Level 3). In cold cup biopsies with “denudation” cystitis, 54% of patients had concurrent positive urine cytology, stressing the importance of performing concurrent bladder wash, which has higher sensitivity for detecting urothelial carcinoma (Level 3) [2]. Denudation may also have some implications in papillary urothelial lesions. Papillary urothelial lesions with extensive urothelial denudation are more often high-grade carcinomas[3]. (Figure 2) In denuded papillary lesions, pathologists should do careful search for residual high-grade cells in order to avoid under diagnosis (Grade C). Denuded flat and/or papillary urothelial neoplasms may occur with prominent cautery artifact or in an anatomically confined area implicating iatrogenic or mechanical contributing factors for the epithelial exfoliation.

Extensive or complete urothelial denudation in bladder biopsy samples should be reported (Grade C). Correlation of denuded biopsy samples with concurrent cytology results may yield a positive diagnosis of malignancy in these patients (Grade C). Urothelial denudation in cold cup biopsies of cystoscopically abnormal areas in patients with prior CIS and without any recent intravesical interventions should be dealt with caution by urologists.

2. UROTHELIAL HYPERPLASIA

Urothelial hyperplasia is defined as markedly thickened urothelium in the absence of cytologic atypia, and can be flat or papillary. Flat hyperplasia may be seen adjacent to low-grade papillary tumors [4]. Papillary urothelial hyperplasia is characterized by presence of undulating hyperplastic urothelium arranged into thin mucosal papillary folds of varying heights in a non inflamed setting [4]. The lack of cytological atypia and true fibrovascular cores distinguishes this lesion from papillary neoplasia. Papillary hyperplasia (Figure 3) is often seen in patients with prior and subsequent diagnosis of low-grade papillary urothelial lesions (Level 3), and for a subset of patients is suggested to be a precursor lesion for mainly the low-grade lesions [4,5]. This hypothesis is further supported by the presence of some genetic alterations found in bladder cancer that also occur in urothelial hyperplasia[6-8]. Hyperplastic urothelium may also harbor a varying degree of atypia, and is suggested to be associated with CIS and high-grade papillary urothelial carcinoma (Level 3) [9].

Figure 1. Urothelial carcinoma in situ with denudation.

Figure 2. High-grade papillary urothelial carcinoma with denudation.
From a practical viewpoint there is difficulty and controversy in diagnosing lesions which do not have fully established features of papillary neoplasia and also have accompanying cytologic atypia exceeding reactive changes. This type of setting may occur in the setting of prior treatment and in surveillance biopsies. As an approach, first, strict criteria including the absence of true fibrovascular cores are necessary for the diagnosis of papillary urothelial hyperplasia versus papillary urothelial neoplasia. Second, the degree of urothelial atypia when present in the hyperplastic urothelium should be reported using the 2004 WHO/ISUP terminology for urothelial neoplasia (e.g. dysplasia or CIS) (Grade C). Third, correlation with cystoscopy would be valuable to ascertain if clinically the lesions were deemed to be papillary. In the absence of true papillae histologically and in the absence of a clinical papillary presentation, terminology such as “dysplasia with early papillary formations” or “CIS with early papillary formations” may be used when criteria for papillary neoplasia are not fulfilled but there is a background of cytologic atypia (Grade C). These terms are only descriptive diagnoses as outcome studies using this terminology are unavailable. Until substantial evidence for urothelial hyperplasia as precursor lesion to papillary urothelial neoplasia becomes available, reporting of papillary hyperplasia in the absence of dysplasia or CIS is optional (Grade D).

3. SQUAMOUS METAPLASIA

There are two type of squamous metaplasia in the urothelial tract, non-keratinizing and keratinizing. Non-keratinizing squamous epithelium is present in the trigone in 75–86% of women and is considered to be a normal finding (Figure 4) (Level 2) [10-12]; its occurrence outside this region is considered metaplastic. Keratinizing type of squamous metaplasia usually occurs in response to chronic irritative stimuli to bladder such as cystitis, lithiasis, diverticula, or schistosomiasis. Keratinizing type of squamous metaplasia can be associated with subsequent or concurrent in situ or invasive carcinomas with squamous differentiation (Level 3) and has been suggested to be a precursor lesion for squamous cell carcinoma, and thus, must be closely followed (Grade C) [13]. Keratinizing squamous metaplasia is also related to vesical carcinoma and associated complications, such as bladder contracture and ureteral obstruction [14]. Squamous metaplasia is not uncommon in patients with spinal cord injury or paraplegia with prolonged catheterization or chronically infected bladders [15,16], and higher risk for squamous cell carcinoma is reported in these patients (Level 3) [17].

The presence of squamous metaplasia in bladder biopsies should be reported by pathologists with specification whether keratinizing or not and focal or multifocal (Grade C). The word “squamoid” should be avoided and unequivocal criteria for squamous differentiation i.e. intracellular bridges or evidence of keratinization should be present. Current evidence does not support any form of intervention including surveillance cystoscopy for patients with focal changes, although multifocal and/or extensive lesions often require intervention due to intractable symptoms or because they precede or may be associated concurrent with neoplasia (Grade C). Spinal cord injury or paraplegic patients with squamous metaplasia must be followed and evaluated regularly because of the increased risk for squamous cell carcinoma (Grade C).

4. GLANDULAR METAPLASIA

Glandular metaplasia (cystitis glandularis) (Figure 5) is a benign proliferative change that may occasionally show presence of intestinal-type goblet cells (cystitis glandularis, intestinal type or intestinal metaplasia) (Figure 6). Glandular metaplasia is supposed to relate the risk of neoplastic transformation because intestinal metaplasia often coexists with adenocarcinoma of the urinary bladder [18,19]. Recent studies however showed that glandular metaplasia of the urinary bladder is not a strong risk factor for adenocarcinoma or urothelial cancer (Level 3) [20,21]. The significance of glandular metaplasia as a pre-neoplastic lesion, particularly in the absence of intestinal metaplasia, is still controversial, however, its
presence should be reported as it is often associated and correlates with a cystoscopic abnormality. Multifocal disease with intestinal metaplasia or that associated with dysplastic changes may warrant close clinical follow-up (Grade C). Rare cases of florid intestinal metaplasia and extensive mucin extravasation (exuberant cystitis cystica) may result in a pseudotumorous mass and histologically may mimic adenocarcinoma [22].

5. REACTIVE CHANGES
Therapeutic procedures for bladder cancer, such as chemotherapy, immunotherapy, radiotherapy, photodynamic and laser treatment, previous resection and gene therapy, may produce alterations in the urothelial mucosa, and some of these changes may be mistaken for carcinoma [23]. (Figures 7-9) Intravesical stones, prolonged indwelling catheter, trauma, infection, etc. also cause epithelial changes that can mimic epithelial malignancy. Radiation or chemotherapy cystitis may show epithelial proliferations that may be confused with invasive urothelial carcinomas even when the therapy was remotely performed [24,25]. Pseudocarcinomatous epithelial hyperplasia occurs most commonly after radiation or chemotherapy but may also occur in relation to localized ischemia or injury to urothelium [26]. Most of these patients without radiation or chemotherapy have conditions that may explain the presence of an environment of ischemia or injury, such as cardiac and vascular diseases. Viral infection related cellular changes, for example polyoma (BK) virus-type cellular changes can also mimic urothelial carcinoma [27]. Knowledge of prior therapy procedures is invaluable for pathologists and clinicians should provide this information as some reactive changes may mimic and complicate the diagnosis of neoplastic conditions.

Figure 5. Cystitis cystica and glandularis.

Figure 6. Cystitis glandularis with intestinal metaplasia.

Figure 7. Urothelial atypia due to radiation.

Figure 8. Urothelial atypia after BCG therapy. Note the presence of granuloma.

Figure 9. Urothelial atypia after mitomycin therapy.
II. LAMINA PROPRIA (LP)

1. INTERPRETATION VARIABILITY OF (EARLY) LAMINA PROPRIA INVASION (PT1)

The morphologic features of stromal invasion include retraction artifact, individual tumor cells, irregular cords, and strands, or isolated single cells, cytoplasmic eosinophilia (paradoxical maturation) and desmoplasia [28-30]. When many or most of these features are appreciable, diagnosis of invasion is more definite and reproducible. However, there are issues with interobserver reproducibility in the diagnosis of early lamina propria (LP) invasion [31,32]. In one study, 35% of pT1 carcinomas were downstaged to pTa, and the reviewer’s staging allowed a better estimate of risk for subsequent progression than the initial staging [32]. Another study showed agreement for pTa versus pT1 in 80% among 15 pathologists and in 88% upon re-review, and consensus and original diagnosis agreed in 68% of cases [33]. Re-staged pT1 by consensus manner had better prognostic significance compared to its original non-pT1 diagnosis [33]. In an interobserver reproducibility study that focused on early invasion, Shen et al. showed diagnostic agreement in at least 15 of 19 genitourinary pathologists in 17 of 26 (65%) of cases and highlighted certain problems when evaluating early invasive cancer (Level 3). von Brunn’s nest involvement by urothelial carcinoma and in the background of inflammation may be mistaken for invasion and has no impact for disease progression [34]. Because of the diagnostic difficulty, when early invasive urothelial carcinoma is suspected, diagnosis through examination of additional levels, or in a consensus manner with a pathology colleague or thru quality assurance meeting is encouraged (Grade C).

2. MICROINVASIVE UROTHELIAL CARCINOMA

The concept of microinvasive urothelial carcinoma is still controversial and criteria for diagnosis had varied. Initially, microinvasion was defined as LP invasion by carcinoma to a depth of 5 mm or less from the urothelial basement membrane [35]. Others defined microinvasion as infiltration to a depth of within 2 mm or less in the LP [30,36]. Lopez-Beltran et al. most recently proposed that the microinvasive tumor into the LP should be composed of no more than 20 invading cells measured from the stroma-epithelial interface [29].

Currently, there are no standardized criteria or prospective study for microinvasive urothelial carcinoma (Level 4). To diagnose early invasion, stringent criteria such as: only focal invasion, less than 1 high power field, or 0.5 mm from the nearest basement membrane, should ideally be employed (Grade C). Studies are needed to establish a clinically significant definition of microinvasive urothelial carcinoma. Future studies should also take into account the LP regional variations such as the trigone where LP is the thinnest (0.46-1.58 mm) and muscularis propria boundary is not well defined [37]. Until there is understanding of the definition, it is recommended that only stringent criteria (similar to those proposed above) be used or the term microinvasive carcinoma not be used (Grade C).

3. SUBSTRATIFICATION OR SUBSTAGING OF LP INVASION (PT1)

The usefulness of subclassification or substaging of LP invasion is still controversial. Subjective and objective methods have been proposed in the literature. Subjective methods rely on the presence of muscularis mucosae (MM) and the vascular plexus in the LP, which are both inconsistent histoanatomic landmarks (Level 3) [37] (Figure 10). Depth of invasion may be established either by two-tiered or three-tiered systems. Two-tiered system is by identifying LP invasion up to (pT1a) or beyond the MM or vascular plexus (pT1b) and three-tiered system is by identifying submucosal tumor invasion up to (pT1a), in (pT1b), or beyond (pT1c) the MM or vascular plexus (Level 3) [38-44]. Since the anatomic landmarks essential for substatification are not always present, substaging is not currently recommended in routine surgical pathology sign out. More objective methods propose measuring the depth of invasion with thresholds of 0.5 mm [45] or 1.5 mm [46,47]. Problems precluding use of the depth of invasion criteria include lack of consistent orientation with the basement membrane, specimen fragmentation, issues with reproducibility in measurement, and lack of established clinical significance. Further, this method may not be practical for general pathologists, as it may be laborious particularly when multiple minute invasion foci are to be measured.

Platz et al. evaluated the reproducibility of pT1 substaging and showed little concordance between participating pathologists (kappa = 0.22; 95% C.I. = 0.08-0.36) [48]. Non-biased specimens obtained from various institutions were used which is important because handling and processing of TURBT materials varied among institutions [48]. They concluded that substaging was technically difficult and has little merit, at least for the general pathologists and urologists. Other than this study, no other study has been done to evaluate the usefulness of pT1 substaging among general pathologists. Substaging of pT1 (Figure 11) is currently not recommended by the WHO/ISUP consensus guidelines and this committee due to the lack of widely accepted and reproducible criteria although we acknowledge there is much need for future studies (Grade C). It is however recommended for
pathologists to provide some form of estimate of
the LP invasion in pT1 tumors with respect to depth
and/or quantity of invasion (e.g. focal, multifocal,
extensive, etc.) (Grade C).

III. MUSCULARIS MUCOSAE

The muscularis mucosae (MM) is an important
histoanatomic structure to differentiate from
muscularis propria (MP) or “deep” muscle when
staging invasive urothelial carcinoma in the bladder.
MM muscle bundles are typically thin slender
bundles arranged in single layer of interrupted,
dispersed, or continuous muscle [37,49]. The
bladder MM was initially described by Dixon et al.
[50], and Ro et al. [49] subsequently emphasized
the importance of histologic recognition of MM and
its implications in pathologic staging. Keep et al.
[51] pointed out the importance of recognition of
MM in TURBT specimens to prevent overstaging
of invasive urothelial carcinoma. Paner et al. [37]
further described morphologic variations of MM and
as it relates to the different topographical regions
of the bladder and the challenges in distinguishing
these variations from MP. Weaver et al. [52] have
shown that MM was more often seen in female than
in male bladder LP.

For staging of invasive bladder cancer, involvement
of MM is equivalent to LP invasion or pT1 and
involvement of MP is staged as pT2. Distinction is
very important in initial tumor resection or biopsy
as a vital determinant for subsequent therapeutic
decisions. MM when hyperplastic may be difficult
to differentiate from MP [37,53]. Hyperplastic MM
is composed of more than 3 layers of muscle fibers
thick appearing either as fibers parallel to the surface
mucosa or as small rounded bundles when cut in
sections [37,53]. Although hyperplastic MM is
not seen in the LP of different topographic regions of
the entire bladder specimen, it is most often seen in
the dome [37,53]. There are two described patterns:
(a) aggregates of hyperplastic MM with haphazard
orientation and irregular outlines morphologically distinct from that of MP and (b)
hyperplastic compact MM with small parallel muscle
fibers and regular outlines arranged singly or in small
groups (Figure 13). The latter may strongly resemble
MP muscle, and the most reliable distinguishing
feature from MP is on the basis of location in LP [37],
which is not always possible in limited specimens
such as in TURBT (Level 3). Attention to quantity
(usually rare and isolated), location, and comparison
(size being much smaller) with more characteristic
MP, if present, would be helpful; isolated bundles
close to urothelium with haphazard fiber orientation
and irregular outlines favor MM over MP [37]. Other
mimickers of MP are cauterized vascular wall and/or
collagen fibers (Level 3).

To avoid confusion in interpretation of the pathology
report, documentation of MM-only invasion by
carcinoma is not required, and should be reported
as “urothelial carcinoma with LP invasion (pathologic
stage atleast pT1)” when MP is not present and
“urothelial carcinoma with LP invasion (pathologic
stage pT1) when MP is present (Grade C). Involvement of MM may be included in a comment
to provide information on depth/extent of invasion. It
is important to document whether MP is present in a
bladder specimen with at least high-grade pTa and
all invasive urothelial neoplasia (Grade B). Based on
institutional and clinical preference, some centers do
not report the presence or absence of uninvolved MP
in TURBT specimens containing low-grade papillary
tumors and mention the presence of uninvolved MP
in TURBT specimens containing high-grade tumors,
irrespective of invasion only. Although formal studies
are lacking, information on the amount of MP included
in the specimen (isolated and rare muscle bundles
versus established groups of muscle bundles); or MP
in the area of tumor or not in the vicinity of the tumor,
may yield useful information in the management of
invasive bladder cancer. At this point, reporting this
information is optional and may be communicated in
multidisciplinary conferences (Grade D).
IV. INDETERMINATE MUSCLE TYPE

It may be difficult to distinguish between MM and MP muscle bundles in some TURBT samples. Hyperplastic MM, desmoplasia, prior procedures, or fracturing of muscle bundles by invasive carcinoma often compound the diagnostic dilemma in reliably distinguishing MM and MP. Identification as hyperplastic MM may become challenging and involvement is equivalent to pT1 and not pT2 invasive carcinoma. On the other hand, MP whose muscle fibers are splayed by invasive carcinoma and mimic MM, when involved is staged as pT2. When indeterminate muscle bundles are observed, the presence of vascular network with thick walled vessels may aid in recognition as MM (Level 3) [37,42,49,54,55]. Also, relationship or distance from the urothelial basement membrane, quantity and muscle fiber bundle morphology (haphazard or in comparison to characteristic MP if present) may provide additional clues for MM (Level 3) [37]. Muscle bundles indeterminate between MM and MP should be reported with terminology such as “invasive urothelial carcinoma with invasion of muscle, indeterminate type” to prompt the urologist for a restaging biopsy procedure (Grade C). A second biopsy may provide more definitive staging information or resolve this problematic situation (Grade C) [56].

V. MUSCULARIS PROPRIA

Documentation of the presence or absence of MP and its status of involvement by invasive carcinoma is required in reporting of biopsy or TURBT specimens with at least high grade pTa and all pT1+ tumors. Pathologic staging is considered not adequate without detailing the presence of uninvolved MP in pTa or pT1 tumors and it’s because of the risk of unsampled MP-invasive disease. Current major guidelines including those by the American Urological Association, European Association of Urology and National Comprehensive Cancer Network recommend reporting whether MP component is sampled and involved by tumor in TURBT specimen. If MP is not present, repeat resection is recommended for verification of pT stage before subsequent management decision is made (Grade B). The recent Japanese bladder cancer guideline under the auspices of the Japanese Urological Association and Japanese Society of Pathology also recommends this approach.

Several terminologies have been used to report MP muscle such as “deep muscle”, “muscle proper” or “detrusor muscle”. MM is sometimes reported as “superficial muscle”. Use of different terminologies for bladder muscles may generate confusion in
staging interpretation and specimen adequacy. These terms are not recommended and use of standardized nomenclature of “MP muscle bundles” is recommended in reporting (Grade C). Obtaining a separate “deep” or post tumor resection biopsy is also recommended to ensure sampling of the muscularis propria.

The MP is composed of three smooth muscle layers – inner and outer longitudinal layer and a central circular layer. MP invasion has been divided into two categories, superficial (pT2a) and deep (pT2b) based on the depth of tumor invasion. Substaging of pT2 disease (Figure 15) and recognition of invasion beyond MP (pT3 disease) is not tenable in TURBT specimens, where only portion of MP can be present. In cystectomy specimens, pT2 substaging is complicated by the lack of a reliable anatomical landmark to aid in their distinction (Level 3). Currently, there are no data regarding the reproducibility of pT2a/b distinction among pathologists (Level 4). Some outcome studies have shown the lack of prognostic impact and are against the use of pT2 substaging [57-59]. Although some reports showed prognostic value of pT2a/b subcategories [60,61]. These varied results may be influenced by the difficult distinction between pT2a/b, and thus, a more objective and reproducible anatomical or extent of disease criterion is needed between pT2a and pT2b subcategories in cystectomy specimens.

VI. ADIPOSE TISSUE

Adipose tissue is frequently present in the LP and MP of the urinary bladder, usually scant in the former and abundant in the latter [62]. When fat is present in the LP, it is more typically in the deeper aspects or in the vicinity of the MP [37] (Figures 16, 17). Pathologic staging (pT1 or pT2 – Figure 18) should be performed based on the type of muscle and not based on adipose tissue. It is necessary to stress that involvement of adipose tissue by tumor in biopsy or TURBT specimens should not be interpreted as perivesical fat involvement or pT3 disease. Involvement of adipose tissue by carcinoma in TURBT or biopsy without MP suggests tumor involving at least the deeper aspects of LP (Level 3).

Because of the consistent presence of adipose tissue (Figure 19) in the MP, the boundary of perivesical adipose tissue from the deep (outer) MP may not be easily delineated (Level 3) [62] (Figure 20). Distinction between pT2b and pT3a in a cystectomy is not usually straightforward and requires the use of low power assessment to identify tumor extending beyond the outermost boundary of MP muscle (Level 3). The prognostic significance of pT3a versus pT2 has also been questioned as it has been shown to have no significant difference in recurrence and mortality rate and incidence of lymph node involvement [63]. Similarly, there is limited reliability of pT3a vs. pT3b subcategorization as gross involvement of perivesical fat (extravesical fat) may not always be readily recognizable (Level 3). Distinction between pT3a and pT3b relies solely on gross findings, which can be ambiguous compared to the microscopic staging.
assessment. Perivesical tissue reactions to the tumor or prior biopsy may be over interpreted as extravesical fat involvement. In addition, residents or physician assistants who are less experienced sometimes perform the bladder gross examination and may not document subtleties at the macroscopic level. The prognostic significance of pT3 subcategory is controversial; some reports did not show survival differences [64-66] while some did show differences between pT3a and pT3b [67,68] (Figures 21, 22) (Level 4).

Figure 18. Unequivocal invasion of A) lamina propria with wispy fascicles of muscularis mucosae (pT1) and B) thick bundles of muscularis propria (pT2).

Figure 19. Urothelial carcinoma invading adipose tissue within the muscularis propria (pT2).

Figure 20. The typically ill-defined boundary between muscularis propria muscle and perivesical adipose tissue. Low power is important in distinguishing pT2b vs. pT3a.

Figure 21. Urothelial carcinoma with microscopic invasion of the perivesical fat (pT3a).

Figure 22. Urothelial carcinoma with macroscopic invasion of the perivesical fat (pT3b).
There are variations in the LP among the different topographical regions of the bladder. The trigonal area has a relatively flatter surface and LP is attenuated where the depth ranges from 0.46 mm to 1.58 mm [37]. In contrast, the LP is deepest at the dome where it ranges from 0.98 to 3.07 mm [37]. The differences of the depth of the LP in the different bladder regions need to be taken into account for future definitions of microinvasive carcinoma or criteria for substaging pT1 disease (e.g. 2 mm depth can already be pT2 at the trigone). The distribution and morphologic features of MM also varies at the different topographical sites of the bladder [37]. The LP MM muscle bundles are not well defined in the trigone and the MP muscle bundles in this region become progressively smaller in caliber more superficially as they almost reach the surface (Figure 23A, B). Further, smooth muscle bundles of the bladder base and the MP of the intravesical segment of the ureter may simulate vesical MP muscle in samples from this region. Hyperplastic MM is most commonly encountered in the dome. In 22%, isolated or small groups of compact regular hyperplastic MM muscle bundles are seen in deep LP situated between the more typical slender MM layer and the MP. The more superficial location of the MP and rarity of MM in the trigone, relative abundance of hyperplastic MM in dome, and presence of the more superficial ureteral MP at its insertion site in the bladder complicate the traditional pT stage evaluation of invasive cancer in these regions (Level 3) [37]. There is no data to indicate that differences in histoanatomy of the bladder influence the prognosis of muscle invasive urothelial carcinoma (Grade D), although knowledge of these variations is essential for accurate staging.

The non-invasive urothelial neoplasms may be flat, papillary (exophytic) and inverted (endophytic) depending on their growth pattern relationship with the surface of the surrounding urothelial mucosa [69]. All 3 growth patterns may be seen concomitantly in a single tumor (Figure 24). Extensive clinicopathological studies have been published related to the first two growth patterns, whereas the clinical significance of the third has been dealt with only at a limited extent.

The World Health Organization (W.H.O.) (2004) / International Society of Urologic Pathologists (ISUP) classification system is the recommended system for classification and grading of urothelial neoplasms. It has also been endorsed by the W.H.O. 2004 Blue Book, the 4th Series Armed Forces Institutes of Pathology Fascicle on Bladder, the 7th edition AJCC Cancer Staging Manual and this consensus group. W.H.O. (2004)/ISUP grading system has prognostic (recurrence and progression potential) significance between different grades for papillary lesions; although risk prediction at an individual patient level is still not possible. There is need for incorporation of the W.H.O. (2004)/ISUP grade along with other clinical and pathologic parameters in nomograms and clinical decision-making algorithms to provide personalized risk stratification in patients with non-invasive urothelial carcinoma. The aggregate data in the literature on the W.H.O. (2004)/ISUP system has shown the following benefits: a) establishment
Figure 24. Examples of the spectrum of tumors in a cystectomy (A), Whole mount section of a bladder with a preoperative diagnosis of muscle invasive high-grade papillary carcinoma; B, Urothelial dysplasia; from the specimen shown in A), a papillary neoplasm (C, The neoplasm grows exophytically into the lumen of the urinary system with a papillary configuration; D, Low-grade papillary carcinoma; from the specimen shown in C), and an inverted neoplasm (E, The neoplasm, even though a polypoid appearance, is characterized by an epithelium that shows a non-infiltrative growth into the subepithelial connective tissue; F, Low-grade inverted urothelial carcinoma; from the specimen shown in E).
of uniform terminology and common definitions for papillary neoplasms; b) establishment of detailed criteria of various preneoplastic conditions and various grades of tumor; c) correlation with urine cytology terminology, facilitating cyto-histologic correlation and making it easier for urologists to manage patients; d) creation of a category of tumor that identifies a tumor with a negligible risk of progression (PUNLMP), whereby patients avoid the label of having cancer which has psychosocial and financial implications, neither is a benign lesion (papilloma) diagnosed in these patients, so they may still be followed up closely; e) approximately half the cases occurring in young patients (patients less than 20 years of age) are now diagnosed as papillary urothelial neoplasms of low malignant potential instead of transitional cell carcinoma grade 1 obviating a carcinoma diagnosis in patients with biologically indolent tumors and in keeping with their molecular profile; f) identification of a distinct group of patients (high-grade papillary urothelial carcinoma) who would be ideal candidates for intravesical therapy; g) identification of a larger group of patients at high risk for progression for urologists to follow up more closely; h) removal of ambiguity in diagnostic categories in WHO 1973 system (e.g., TCC grade I-II, TCC grade II-III); h) stratification of bladder tumors into prognostically significant categories; and i) emergence of molecular correlates and signatures for high grade tumors and tumors at the low-grade end of the spectrum which may help provide ancillary grading tools, facilitate patient management, and possibly guide in future refinements of the current grading system.

2. FLAT LESIONS AND NEOPLASMS

The 2004 WHO/ISUP classification of the flat lesions includes flat hyperplasia, dysplasia and carcinoma in situ. In addition, this classification also lists reactive atypia, secondary to inflammation, and atypia of uncertain significance.

a) Flat Urothelial Hyperplasia

Urothelial hyperplasia is characterized by markedly thickened urothelium with an increase in the number of cell layers, usually 10 or more, usually with increased cellularity (increased cells per unit area). The cells do not show cytological abnormalities, although slight nuclear enlargement may be focally present. There is cellular order and morphologic evidence of maturation from base to surface epithelium is evident. Mitoses are generally absent. It has been described in association with inflammatory disorders as well as adjacent to low-grade papillary tumours [28]. Molecular analyses have shown that this lesion may be clonally related to the papillary tumors in patients with bladder cancer and suggest a role in the pathogenesis of low-grade papillary urothelial carcinoma (Level 3) [70,71].

b) Urothelial Dysplasia

Urothelial dysplasia is characterized by architectural distortion and a variable degree of atypia. The thickness is usually normal (but may be attenuated or hyperplastic) and cytological changes are often restricted to the intermediate and basal cells. The nuclei are irregularly enlarged with loss of polarity. Nuclear outlines are irregular and chromatin abnormalities, although subtle, are present. Nucleoli are variable, absent but not conspicuously present. Mitotic activity is scant, usually involving only the basal and intermediate cell layers. Overall features are those of a neoplastic atypia (clear cut nuclear atypia) but which fall short of the criteria for CIS; dysplasia is not further graded. Low-grade intraurothelial lesion is a synonym. There is some evidence, largely genetic, that dysplasia shares some abnormalities with CIS and therefore likely represents a precursor lesion. Few studies, most dated, indicate a 5-19% risk of developing cancer [72]. The diagnosis of de novo dysplasia (i.e. in a patient without history of bladder neoplasm) should not be made or should be made with great caution as the vast majority of patients, in the limited studies, do not progress to cancer (Level 3). While dysplasia likely represents a marker of urothelial instability, the diagnosis should not by itself invoke any therapy; continued surveillance is recommended (Grade C).

c) Urothelial Carcinoma In Situ (CIS)

CIS is characterized by architecural distortion and distinct high-grade nuclear atypia (definitioanal feature) including marked irregularities of the nuclear outlines and chromatin distribution, nuclear pleomorphism, prominent nucleoli throughout (if nucleoli are present), nucleolar pleomorphism, and atypical mitoses on the surface. There is usually loss of nuclear polarity and the cells show a high degree of atypia. Mitoses are generally frequent and may be seen at any level of the epithelium. There is a spectrum of nuclear and architectural atypia. CIS defined by WHO (2004) / ISUP includes cases diagnosed previously as severe dysplasia and even some cases previously diagnosed as moderate dysplasia. The classification system provides detailed criteria for pathologists, as CIS may be both over- and under-diagnosed. The development of invasion is seen in 20 to 30% of the cases (Level 2) [73-78]. Urothelial carcinoma in situ of the urethra may extend into underlying prostatic glands (Figure 25).

3. PAPILLARY (EXOPHYTEC) NEOPLASMS

The lesions and neoplasms of this group grow exophytically into the lumen of the urinary system with a papillary configuration. According to the 2004 WHO classification, this group includes urothelial papilloma, papillary urothelial neoplasm of low malignant potential (PUNLMP), low-grade papillary carcinoma and high-grade papillary carcinoma.
a) Urothelial Papilloma

Urothelial papilloma is characterized by a few fine papillary fronds lined by normal-appearing urothelium. Tumors contain slender minimally branching papillae and the superficial umbrella cells are often prominent which may show vacuolization. Urothelial papilloma shows a very low recurrence rate and minimal to absence progression rate (Level 2) [79-81].

b) Papillary Urothelial Neoplasm of Low Malignant Potential (PUNLMP)

PUNLMP is characterized by cytologically bland / normal appearing cells with hyperplasia (increased cells per unit area and increased cell layers) on a fibrovascular core. PUNLMP largely, though not completely, corresponds to grade 1 papillary transitional cell carcinoma (TCC) of the old 1973 WHO system. The lesion consists mostly of delicate papillae with little or no fusion. The covering urothelium shows monotony with normal size and preserved polarity characterized by upward streaming of cells perpendicular to basement membrane. The umbrella cell layer is often preserved and basal cells may show palisading. Nuclei lack significant nuclear hyperchromasia or pleomorphism. The chromatin is fine and nucleoli are inconspicuous. Mitoses are infrequent and may be seen at any level of the epithelium. There is a range of nuclear atypia, some have obvious pleomorphism while some have monomorphic nuclei with rounding, nucleomegaly and irregular clumped chromatin. The chromatin is dense, irregularly distributed and often clumped. Nucleoli may be single or multiple and are often prominent. Mitoses are generally frequent and may be seen at any level of the epithelium. It is often associated with invasive disease at the time of diagnosis [82-89]. These tumors not only have a risk of invasion but also have a significant risk of recurrence and progression; association with multifocality and CIS is common (Level 2). The overall progression rate (to invasive carcinoma) ranges from 15% to 40%; more than half the cases are prone to recurrences.

c) Low-grade Papillary Carcinoma

Low-grade papillary urothelial carcinoma shows cells with low-grade cytologic atypia (resembling urothelial dysplasia in a flat lesion) on a fibrovascular core. Cases would span some tumors considered grade 1 TCC and approximately 70% of grade 2 TCC in the old 1973 WHO system. WHO grade 1 neoplasms showing mild but distinct cytological atypia and mitoses, are diagnosed in the 2004 WHO system as low-grade papillary urothelial carcinomas. At low magnification the cells are relatively uniform but enlarged in size with frequent loss of cellular polarity (loss of linear perpendicular orientation to basement membrane). There is no significant pleomorphism. The nuclei tend to be uniformly enlarged with occasional to consistent irregularities of nuclear contours. The chromatin is relatively fine to mildly abnormal with small nucleoli. Mitoses may be present but are few and remain basally located. These tumors have a significantly higher recurrence rate than for PUNLMP (Level 2). They also have a significantly higher rate of stage progression than PUNLMP but significantly lower than for high-grade papillary carcinoma (Level 2). A review of the literature reveals a mean recurrence rate of 50% and mean stage progression rate of 10%.

d) High-grade Papillary Carcinoma

High-grade papillary carcinoma is characterized by cells with high-grade cytologic atypia (resembling CIS in a flat lesion) on a fibrovascular core. Cases exhibit a spectrum with some tumors (approximately 30%) considered grade 2 TCC and most cases of TCC grade 3 in the old 1973 WHO system. On low power magnification, the tumor often exhibits complex papillary architecture and fusion. Individual cells are haphazardly arranged within the epithelium and have a generally discohesive nature. The tumor may show extensive denudation. There is a range of nuclear atypia, some have obvious pleomorphism while some have monomorphic nuclei with rounding, nucleomegaly and irregular clumped chromatin. The chromatin is dense, irregularly distributed and often clumped. Nucleoli may be single or multiple and are often prominent. Mitoses are generally frequent and may be seen at any level of the epithelium. It is often associated with invasive disease at the time of diagnosis [82-89]. These tumors not only have a risk of invasion but also have a significant risk of recurrence and progression; association with multifocality and CIS is common (Level 2). The overall progression rate (to invasive carcinoma) ranges from 15% to 40%; more than half the cases are prone to recurrences.

4. INVERTED (ENDOPHYTIC) NEOPLASMS

Papillary tumors may be associated with a variable degree of inverted growth patterns. Although focal areas of inverted growth are not uncommon, prominent or exclusive inverted growth is much rarer and when encountered may pose problems related to grading or assessment of invasion. The neoplasms with inverted growth are basically
characterized by an epithelium that shows a non-infiltrative growth into the subepithelial connective tissue, even though, cystoscopically they might show a polypoid or dome shaped appearance. Although a formal grading system is not proposed specifically for lesions with a predominant inverted growth, nor is one universally used, we recommend that for tumors with predominantly inverted growth patterns criteria which essentially parallels the W.H.O. (2004) / ISUP system for exophytic tumors and flat lesions be used (Table 2).

Although prospective formal studies with uniform criteria or assessing the clinical significance of the classification terminology are not yet performed, standardized nomenclature proposed herein may facilitate such much needed data (Level 4).

The classification system includes urothelial papilloma, inverted papillary urothelial neoplasm of low malignant potential, inverted low-grade urothelial carcinoma and inverted high-grade urothelial carcinoma; the last category may be non-invasive or invasive.

Inverted urothelial papilloma consists of thin anastomosing trabeculae of urothelial cells within the subepithelial connective tissue and covered by a normal or attenuated urothelium without cytologic atypia [90-92]. Inverted papilloma is associated with a low risk of recurrence (<5%) (Level 2). In comparison with inverted urothelial papilloma, the architectural features favoring a diagnosis of urothelial neoplasms with inverted growth pattern include thick columns with irregularity in their width and transition into more solid areas. The characteristic orderly maturation, spindling, and peripheral palisading seen in inverted papilloma are generally absent or inconspicuous.

Inverted papillary neoplasms of low malignant potential show thicker or irregular cords, solid or nodular growth lacking cytologic atypia; when cytologic atypia is present tumors are graded as low-grade or high-grade based on the degree of atypia. Reports of non-invasive urothelial carcinomas with inverted growth pattern are found in the literature using variable nomenclature [28,70,93,94] with two patterns - inverted papilloma-like pattern), or broad-front pattern (Table 3). Minor degrees of inverted papilloma may also be associated with papillary urothelial neoplasms.

### Table 2. Analogy in nomenclature for inverted lesions

<table>
<thead>
<tr>
<th>Flat Lesions</th>
<th>Papillary Lesions*</th>
<th>Predominant or Exclusive Inverted Lesions*</th>
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<tbody>
<tr>
<td>Normal</td>
<td>Papilloma</td>
<td>Inverted papilloma</td>
</tr>
<tr>
<td>Urothelial hyperplasia</td>
<td>Papillary neoplasm of low malignant potential</td>
<td>Inverted papillary neoplasm of low malignant potential</td>
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<tr>
<td>Urothelial dysplasia</td>
<td>Papillary urothelial carcinoma, low grade, non-invasive</td>
<td>Inverted papillary urothelial carcinoma, low grade, non-invasive</td>
</tr>
<tr>
<td>Urothelial CIS</td>
<td>Papillary urothelial carcinoma, high grade, non-invasive</td>
<td>Inverted papillary urothelial carcinoma, high grade, non-invasive</td>
</tr>
<tr>
<td>-</td>
<td>Papillary urothelial carcinoma, high grade, invasive</td>
<td>Inverted papillary urothelial carcinoma, high grade, invasive</td>
</tr>
</tbody>
</table>

*Lesions may be both exophytic and endophytic

### Table 3. Morphologic, immunologic and molecular genetic features of inverted urothelial papilloma and urothelial carcinoma with inverted pattern

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Inverted urothelial papilloma</th>
<th>Urothelial carcinoma with inverted growth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surface</td>
<td>Smooth, domed shaped, usually intact cytologically normal</td>
<td>Usually exophytic papillary lesions present</td>
</tr>
<tr>
<td>Growth pattern</td>
<td>Endophytic, expansive, sharply delineated, anastomosing cords and trabeculae</td>
<td>Endophytic, lesional circumscription variable</td>
</tr>
<tr>
<td>Cytologic features</td>
<td>Orderly polarized cells, some with spindling and palisading at the periphery. No significant atypia, mitoses rare</td>
<td>Variable, nuclear pleomorphism and atypia present</td>
</tr>
<tr>
<td>Immunohistochemistry</td>
<td>Low p53 expression and Ki-67 proliferation index</td>
<td>Variable, usually high p53 and Ki-67 proliferation index</td>
</tr>
<tr>
<td>Molecular analysis</td>
<td>Rare deletions at chromosome 9 or 17, rare FGFR3 mutations, low rate of LOH**</td>
<td>Frequent FGFR3 mutation, chromosome 9 and 17 deletions</td>
</tr>
<tr>
<td>Biological potential</td>
<td>Benign, rare recurrences*</td>
<td>Recurrences and progression may occur</td>
</tr>
</tbody>
</table>

*Rare recurrences related to incomplete excision
**Loss of heterozygosity
pattern should not be acknowledged in the pathologic diagnosis. Prominent of predominant patterns may be diagnosed using terminology such as “papillary urothelial neoplasm of low malignant potential with prominent inverted growth pattern, no evidence of invasion” or “papillary urothelial carcinoma, low-grade, non invasive, with prominent areas of inverted growth pattern”.

High grade inverted tumors may be non invasive or invasive. The diagnosis of invasion requires the unquestionable presence within the lamina propria of irregularly shaped nests or single cells that may have evoked a desmoplastic or inflammatory response. When a stromal response is absent, irregularity of the contours of the invasive nests, architectural complexity and recognition of single-cell invasion are helpful (Table 4).

C. UPDATES ON GRADING OF NON-INVASIVE AND INVASIVE UROTHELIAL CARCINOMA OF THE URINARY BLADDER

Since its introduction in 1998, the different components of 2004 WHO (1998 ISUP/WHO) grading system for urothelial neoplasms have been the subject of several clinicopathological validation studies, observer variability studies, and comparative analysis with the older 1973 WHO grading system. This review focuses on critical diagnostic pathology-related issues of the 2004 WHO/ISUP grading system, with appropriate comparison with the 1973 WHO grading system based on published studies.


Table 5 shows a comparative distribution of non-invasive papillary urothelial neoplasms according to the 2004 WHO/ISUP and 1973 WHO grading systems in same patient cohorts. In most studies, low-grade papillary carcinoma represented the largest grade category by 2004 WHO/ISUP system which comprised 36-74% of the papillary tumors, and G2 (31-84%) the largest when 1973 WHO system was applied. High-grade papillary carcinoma (2004 system) generally had greater proportion of tumors than G3 (1973 system). In 6 of 7 series, high-grade papillary carcinoma constituted > 10% of tumors, whereas, G3 was comparatively smaller and constituted > 5% of tumors in only 1 out of the 7 studies. In most studies, PUNLMP generally had lower number of tumors than G1 tumors. In summary, studies have attempted to correlate the 1973 and the 2004 system with variable success as there is not a direct correlation between the 2 systems due to differing criteria[70,79,83-85,90,91].

Since its introduction, several studies had compared the impact to disease outcome of the 1998 ISUP/WHO (2004 WHO) system to the 1973 WHO system in same patient cohort of non-invasive papillary urothelial neoplasm (Table 6). To eliminate the influence of stage, studies that combined non-invasive with pT1 tumors or deep muscle-invasive tumors were not included in this review. Some studies have shown advantage for the 2004 WHO grading system over the 1973 WHO grading system.

Cao et al [95] reviewed 172 pTa (out of 269 non muscle–invasive tumors) with long follow-up (up to 10 years) and demonstrated significant differences between low-grade papillary carcinoma and high-grade papillary carcinoma in recurrence-free survival (p= 0.05, log-rank test) and progression free-survival (p= 0.01, log-rank test). No PUNLMP was identified in the study cohort. The 1973 WHO system in contrast showed significant difference only in progression free-survival (p=0.03, log-rank test) and not in recurrence-free survival. Both WHO grading systems were unable to predict the overall survival.

Burger et al [96] reviewed 104 pTa tumors that included 51 early onset (< 45 years old patients) (median follow-up of 48 months) and 63 regular onset (> 45 years old patients) (median follow-up of 43 months) tumors. In early onset pTa tumors, both WHO grading systems were not significantly related to recurrence-free survival or to progression to muscle invasive disease. In regular onset, both 2004 WHO system (p=0.021, log-rank test) and 1973 WHO system (p=0.035, log-rank test) were predictive of recurrence-free survival, however only

Table 4. Urothelial carcinoma with inverted pattern. Criteria for invasion.

<table>
<thead>
<tr>
<th>Features</th>
<th>Non-invasive</th>
<th>Invasive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contours of neoplastic nests/cords</td>
<td>Regular</td>
<td>Irregular</td>
</tr>
<tr>
<td>Size and shape of nests</td>
<td>Similar, rounded edges</td>
<td>Variable, irregular and jagged edges</td>
</tr>
<tr>
<td>Inflammatory and desmoplastic stroma</td>
<td>Absent</td>
<td>Present</td>
</tr>
</tbody>
</table>
the 2004 WHO system was related to progression (p=0.002).

Yin and Leong [97] reviewed 84 pTa tumors and showed significant differences in recurrence within 36 months between PUNLMP (17% recurrence) and low-grade papillary carcinoma (45% recurrence) and between low-grade papillary carcinoma and high-grade papillary carcinoma (74% recurrence) (p<0.5). In contrast, no significant difference in recurrence was observed between the 1973 WHO grades (urothelial papilloma, G1, G2 and G3 with recurrence of 0%, 41%, 54% and 67%, respectively).

Some studies did not show a clear-cut advantage in terms of impact to outcome for the 2004 WHO system over the 1973 WHO grading system.

May et al [76] compared the prognostic implications of both WHO grading systems in 200 non-invasive tumors and with mean follow-up of 72 months using consensus diagnosis of 4 genitourinary pathologists. No PUNLMP was identified in the series. By 2004 WHO system, low-grade papillary carcinoma and high-grade papillary carcinoma had 5-year recurrence free survival of 69.1% and 46.1%, respectively (p=0.007) and 5-year progression free survival of 93.5% and 80.2%, respectively (p=0.084). By 1973 WHO system, G1, G2 and G3 had 5-year recurrence free survival of 64.5%, 68.1% and 11.1%, respectively (p<0.001) and 5-year progression free survival of 97.2%, 86.9% and 64.8%, respectively (p=0.002).

Schned et al [98] reviewed 504 non-invasive tumors (mean follow-up 7.2 years) and similarly showed a gradient of progressive lower survival times from the lowest to the highest grade tumors in both 2004 and 1973 WHO grading systems. Compared with survival times for PUNLMP, the hazard ratio for low-grade papillary carcinoma was 1.9 (95% CI 1.0-3.4) and for high-grade papillary carcinoma was 3.0 (95% CI 1.5-6.0). For the 1973 WHO system, compared to G1 tumors, the hazard ratio for G2 was 1.8 (95% CI 1.1-3.1) and for G3 was 2.4 (95% CI 1.2-4.7). The study however did not provide information on recurrence, progression and disease-specific survival of these cases.

Samaratunga et al [99] investigated 134 patients with pTa tumors and showed no statistical significance in recurrence rates among the 1998 ISUP/WHO grades. The only statistically significant difference in the 1973 WHO system was that G3 had increased recurrences per year compared with papilloma (p=0.02), G1 (p=0.0001), and G2 (p=0.0001). Separate analyses showed both 2004 WHO system and 1973 WHO system independently predicted progression (p=0.003 and p=0.002, respectively) together with tumor size.

Oosterhuis et al [100] reclassified 322 pTa tumors to 1998 ISUP/WHO and log rank test for five year progression free survival (p=0.06) and five year recurrence free survival (p=0.13) were not significantly different between the grade groups as a whole. The only significant difference between

### Table 5. Distribution of non-invasive papillary urothelial neoplasms according to 2004 WHO (1998 ISUP/WHO) and 1973 WHO grading systems.*

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Papilloma (%)</td>
<td>PUNLMP (%)</td>
</tr>
<tr>
<td>Cao et al, 2010</td>
<td>172</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>May et al, 2010</td>
<td>200</td>
<td>-</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Burger et al, 2007</td>
<td>114</td>
<td>-</td>
<td>6 (5)</td>
</tr>
<tr>
<td>Schned et al, 2007</td>
<td>504</td>
<td>-</td>
<td>179 (38)</td>
</tr>
<tr>
<td>Yin and Leong, 2004</td>
<td>84</td>
<td>3 (4)</td>
<td>32 (38)</td>
</tr>
<tr>
<td>Samaratunga et al, 2002</td>
<td>134</td>
<td>3 (2)</td>
<td>29 (22)</td>
</tr>
<tr>
<td>Oosterhuis et al, 2002</td>
<td>322</td>
<td>18 (5)</td>
<td>116 (36)</td>
</tr>
<tr>
<td>Range</td>
<td>2-5%</td>
<td>0-38%</td>
<td>36-74%</td>
</tr>
</tbody>
</table>

*Includes only studies that accounted the purely non-invasive tumors; studies combining non-invasive and invasive tumors and/or without the use of the two grading systems were not included; ** Modified 1973 WHO 2a (214, 66%) and 2b (72, 22%).
<table>
<thead>
<tr>
<th>Study</th>
<th>Grade</th>
<th>Total</th>
<th>Recurrence</th>
<th>p-value</th>
<th>Progression</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>May et al, 2010</td>
<td>2004 WHO PUNLMP</td>
<td>1</td>
<td>0 (0%)</td>
<td>&lt;0.001</td>
<td>0</td>
<td>0.084</td>
</tr>
<tr>
<td></td>
<td>LG PUC</td>
<td>149</td>
<td>55 (37%)</td>
<td></td>
<td>10 (67%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HG PUC</td>
<td>50</td>
<td>29 (58%)</td>
<td></td>
<td>8 (16%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1973 WHO G1</td>
<td>82</td>
<td>36 (44%)</td>
<td>&lt;0.001</td>
<td>4 (5%)</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>G2</td>
<td>109</td>
<td>40 (37%)</td>
<td></td>
<td>11 (10%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>G3</td>
<td>9</td>
<td>8 (89%)</td>
<td></td>
<td>3 (30%)</td>
<td></td>
</tr>
<tr>
<td>Burger et al, 2007</td>
<td>2004 WHO PUNLMP (&lt; 45 years)</td>
<td>0</td>
<td>-</td>
<td></td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LG PUC (&lt; 45 years)</td>
<td>34</td>
<td>-</td>
<td></td>
<td>2 (6%)</td>
<td>0.085</td>
</tr>
<tr>
<td></td>
<td>HG PUC (&lt; 45 years)</td>
<td>12</td>
<td>-</td>
<td></td>
<td>3 (25%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1973 WHO G1 (&lt; 45 years)</td>
<td>30</td>
<td>-</td>
<td></td>
<td>1 (3%)</td>
<td>G1 vs. G2/3, 0.0105</td>
</tr>
<tr>
<td></td>
<td>G2 (&lt; 45 years)</td>
<td>15</td>
<td>-</td>
<td></td>
<td>3 (20%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>G3 (&lt; 45 years)</td>
<td>1</td>
<td>-</td>
<td></td>
<td>1 (100%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2004 WHO PUNLMP (&gt; 45 years)</td>
<td>6</td>
<td>-</td>
<td></td>
<td>0 (0%)</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>LG PUC (&gt; 45 years)</td>
<td>43</td>
<td>-</td>
<td></td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HG PUC (&gt; 45 years)</td>
<td>14</td>
<td>-</td>
<td></td>
<td>5 (36%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1973 WHO G1 (&gt; 45 years)</td>
<td>28</td>
<td>-</td>
<td></td>
<td>2 (71%)</td>
<td>G1 vs. G2/3, 0.310</td>
</tr>
<tr>
<td></td>
<td>G2 (&gt; 45 years)</td>
<td>31</td>
<td>-</td>
<td></td>
<td>2 (65%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>G3 (&gt; 45 years)</td>
<td>4</td>
<td>-</td>
<td></td>
<td>1 (25%)</td>
<td></td>
</tr>
<tr>
<td>Yin and Leong, 2004</td>
<td>1998 ISUP/WHO PUNLMP</td>
<td>12</td>
<td>2 (17)</td>
<td>&lt;0.05</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>LG PUC</td>
<td>53</td>
<td>24 (45)</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>HG PUC</td>
<td>19</td>
<td>14 (74)</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>1973 WHO Papilloma</td>
<td>3</td>
<td>0</td>
<td>&lt;0.05</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>G1</td>
<td>32</td>
<td>13 (41)</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>G2</td>
<td>46</td>
<td>25 (54)</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>G3</td>
<td>3</td>
<td>2 (67)</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Samaraputu et al, 2002</td>
<td>1998 ISUP/WHO Papilloma</td>
<td>3</td>
<td>0.0/year</td>
<td>NS</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PUNLMP</td>
<td>29</td>
<td>0.025/year</td>
<td></td>
<td>8%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LG PUC</td>
<td>73</td>
<td>0.045/year</td>
<td></td>
<td>13%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HG PUC</td>
<td>29</td>
<td>0.047/year</td>
<td></td>
<td>51%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1973 WHO Papilloma</td>
<td>7</td>
<td>0.02/year</td>
<td>G3 vs. papilloma, 0.02</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>G1</td>
<td>42</td>
<td>0.027/year</td>
<td>G3 vs. G1, 0.00001</td>
<td>11%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>G2</td>
<td>79</td>
<td>0.059/year</td>
<td>G3 vs. G2, 0.00001</td>
<td>24%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>G3</td>
<td>6</td>
<td>0.3/year</td>
<td></td>
<td>60%</td>
<td></td>
</tr>
</tbody>
</table>
The percentages of the grading categories for both

**GRADE**

**REPRODUCIBILITY STUDIES ON**

**II. INTER- AND INTRA-OBSERVER**

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<table>
<thead>
<tr>
<th>1998 ISUP/WHO</th>
<th>2004 WHO</th>
<th>PUNLMP</th>
<th>LG PUC</th>
<th>HG PUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>18</td>
<td>PUNLMP</td>
<td>116</td>
<td>HG PUC</td>
</tr>
<tr>
<td>G2a</td>
<td>0.35</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G2b</td>
<td>0.04</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G3</td>
<td>0.10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G3a</td>
<td>0.10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G3b</td>
<td>0.22</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G4</td>
<td>0.02</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

WHO grading systems in non-invasive papillary urothelial neoplasms had varied significantly in previous studies (Table 5). The percentages of 2004 WHO PUNLMP, low-grade papillary carcinoma and high-grade papillary carcinoma were 0-38%, 36-74% and 4-64%, respectively. The percentages of 1973 WHO G1, G2 and G3 were 9-58%, 31-84% and 1-23%, respectively. Differences in patient cohort geography may partly explain the broad differences, but the influence of interpretation variability among pathologists as well cannot be discounted.

Table 7 summarizes several published grading observer variability studies in papillary urothelial neoplasms, and includes some that compares the 2004 WHO system with the 1973 WHO grading system.

In the study by May et al [76], 200 papillary urothelial carcinomas were reviewed independently by 4 genitourinary pathologists and graded according to both 2004 WHO and 1973 WHO grading systems. Owing to the rare PUNLMPs in the cohort, the WHO 2004 approached a two-tiered system (low and high grades) and showed less interobserver variability than the 1973 classification (κ 0.30-0.52 vs. 0-0.37, respectively). In comparing the power of both classifications to separate indolent from aggressive papillary carcinoma, striking pathologist-dependent differences were observed. Only 2 of 4 pathologists provided a grading under the 2004 WHO system that was significantly prognostic regarding recurrence and progression.

In the review by Miyamoto et al [102] of a single institution cohort of 112 low-grade urothelial carcinomas, 8 of 55 cases (14.5%) originally diagnosed as low grade by general surgical pathologists were reclassified as high-grade urothelial carcinomas after review by 2 genitourinary pathologists. The main reason for the upgrade was the presence of previously undetected focal high-grade areas amidst the predominantly low-grade urothelial carcinoma.

Van Rhijn et al [103] compared the 2004 WHO system and 1973 WHO system for observer variability and prognosis in 173 non-muscle invasive bladder cancers. For 2004 WHO system, the intraobserver and interobserver agreements were 71% to 88% (κ 0.55-0.81) and 39% to 74% (κ 0.17-0.58 in first round and κ 0.14-0.41 in second review), respectively. If PUNLMP and low-grade papillary carcinoma were condensed, the intraobserver agreement increased to 85-97% (κ 0.68-0.91) and interobserver agreement varied from 68% to 87% (κ 0.68-0.91). For WHO 1973, intraobserver and interobserver agreements (for 2 pathologists) were 80% to 81% (κ 0.67-0.69) and 39% to 64% (κ 0.15-0.41). If G1 and G2 were condensed to one grade, intraobserver agreement increased to 91-98% (κ 0.64-0.88) and interobserver agreement ranged from 81% to 91% (κ 0.47-0.67).

Thus, the 2004 WHO system did not show better intra or inter-observer reproducibility than the 1973 WHO system. The group suggested that the degree of variability between pathologists could be quantified using a mean grade, and such can be a potential tool for quality assurance in pathology.

In the study by Gönül et al [104] of 258 papillary urothelial carcinoma, the overall degree of reproducibility between 2 pathologists was higher in the 2004 WHO system (κ 0.59) than the 1973 WHO system (κ 0.41), although both were still moderate in agreement. PUNLMP showed the lowest degree of agreement and if excluded from the analysis, interobserver concordance of the 1998 WHO/ISUP increased significantly (κ 0.84).

In the study by Mamoon et al [105], the agreement on 80 urothelial neoplasms between 2 pathologists for the 2004 WHO system was excellent (κ 0.91), whereas agreement for 1973 WHO system was good (κ 0.68). By 2004 WHO system, the kappa value for low grade and high grade tumors showed excellent agreement while the kappa value for papilloma and PUNLMP showed fair to good agreement.

Campbell et al [106] showed moderate agreement in grading 49 non-invasive papillary urothelial neoplasm using WHO 2004 system whether by one (κ 0.45) or two (κ 0.60) pathologists.

Yorukoglu et al [107] in a review of 30 papillary urothelial neoplasms with 6 genitourinary pathologists showed for both 1998 ISUP/WHO system and 1973 WHO system moderate interobserver agreement (κ 0.56 and κ 0.48, respectively). For both grading system the mean rate of agreement was lowest for the lowest grades (PUNLMP and G1) and highest for highest grades (high grade papillary carcinoma and G3). There was substantial intraobserver agreement for both 2004 WHO system and 1973 WHO system (κ 0.67 and κ 0.66, respectively).

In the study by Murphy et al [108], 247 biopsies were reviewed by 3 pathologists and by the 1998 ISUP/WHO system, there were substantial interobserver agreement for high grade papillary carcinoma and CIS (κ 0.75 to 0.82) compared with slight to moderate agreement for PUNLMP and low-grade papillary carcinoma (κ 0.12 to 0.50). When discriminating PUNLMP vs. low-grade papillary carcinoma, discrepancies were 50% after educating the pathologists compared to 39% before education. In discriminating low-grade vs. high-grade papillary carcinoma and PUNLMP vs. high-grade papillary carcinoma, discrepancies were 15% and no discrepancy after education.

Most published observer variability studies showed that both 2004 and 1973 WHO grading systems for bladder urothelial neoplasms suffered from suboptimal observer agreement among pathologists, with most
<table>
<thead>
<tr>
<th>Study</th>
<th>Cases</th>
<th>Grading system</th>
<th>Grades (No.)</th>
<th>No. of pathologists</th>
<th>Interobserver agreement</th>
<th>No. of times reviewed</th>
<th>Intraobserver agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>May et al, 2010</td>
<td>200 papillary urothelial neoplasm</td>
<td>2004 WHO</td>
<td>PUNLMP (1)</td>
<td>4</td>
<td>71.5% to 82.5% (κ 0.30-52, fair to moderate)</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LG PUC (149)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HG PUC (50)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1973 WHO</td>
<td>G1 (82)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
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<td>G2 (109)</td>
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<td>G3 (9)</td>
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<tr>
<td>Otto et al, 2010</td>
<td>310 pT1 papillary urothelial carcinoma</td>
<td>2004 WHO</td>
<td>LG PUC (13)</td>
<td>3</td>
<td>90.3%</td>
<td>1</td>
<td>-</td>
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<td></td>
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<td>HG PUC (297)</td>
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<td></td>
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<td>1973 WHO</td>
<td>G1 (0)</td>
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<td>G2 (112)</td>
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<td>G3 (198)</td>
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<tr>
<td>Van Rhijn, 2009</td>
<td>173 non-muscle invasive papillary urothelial neoplasm</td>
<td>2004 WHO</td>
<td>PUNLMP</td>
<td>4</td>
<td>39% to 74% (first round κ 0.17-0.58 and second round κ 0.14-0.41)</td>
<td>4</td>
<td>71% to 88% (κ 0.55-0.81)</td>
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<td>LG PUC</td>
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<td>HG PUC</td>
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<td></td>
<td></td>
<td>1973 WHO</td>
<td>G1 (68)</td>
<td>2</td>
<td>39% to 64% (κ 0.15-0.41)</td>
<td>4</td>
<td>80% to 81% (κ 0.67-0.69)</td>
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<td>G2 (79)</td>
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<td>G3 (26)</td>
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<tr>
<td>Gönül et al, 2007</td>
<td>258 papillary urothelial neoplasm</td>
<td>2004 WHO</td>
<td>PUNLMP</td>
<td>2</td>
<td>75% (κ 0.59, moderate)</td>
<td>1</td>
<td>-</td>
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<td></td>
<td></td>
<td></td>
<td>LG PUC</td>
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<td>HG PUC</td>
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<td></td>
<td></td>
<td>1973 WHO</td>
<td>G1</td>
<td>62% (κ 0.41, moderate)</td>
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<td>G2</td>
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<td>G3</td>
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</table>
### Table 7. Inter and intra observer variability studies in grading of papillary urothelial neoplasm.

<table>
<thead>
<tr>
<th>Study</th>
<th>Cases/Type</th>
<th>Methodology</th>
<th>2004 WHO</th>
<th>1973 WHO</th>
<th>Pathologists</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mamoon et al, 2006</td>
<td>100 papillary urothelial neoplasm</td>
<td>2004 WHO</td>
<td>95% (κ 0.91, excellent)</td>
<td>80% (κ 0.68, good)</td>
<td>1</td>
<td>-</td>
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<tr>
<td></td>
<td></td>
<td>1973 WHO</td>
<td></td>
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<tr>
<td>Campbell et al, 2004</td>
<td>49 non-invasive papillary urothelial neoplasm</td>
<td>1998 WHO/ISUP</td>
<td>52% (κ 0.45, moderate)</td>
<td>71% (κ 0.60, moderate)</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Yorukoglu et al, 2003</td>
<td>30 non-invasive papillary urothelial neoplasm</td>
<td>1998 WHO/ISUP</td>
<td>70.9% (κ 0.56, moderate)</td>
<td>65.1% (κ 0.48, moderate)</td>
<td>2, at least 4 weeks interval</td>
<td>78.3% (κ 0.67, substantial)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1973 WHO</td>
<td></td>
<td></td>
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<tr>
<td>Murphy et al, 2002</td>
<td>247 biopsies</td>
<td>1998 WHO/ISUP</td>
<td>κ 0.12 - 0.50, slight to moderate</td>
<td>κ 0.7 - 0.82, substantial</td>
<td>1 (divided into learning and study sets)</td>
<td>-</td>
</tr>
</tbody>
</table>
studies showed only moderate agreement (Level 2). When compared, the 2004 WHO system showed relatively better reproducibility than the 1973 WHO system (Level 3). Among the WHO 2004 grades, PUNLMP and papilloma had the lowest interobserver reproducibility and distinction of PUNLMP from low-grade papillary carcinoma appeared to be the most difficult. Condensing PUNLMP and low-grade papillary carcinoma improved grading reproducibility of the 2004 WHO system. Evidence showed that education of pathologists might help improve interobserver reproducibility of PUNLMP versus low-grade papillary tumor. The few studies that reviewed intraobserver reproducibility among pathologists showed no differences between the 2004 and 1973 grading systems with both showed moderate to substantial agreement (Level 3).

III. Grading Papillary Urothelial Neoplasms with Histologic Heterogeneity

Grade represents a morphological spectrum, and variation in the degree and distribution of atypia within one tumor is well-recognized by pathologists (Figure 26). Admixture of at least two different grades in a papillary urothelial neoplasms is not uncommonly encountered, and is reported in 3% to 43% of tumors [76,109-112]. This histologic heterogeneity contributed to the lumping of grades (e.g. G1-G2, G2-G3 or G2-G3) in the older grading systems, and avoidance of these non-definitive lumped grades was one impetus for modifications toward a more defined grading system. The 1998 ISUP consensus, cognizant of urothelial tumors with variable histology, suggested that grade should be reported according to the highest grade present in heterogeneous tumors, but stressed the need of studies to determine how significant a minor component must be in order to have an impact on overall prognosis [113].

Cheng et al [111] took into account the heterogeneity in papillary urothelial neoplasms and proposed a modified grading approach by combining the most and secondary (p=0.001) and combined (p=0.0001) were all significant in predicting progression. Significant difference in progression free survival between patients with a combined score of 5 (low grade + high grade) and those with a score of 6 (pure high grade papillary carcinoma) (p=0.02) was observed. Of note among mixed tumors with predominant low-grade papillary carcinoma, more minor component of high-grade papillary carcinoma (21%, score of 5) than PUNLMP (6%, score of 3) was observed, the former by conventional WHO 2004 grading will be designated as high-grade papillary carcinoma.

Billis et al [109] applied a similar approach to Cheng et al [114] in 293 bladder tumors but instead used the 1999 WHO grading system and correlated with stage. The study was able to stratify G2 into subgroups (mixed [G1 + G2] and pure [G2+G2]), which were statistically different when considering stage. In G3, there was also a trend for statistical difference between mixed (G2 + G3) and pure (G3 + G3) tumors. The study however provided no information on disease outcome.

Bircan et al [110] applied a similar approach to Cheng et al [111] and Billis et al [109] in 87 bladder carcinomas and used 1998 ISUP/WHO, 1973 WHO and 1999 WHO grading systems and correlated with stage. Mixed histology (odd number scores) constituted 18%, 29% and 33% of tumors by 1998 ISUP/WHO, 1973 WHO and 1999 WHO grading systems, respectively. In the 1998 ISUP/WHO system, there was significant difference between low-grade and high-grade carcinomas (p= 0.000) and between mixed low-grade and high-grade (p= 0.011) when correlated to stage. The 1998 ISUP/WHO system positively correlated with stage, but the 1998 combined scoring did not. The 1973 WHO system positively correlated with stage, and there was a weak association between the 1973 combined scoring and stage. The study also did not provide information on disease outcome.

Figure 26. Grade heterogeneity in papillary urothelial carcinoma. Low (right) and high grade (left) areas
interobserver reproducibility is tumor heterogeneity. Using the 1998 ISUP/WHO grading system, 43% of tumors had mixed low-grade and high-grade papillary carcinoma components, which resulted in a three-tiered grading of low-grade, mixed and high-grade papillary urothelial carcinomas. By Kaplan-Meier analysis, both the 1998 ISUP/WHO grading system and the three-tiered grading failed to reach the level of statistical significance. However, when low-grade were combined with mixed versus high-grade, this approach allowed stratification of patients showing a significant difference in disease-related survival (p=0.0404). In multivariate analysis however, this two-tiered grading approach did not reach the level of significance.

May et al [76] identified 3% in 269 non-muscle invasive tumors that contained elements of both low-grade papillary carcinoma and high-grade papillary carcinoma and were able to classify these tumors into low-grade or high-grade grades by separating high-grade papillary carcinoma based on 5% cut-off for high grade areas.

Grade heterogeneity is uncommonly encountered in papillary urothelial neoplasms. The 2004 WHO (1998 ISUP/WHO) system recommends grading of heterogeneous tumor to be based on the highest grade present in a tumor (Grade C). There is no current widely acceptable definition or criteria to provide quantitative estimate of size of smallest focus required to “upgrade” a lesion. While arbitrary criteria of ignoring less than 5% have been proposed, the prognostic impact of this criterion in unknown (Level 4). Studies are needed to establish quantitative/semi-quantitative criteria that need to be present to alter assignment of grade in tumors with grade heterogeneity.

For high-grade papillary carcinoma, a reason for interobserver reproducibility is tumor heterogeneity wherein a focus of high grade is not accounted amidst a predominantly low-grade carcinoma. Some authors use the term high-grade urothelial carcinoma arising in a background of low-grade urothelial carcinoma when unequivocal areas of high-grade carcinoma are seen. While the distinction between PUNLMP and low-grade papillary carcinoma is not that critical in an individual patient, distinction of low grade from high-grade carcinoma is very important. When assigning the tumor grade in tumors with borderline grade histology, other tumor parameters such as multifocality, previous grade of the tumor, size of lesions, frequency of recurrence, presence of concurrent CIS, positive cytology may be factored in the grading; and the presence of a few or many of these parameters may influence “upgrading” to a high grade lesion (Grade C). Urologists often use these tumor parameters in addition to W.H.O. (2004) / ISUP grade to manage patients and to determine intervention. Sharing such difficult cases in a consensus manner either with other pathology colleagues or through quality assurance meeting is encouraged (Grade B). While currently there are no reliable or acceptable immunohistochemical or molecular markers to assist in grading of borderline lesions, there are promising markers under investigation that may complement histological grading in the future, especially for difficult cases.

From the few studies available, there is evidence to suggest that pure high-grade papillary carcinoma has a different biologic behavior or has higher disease progression than mixed high-grade and low-grade tumors (Level 3). Additional studies with long-term follow-up are needed to determine the prognostic impact and define the allowable extent or percentage cut-off of high-grade focus in heterogeneous papillary urothelial neoplasm. More studies are needed to determine whether the broader scale summation grading provides advantage in outcome information and observer agreement than the conventional WHO 2004 grading system.

### IV. GRADING OF INVASIVE UROTHELIAL CARCINOMAS (PT1 AND PT2+ TUMORS)

Unlike non-invasive papillary urothelial neoplasms (pTa), the role of histologic grade in pT1 and higher stage tumors has been suggested to be of only relative importance. The 1998 ISUP consensus proposed that invasive tumors should be graded as low or high grade similar to the scheme used for grading non-invasive lesions [113]. Herein, we review the impact of 2004 WHO (1998 ISUP/WHO) system and 1973 WHO system in grading pT1 tumors. Distribution of pT1 tumors from previous studies according to the 2004 WHO and 1973 WHO system is shown in Table 8. In this summary, studies combining pT1 with pTa tumors are not included, as it is known that grading has impact on non-invasive papillary tumors.

In the study of Cao et al [95], 41 of 42 (98%) pT1 tumors were classified as high grade based on the 2004 WHO system. By 1973 WHO system, these high grade tumors were classified into 27 (64%) G2 and 15 (36%) G3. No significant differences were noted in recurrence-free survival, progression-free survival, or overall survival between G2 and G3 pT1 tumors. Analysis cannot be performed with the 2004 WHO system because of the few numbers of invasive low-grade tumors.

In the study of Otto et al [115], 310 pT1 tumors were mostly graded as high grade (96%) and only few were low grade (4%) by 2004 WHO system. By 1973 WHO system, these invasive tumors were classified...
into G2 (36%) and G3 (64%) with no G1 tumors identified. The 10-year recurrence–free survival and overall survival did not differ significantly between high grade and low-grade tumors (2004 WHO) or between G2 and G3 tumors (1973 WHO), but the cancer-specific survival between pT1G2 and pT1G3 by 1973 WHO system was shown to be highly significant (p<0.001). This is in contrast to the low grade versus high-grade tumors by 2004 WHO system that did not significantly differ in cancer-specific survival.

In the study by van Rhijn et al [103] of 164 pT1 tumors, the 1973 WHO system (p=0.032) and not 2004 WHO system was significant in univariate analyses for tumor progression. But both WHO grading systems were not significant in the multivariate analysis, in contrast to the reviewed stage and presence of CIS. Kamel et al [116] reviewed 105 pT1 high-grade tumors by 2004 WHO system with median follow-up of 4 years and divided these tumors into G2 (61) and G3 (44) by 1973 WHO grading system. In terms of actuarial disease specific survival, 20 of 44 (45%) patients with high-grade/G2 tumors were alive versus 22 of 61 (36%) patients with high-grade/G3 tumors (p=0.04). In terms of tumor progression, 13 of 44 (30%) of high-grade/G3 tumors progressed versus 12 of 61 (20%) high-grade/G2 tumors (p=0.02). There was a trend for high-grade/G3 tumors to have worse progression free survival rates than high grade/G2 tumors after controlling treatment modality chosen, and was not statistically significant owing to the smaller numbers. In multivariate analysis high grade/G3 was a significant predictor of tumor progression (p=0.05) and marginally non-significant predictor of poor patient survival (p=0.056).

Both W.H.O. (2004) / ISUP and the older 1973 WHO grading systems when applied to pT1 tumors are confronted by the fact that the vast majority of invasive tumors are high-grade (high grade by the W.H.O. (2004) / ISUP system or G2 and G3 by 1973 WHO system), with only few tumors classified as low-grade. Because of the predominance of high-grade tumors, no study has shown the value of W.H.O. (2004) / ISUP system in pure pT1 tumors (without including pTa tumors). The older WHO (1973) system has shown the ability in some studies to provide grade dichotomy (or divisions) in the invasive pT1 tumors (i.e. G2 versus G3 or high-grade G2 versus high-grade G3) (Level 3); such grade assignments are difficult in routine practice, and criteria for grading in invasive settings or impact on management based on grade are not well defined.

It is recommended therefore that when tumors are invasive, irrespective of depth, they should be graded as high grade (Grade C). This rule is also applicable to the general surgical and urologic pathology community as deceptively bland variants such as the nested or small tubular variants that histologically appear low-grade, tend to behave like invasive high-grade tumors of similar stage (Grade C). If for institutional disease management teams or clinical trials (e.g. for some institutions and protocols in Europe), assigning grade G2 and G3 is important, the practice should continue based on respective protocols or institutional guidelines.
endometriosis and resemble its counterparts in the female genital tract. Finally, neuroendocrine carcinoma may arise in pure form or be associated with other forms of bladder carcinoma.

Level I evidence is limited for most bladder carcinoma variants, given their relative rarity. Especially aggressive forms include micropapillary urothelial carcinoma, sarcomatoid carcinoma, undifferentiated carcinoma NOS, signet ring adenocarcinoma and small cell carcinoma, among others. Variants that are easily missed due to challenging histopathological features may result in delayed diagnosis and treatment; a sampling of such variants includes nested urothelial carcinoma, large nested variant of urothelial carcinoma, urothelial carcinoma with small tubules and plasmacytoid urothelial carcinoma.

In general, treatment for muscle-invasive disease involves complete surgical resection (generally radical cystectomy) and lymph node dissection, regardless of morphological subtype. Neoadjuvant or adjuvant chemotherapy may have a role although treatment regimens may vary for some of the histologic types or between institutions. Earlier interventions have been recently described to improve survival and outcomes for patients with micropapillary urothelial carcinoma. As our knowledge of these variants expands, it is likely that more tailored, “personalized” therapies may evolve depending on pathological diagnosis.

I. UROTHELIAL CARCINOMA VARIANTS

1. UROTHELIAL CARCINOMA WITH DIVERGENT DIFFERENTIATION

a) Definition: Urothelial carcinoma has propensity for divergent differentiation, with the most common being squamous differentiation followed by glandular differentiation [117-124]. Virtually the whole spectrum of bladder cancer variants may be seen in variable proportions accompanying otherwise conventional urothelial carcinomas, mostly in cases of high-grade and high-stage disease. The clinical outcome of some of these variants differs from typical urothelial carcinoma, therefore recognition of these variants is important [125-131]. When divergent differentiation is seen together with conventional urothelial carcinoma, the pathologist should use the terminology of “urothelial carcinoma with _____ differentiation”, inserting the type of differentiation observed.

b) Incidence: The actual frequency varies, as this information is not consistently recorded by pathologists. Some form of divergent differentiation may be seen in 7% to 27% depending on the type of specimen (cystectomy vs. transurethral resection) [125-131].

c) Clinical: The presenting symptoms are nonspecific and typical for urothelial neoplasms in general with hematuria as the most common manifestation[125-131].

d) Gross Appearance: No information available.

e) Microscopic Features: Approximately 10% of urothelial carcinomas contain foci of glandular (Figure 27) and approximately 60% show variable amounts of squamous (Figure 28) differentiation. This may not reflect the actual frequency as this information is not consistently or accurately recorded by pathologists. Glandular differentiation is usually in the form of small tubular formations in conventional urothelial carcinoma or as a histology similar to enteric adenocarcinoma (Figure 27). Rarely, a coexistent signet ring cell or mucinous component may be present [117-124].

To designate squamous differentiation, one must see clear-cut evidence of squamous production (intracellular keratin, intercellular bridges or keratin pearls), and the degree of squamous differentiation - when present - usually parallels the grade of urothelial carcinoma (Figure 28). Therefore, the presence of squamous or glandular differentiation in a poorly differentiated neoplasm, particularly at metastatic sites and in the context of a bladder primary, should suggest the possibility of urothelial differentiation. To designate a bladder tumor as squamous cell or adenocarcinoma, a pure or almost pure histology of squamous cell carcinoma or adenocarcinoma is required. From a practical viewpoint, we do make note of prominent squamous or glandular differentiation in urothelial carcinoma using diagnostic terminology such as “invasive urothelial carcinoma with prominent squamous (40%) and glandular (25%) differentiation” [117-124]. In the case of metastatic tumors from the bladder, knowledge of the presence and percentage of divergent differentiation may be useful to facilitate comparison with the bladder primary. The diagnosis of adenocarcinoma is reserved for pure tumors [117-124].

f) Differential Diagnosis: The main differential diagnostic considerations include squamous cell carcinoma and adenocarcinoma. In the urinary bladder, the term squamous cell carcinoma should be reserved for tumors with an exclusive squamous cell component. Basaloid or clear cell-type squamous differentiation can be observed rarely, and the pathologist should be aware of this before making a diagnosis of urothelial carcinoma with a mixed squamous cell component [117-124]. The diagnosis of adenocarcinoma of the bladder is reserved for pure tumors.

g) Ancillary Diagnostic Tests: A recent study found 74% of urothelial carcinomas with squamous differentiation showed expression of urothelial and squamous associated markers (S100P 83%, GATA3
35%, uroplakin III 13%, CK14 87% and desmoglein-3 70%)[132]; although reactivity for individual markers within some tumors did not always correspond with morphologic differentiation. Of the remaining 26%, 4 cases showed an overall ‘squamous’ immunoprofile while 2 cases showed an ‘urothelial’ immunoprofile [132]. This particular study showed that a panel of five antibodies reliably distinguishes carcinomas of the urothelial tract with squamous and urothelial differentiation suggesting potential utility due to management implications. Immunostaining in tumors with both urothelial and squamous differentiation showed a mixed profile. The expression of MUC5AC-apomucin may be useful as immunohistochemical marker of glandular differentiation in urothelial tumors [133].

h) Prognosis: The prognostic significance of squamous or glandular differentiation is unclear, although some studies have suggested an adverse outcome [117-124]. This difference in prognosis may not be apparent when corrected for stage of the disease. Some studies have shown poor response to chemotherapy or radiation therapy, but it is unclear whether the poor response is a reflection of histology or the advanced stage of the disease [125-131]. Some studies have suggested that these variants may be more resistant to chemotherapy or radiation therapy than pure urothelial carcinoma, but this has not been confirmed [125-131]. A recent meta-analysis of reported data suggested that all of the variant histologies portend a worse prognosis than pure urothelial carcinoma [126]. Classic studies suggest that squamous differentiation is associated with high-grade disease and advanced stage and predicts a poor response to chemotherapy, radiotherapy, and surgery [125-131]. In the context of radical cystectomy, a recent series determined that squamous differentiation within urothelial carcinoma was an independent predictor of local recurrence on multivariate analysis [125]. Also, there is no indication that radiotherapy would offer any benefit to mixed urothelial carcinoma with squamous differentiation [125-131]. The presence of mixed histologic features at transurethral resection could indicate locally aggressive disease. Of 91 patients with metastatic carcinoma, cancer progressed despite intense chemotherapy in 83% with mixed adenocarcinoma and 46% with mixed squamous cell carcinoma, whereas it progressed in <30% of patients with pure urothelial carcinoma[125-131].

The presence of squamous or glandular differentiation in locally advanced urothelial carcinoma of the bladder does not confer resistance to MVAC and in fact may be an indication for the use of neoadjuvant chemotherapy before radical cystectomy [131]. Low-grade urothelial carcinoma with focal squamous differentiation has a higher recurrence rate [123].

2. MICROPAPILLARY VARIANT OF UROTHELIAL CARCINOMA

a) Definition: Micropapillary carcinoma (MPC) of the urinary tract is a special type of urothelial carcinoma, which has papillary structures reminiscent of those seen in ovarian papillary serous neoplasms and typically lacks central fibrovascular cores seen within usual papillary urothelial carcinoma [134]. Most cases of MPC have been reported in the urinary bladder, and MPCs of the upper urinary tract including renal pelvis, ureter and ureteropelvic junction have rarely been reported [135,136].

The majority of tumors present with advanced stages and are muscle invasive (≥ T2) at the time of presentation. Histologically, the MP component is encountered in the (a) non-invasive surface component, (b) invasive component and (c) in metastasis. The MP pattern may be pure, but is frequently associated with a high grade conventional urothelial carcinoma. There is no specified criterion required to designate a case as MPC, but most series in the literature have included cases even with <10% to almost pure MP histology [137,138]. The percentage of MP component has been shown
to be a significant adverse prognostic factor with the more MPC component, the worse prognosis[139]. However, since any amount of MPC impacts the prognosis, no percent limitation is required for the diagnosis of MPC, but the percentage of the MPC component should be reported.

b) Incidence: Although it is difficult to estimate the exact number of reported cases of MPC, at least 500 cases of this variant have been reported since the first description of a series of cases in the urinary bladder in 1994 by Amin et al [134]. This rare histological variant comprises 0.6–8.2% of urothelial carcinomas and shows a definite male predominance (male to female ratio, 5:1–10:1), which is higher than in conventional urothelial carcinoma (3:1)[134,137,138,140]. As mentioned above, since the amount of MPC component necessary to make the diagnosis has not been specified, the reported incidence has varied depending on the amount of MPC component deemed necessary for diagnosis. In early studies, the reported incidence of MPC was 0.6–1.0% of UC. Tumors in these series had at least 10% or 20% with most cases displaying greater than 50% of MPC. In a recent series, the incidence was found to be 6-8.2%[140]. In the largest series reported to date, urothelial carcinoma with any amount of a MP component was considered as MPC [137,138]. It is likely that the recently increased incidence of MPC is due to reporting cases with any MPC as well as the increased awareness of MPC by pathologists. Another factor for the different incidence may be the diagnostic criteria of MPC. A recent consensus opinion diagnosis result showed only moderate overall diagnostic reproducibility (k: 0.54). Depending on pathologists, MPC may be overdiagnosed or underdiagnosed[140].

c) Gross Appearance: There are no specific gross features to distinguish from other variants of urothelial carcinoma. MPC shows both surface papillary and deep invasive component. MPC may be grossly papillary, polyloid, nodular, ulcerative and or solid infiltrative. MPC is usually solitary, but may be multifocal. The size of the tumor is variable, ranging from a few millimeters to about 10 cm in greatest dimensions. The appearance of the underlying bladder wall significantly depends on the extent of invasion, which is commonly extensive in MPC [141].

The uninvolved mucosa is usually normal, but sometimes erythematous which may represent microscopic areas of CIS. No currently well defined imaging techniques can reliably diagnose MPC [142].

d) Microscopic Features: The MPC histology has two distinct patterns; on the surface, it forms slender, delicate filiform processes with no or rarely with a fibrovascular core. When cut in cross-sections, these papillae appear as glomeruloid bodies. In the invasive component and in all metastatic sites, the tumor cells are arranged in small tight nests or balls (Figure 29). The tumor cells in the invasive and metastatic components are aggregated in lacunar or stromal retraction spaces, which mimic vascular invasion. This feature is characteristic of the invasive MPC. The spaces may be lined focally by flattened spindled cells or may be devoid of any lining. In most instances, there is no host response to the tumor cells that merely seem to occupy hollow spaces at various random intervals within the tumor. This pattern of lacunae containing neoplastic cells is also seen in the metastatic sites. Multiple small cell nests in the same lacunar spaces are characteristically and frequently seen. MPC always shows a high nuclear grade (high grade by the WHO/ISUP classification) with peripherally oriented nuclei and inverted pattern, although some areas within a neoplasm may parallel low-grade urothelial carcinoma. Lymphovascular invasion (LVI) is present in most of invasive MPCs. A high frequency has been confirmed by Factor VIIIIR-Ag and Ulex europaeus agglutinin I lectin[1] as well as CD 31, CD34 and D2-40 [143]. However, awareness that lacunae of MPC may mimic LVI is important so as not to overdiagnose the presence of this feature as LVI. Psammoma bodies, a feature of ovarian papillary serous neoplasia, are either not present or exquisitely rare.

Cytologic features of MPC include the presence of singly scattered tumor cells with high nuclear to cytoplasmic ratio and pleomorphic nuclei, clustered cells devoid of fibrovascular core (micropapillae), 3-dimensional cell aggregates, cytoplasmic vacuoles, and micropapillae exhibiting some features of low-grade urothelial neoplasms[144]. In addition, urothelial carcinoma in situ is demonstrable in >1/3 of the cases and concurrent glandular or villoglandular differentiation is known to occur; rare cases of mixed trophoblastic differentiation, carcinosarcoma (sarcomatoid carcinoma), pleomorphic giant cell carcinoma, lipid cell variant or plasmacytoid UC have also been reported [145-151].

Figure 29. Micropapillary variant of urothelial carcinoma.
**Differential Diagnosis:** The main differential includes: 1) distinguishing MPC of the bladder from that of the different sites; and 2) how to separate classic MPC from conventional UC with retraction artifact [140,152]. In women, a metastatic papillary serous carcinoma of the ovary or peritoneal primary is the main differential diagnosis from MPC of the bladder, especially if the tumor is originally discovered in the peritoneum, abdominal lymph nodes and mesentery or as a carcinoma of unknown origin. Clinical/radiographic correlation is usually required, but the possibility of a bladder primary may be suggested if there is no obvious primary tumor at another anatomic site. Identification of an admixed urothelial carcinoma of more typical morphology or immunohistochemical support (CK 7, CK 20 and uroplakin III positivity) would be helpful. In a bladder tumor, pure MP histology may raise concern for a primary adenocarcinoma of the bladder; however, the MP architecture is due to neoplastic urothelial cells in a MP configuration and not due to true glandular differentiation as also supported by immunohistochemistry. In primary adenocarcinoma of the bladder, there is a greater variability of gland shape and size and of the range of differentiation in contrast to the typically uniform appearance of MP component of UC. Carcinomas with MP histology have also been reported in the lung, breast, pancreas, colon, stomach and salivary glands. The best markers to identify urothelial MPC are uroplakin and CK20, whereas p63, high molecular weight cytokeratin, and thrombomodulin are less sensitive and specific. Lung MPC is uniformly TTF-1 positive. Breast MPC is ER and mammoglobin positive, while ovarian MPC is ER positive and PAX8/WT-1 positive. No reliable markers for pancreas, stomach and salivary glands have been reported, but CK20 and CDX2 positivity may be useful to make a diagnosis of colon primary. In the metastatic setting, or when MPC occurs without an associated in situ or conventional carcinoma component for the certain organ, staining for uroplakin, CK20, TTF-1, ER and WT-1, and/or PAX8, and mammoglobin is the best panel for accurately classifying the likely primary site of MPC [152].

Another diagnostic challenge is the differentiation of classic MPC from conventional UC with retraction (non-classic). A recent consensus study conducted by Sangoi et al [140] found that interobserver reproducibility for a diagnosis of "classic" and "non-classic" MPCs in the 30 study cases was only moderate (k: 0.54). Although classification as MPC among the 10 "classic" MPC cases was relatively uniform (93% agreement), the classification in the subset of 20 invasive UCs with extensive retraction and varying sized tumor nests (non-classic) was more variable. Classic MPC features included 1) multiple nests within the same lacunar space, 2) intracytoplasmic vacuolization, 3) epithelial ring forms, and 4) micropapillae with elongated and slender nests with average width <4.5 nuclei. Whereas non-classic MPC with retraction usually showed large to medium sized nests with >4.5 nuclei and nest anastomosis and confluence or branching. This study demonstrated that the overall reproducibility for the diagnosis of MPC in invasive UCs showing stromal retraction was only moderate. The diagnosis of MPC was more reproducible when very restrictive criteria were applied, but it is not known whether the use of this diagnostic threshold correlates best with the clinical outcome. These findings clearly suggest that more studies are needed to identify the individual pathological features that might potentially correlate with an aggressive outcome and lack of response to intravesical therapy. Finally, caution should be exercised when considering the use of a reported MPC diagnosis as the sole determinant in selecting therapeutic options for individual patients with invasive urothelial carcinoma.

**Ancillary diagnostic tests:** To make a MP morphology diagnosis, MUC1 expression along the membrane segment facing the stroma [153] has been reported to be a feature of MPCs in other organ systems. Similarly immunohistochemical expression of CA125, HER2/neu and KL-6 [154,155] has been reported as distinctive markers of MPC. However, Sangoi et al stained immunohistochemical expression of MUC1, CA125 and HER2/neu and reported that these markers are not entirely specific for MPC when compared specifically with invasive urothelial carcinoma having prominent stromal retraction. As such, these markers lack reliable diagnostic utility in challenging cases, further case-controlled studies are needed to compare specificity versus invasive urothelial carcinoma with prominent stromal retraction. At present, there are no specific markers for MPC and no published molecular comparative data to address this specific diagnostic issue.

As mentioned in the differential diagnosis, to make a diagnosis of bladder MPC and to differentiate from other sites of primary tumor, the most sensitive marker is reported to be pan-uroplakin, which shows membranous and/or cytoplasmic staining in most of bladder cases with negative for breast, lung and ovary, making it a specific marker for urothelial MPC. Other markers including EMA, CK20, high molecular weight cytokeratin, p63, and thrombomodulin are also positive in urothelial MPC, but less sensitive and specific compared to pan-uroplakin. Other markers including CA125, B72.3, Leu M1, BerEp4, placental alkaline phosphatase have been reported to be positive. Samaratunga and Khoo also reported immunohistochemical findings of MPC similar to conventional urothelial carcinoma with CK7, CK20, EMA, CEA and high molecular cytokeratin. However, CA125 staining was seen only in MPC.
Based on the morphology and immunohistochemical profile of the MPC, Samaratunga and Khoo [156] suggest that MPC may be a form of glandular differentiation in urothelial carcinoma. MPC displays overexpression of p53 and MIB-1, Aurora-A, but no statistically significant difference could be made with conventional urothelial carcinoma except for Aurora-A. Aurora-A overexpression in MPC may play a role in aggressive clinical behavior of MPC [157]. E-cadherin is positive in MPC as seen in usual urothelial carcinoma, whereas plasmacytoid and signet ring cell differentiation in UC shows loss of E-cadherin [158]. The immunoreactivity to Her2Neu and PTEN has been reported in MPC and might be relevant in terms of future targeted therapy [159].

g) Prognosis: There are several important reasons for recognizing MP variant of urothelial carcinoma. Most are muscle invasive at presentation and frequent lymph node and distant metastases with common sites being lung, liver, and bone. (1) There is an ample evidence to suggest that this unique MP configuration of UC connotes a more aggressive clone of neoplastic cells—(a) these tumors are invariably high grade and usually of high stage and are frequently associated with LVI; (b) the amount of MP component is correlated inversely with prognosis, (c) the MP component has a higher DNA index than did conventional urothelial carcinoma; and (d) metastatic sites of tumors have a predominant MP component. (2) Initial presentation with MP histology in metastatic sites should prompt consideration of the possibility of UC, especially if the MP configuration is encountered in the peritoneum, abdominal lymph nodes or mesentry of a male patient with an unknown primary or in a female with normal appearing ovaries. (3) The high association of MPC with muscle-invasive disease should alert the pathologists to recommend a clinician to get a deep biopsy, if the initial biopsy is superficial and lacks muscularis propria. (4) Recent data suggest that because of limited response to intravesical BCG, one group has advocated for early cystectomy for pTa and pT1 tumors with MP histology, as these tumors are unlikely to respond to chemotherapy when used as a secondary treatment modality. Kamat et al [138] from MD Anderson Cancer Center reported BCG treatment in 27 of 44 non-muscle invasive MPCs of bladder (5Ta, 4 CIS and 3ST1), and of these 27 patients, 67% had progression (T2 or greater), including 22% in whom metastatic disease developed. Based on their findings, they reported that the optimal treatment strategy for nonmuscle invasive MPC is radical cystectomy performed before progression. However, this recommendation is not universally accepted as there needs to be confirming studies from other institutions and also due to the interobserver variability in the diagnosis of MPC.

Gaya et al [139] recently reported that tumor stage and patient outcome of MPC may be related to the percentage of the MP component of the carcinoma. Radical surgery is mandatory in muscle-invasive disease, even though patients with lymph node involvement die from the disease. However, in non-muscle-invasive disease and in the absence of associated carcinoma in situ, intravesical BCG treatment may be offered when the MP component of the carcinoma component is a small percentage. The prognosis is uniformly unfavorable; the 5-year and 10-year survival in the largest study was 51 and 24%, respectively. Samaratunga and Khoo [156] reported that the prognosis is related to the proportion and location of the MPC. Cases with moderate or extensive (≥ 10%) MPC are at high risk of being advanced at presentation. Cases with focal (<10%) MPC and surface MPC have a high chance of detection at an early stage.

3. NESTED VARIANT OF UROTHELIAL CARCINOMA

a) Definition: A variant of invasive urothelial carcinoma consisting of small irregularly distributed nests with bland cytology which may simulate benign processes such as Von Brunn nests [143,160-164].

b) Incidence: Rare with less than 100 cases reported in literature between 1979 and 2007 the estimated incidences 0.3% [143].

c) Clinical: The tumor typically affects men in later adulthood (after 50 years of age) [143,162]. The most frequent clinical manifestations are hematuria, urgency and signs of ureteral obstruction. At endoscopy, the tumors may be slightly raised and erythematous or nodular and infiltrative.

d) Gross Appearance: Tumors typically involve urinary bladder most commonly involving a trigone or ureteric orifice. Involvement of ureter or renal pelvis may also be noted. The size range is from less than 1 cm to 8 cm [143].

e) Microscopic Features: The nested variant of urothelial carcinoma typically consists of nests of bland appearing urothelial cells irregularly distributed within lamina propria and often showing invasion of muscularis propria (Figures 30, 31). Overlying papillary tumor or in-situ disease is generally not present. This tumor has different appearances in the superficial and deep aspects. In the superficial zone, the nests are tightly packed but somewhat haphazardly arranged and often confluent with little intervening fibromuscular stroma. Sometimes abortive tubules are noted and this pattern overlaps with urothelial carcinoma with small tubules (see later section). The nests generally have bland cytologic appearance but occasional ones may demonstrate more atypia with pleomorphic nuclei and enlarged nucleoli (Figure 31) [165,166]. In the deeper portions, the tumor cells have a greater degree of cytologic atypia and the cytoplasm tends to be
more eosinophilic than the nests in the superficial portions. Commonly the nested variant is associated with deep infiltration of muscularis propria.

**Figure 30. Nested variant of urothelial carcinoma, low power.**

**Figure 31. Nested variant of urothelial carcinoma, high power.**

**f) Differential Diagnosis:** The main differential diagnosis is a proliferation of Von Brunn nests [167-169]. The latter are generally superficial and closely related to the overlying urothelium. Proliferating Von Brunn nests tend to have a rounded interface with lamina propria and exhibit both architectural and cytological uniformity. In contrast the nested variant of urothelial carcinoma is more architecturally complex with irregularly distributed nests within lamina propria. Confluence and anastomosis of nests is seen and the lesion is often deeply invasive into a muscularis propria. Nephrogenic adenoma may occasionally enter the differential diagnosis although that lesion does not often consist entirely of small nests and cords. It usually has tubular, papillary, cystic or signet-ring features [167,169]. Other neoplasms including paraganglioma, carcinoid tumor, secondary prostatic adenocarcinoma and melanoma may enter the broad differential diagnosis [143,170]. In these cases the selective use of immunohistochemistry can help to resolve the diagnostic problem[170].

g) **Ancillary Studies:** The nested variant of urothelial carcinoma typically displays positivity for high molecular weight keratin (34BE12), cytokeratins 7 and 20 and p63, similar to usual urothelial carcinoma [143,170]. In comparison to benign mimickers such as Von Brunn nests, nested urothelial carcinoma typically shows higher MIB-1 labelling although examples of nested variant of urothelial carcinoma showing low MIB-1 expression have been reported [160,168]. The nested variant of urothelial carcinoma has also been shown to high positivity for p53 in comparison to Von Brunn nests. Loss of p21 and p27 expression has also been observed [160].

**h) Prognosis:** The nested variant of urothelial carcinoma usually presents with muscle invasion and tends to be aggressive [143]. The reported series are relatively small and it is difficult to extrapolate specific prognostic information. Some authors suggest that this tumor is more aggressive than usual invasive urothelial carcinoma while others suggest that the prognosis and clinical course is similar to high grade urothelial carcinoma stage for stage [143,162,171,172]. The optimum treatment for nested urothelial carcinoma has not been established due to the rarity of the tumor. Specifically, no significant benefit of adjuvant chemotherapy or radiation has been established [143,162,172].

**4. LARGE NESTED VARIANT OF UROTHELIAL CARCINOMA**

**a) Definition:** A variant of nested urothelial carcinoma consisting of large, irregular to regular nests with bland cytology [164].

**b) Incidence:** Rare with the only series reporting 23 consult cases over a 9 year interval.

**c) Clinical:** Mean patient age is 63.7 years (39-89) and 86% are male. Typically present with hematuria.

**d) Gross Appearance:** No information available.

**e) Microscopic Features:** Cases are composed of medium to large sized nests with either rounded or irregularly shaped borders, composed of cytologically bland urothelial cells (Figure 32). In a minority of cases the invasive component has a broad, pushing invasive front, similar to that identified in verrucous squamous cell carcinomas. Unlike the nested variant of urothelial carcinoma, the large nests are often separated by broad areas of fibrous tissue and/or smooth muscle with little to no back-to-back nests present. Also unlike usual nested carcinoma a surface component is present in most cases, typically low grade papillary urothelial carcinoma. At the time of diagnosis, the large nests are invasive into the muscularis propria in almost all cases. In a minority of cases, focal areas of conventional patterns of invasive urothelial may be identified [167,169,173].
f) **Differential Diagnosis:** The major diagnostic pitfall is in distinguishing large nested variant from either a proliferation of von Brunn nests or from an inverted growth pattern of non-invasive papillary urothelial carcinoma.

g) **Ancillary Diagnostic Tests:** None available.

h) **Prognosis:** Follow-up was available for 17 of the 23 reported cases with an average interval of 43 months (range 5 months - 9 years). In 11 of 17 patients, there was no evidence of disease, while 3 patients were alive with disease and 3 had died of their disease. In two cases, metastases to the lung were present. While distinguishing the presence of invasion from either an inverted growth pattern of non-invasive papillary urothelial carcinoma or a florid proliferation of von Brunn nests is difficult, recognition of large nested variant of urothelial carcinoma is imperative, as they have the ability to metastasize and result in death [167,169,173].

5. **UROTHELIAL CARCINOMA WITH SMALL TUBULES**

a) **Definition:** A variant of nested urothelial carcinoma having a major component of small to medium sized tubules which may be confused with benign or malignant glandular processes [164,167,169].

b) **Incidence:** Extremely rare with less than a dozen reported cases.

c) **Clinical:** Similar to a nested variant of urothelial carcinoma.

d) **Gross Appearance:** Similar to a nested variant of urothelial carcinoma.

e) **Microscopic Features:** This deceptively bland variant of nested urothelial carcinoma is characterized by irregularly infiltrative small to medium sized tubules usually admixed with small solid nests (Figure 33). The tubules are lined by urothelial-type cells which may be quite attenuated. True cuboidal or columnar cells are not seen. The tumor shows a diffuse pattern of infiltration with haphazard arrangement of nests and tubules. The cytologic appearance is low grade but at least focally, some degree of nuclear pleomorphism may be seen. Invasion of muscularis propria is often seen.

f) **Differential Diagnosis:** The differential diagnosis includes cystitis glandularis and nephrogenic adenoma. The glands of cystitis glandularis are architecturally uniform and are lined by cuboidal to columnar lining cells in contrast to the urothelial-type cells of urothelial carcinoma with small tubules. Nephrogenic adenoma typically displays a tubular pattern but the tubules are often tiny and associated with other typical patterns of nephrogenic adenoma such as microcystic, signet-ring and cord-like areas. Adenocarcinoma of the urinary bladder displays true glandular structures lined by cuboidal or columnar cells. Another important differential diagnosis is secondary adenocarcinoma of prostate [173]. Marker studies for PSA, PAP, high molecular weight keratin, cytokeratins 7 and 20 and p63 are useful to distinguish between secondary prostatic carcinoma and urothelial carcinoma with tubular differentiation [173].

g) **Ancillary Studies:** Urothelial carcinoma with small tubules typically shows the marker profile of urothelial carcinoma which includes positivity for high molecular weight keratin (34BE12, CK7, CK20) [173].

h) **Prognosis:** Little is known about the prognosis of urothelial carcinoma with small tubules. Since urothelial carcinoma with small tubules is often admixed with solid nests and likely represents part of the spectrum of nested urothelial carcinoma, an adverse outcome may occur [174].
6. MICROCYSTIC UROTHELIAL CARCINOMA

a) Definition: A variant of urothelial carcinoma characterized by dilated tubules with microcyts and macrocysts [169,175-177]. It has been suggested that the tumor should have at least 25% microcystic change in order to be designated as microcystic urothelial carcinoma [143].

b) Incidence: Rare with less than 20 reported cases [143].

c) Clinical: No specific clinical features.

d) Gross Appearance: Gross features similar to nested and small tubular variants of urothelial carcinoma occasional 1-2 mm macrocysts may be identified.

e) Microscopic Features: The tumor consists of tubular structures which are cystically dilated forming microcysts and occasionally macrocysts (Figure 34). Eosinophilic luminal material and necrotic debris are often seen. Luminal secretions may display a targetoid appearance. The luminal secretions stain positively for periodic acid-Schiff and alcian blue stains. Calcifications may be present within the cysts. Urothelial cells, many of which are flattened, line the cystic structures. Focal mucinous differentiation may be noted but cuboidal or columnar cells are not seen. The nuclei are typically bland although focal atypia may be identified. The tumor has an infiltrative appearance with involvement of lamina propria and muscularis propria. A stromal reaction of varying degree may be identified. The microcystic pattern may be associated with more typical nested and small tubular patterns of urothelial carcinoma as described in prior sections of this publication.

f) Differential Diagnosis: The most common differential diagnosis is nephrogenic adenoma and cystitis cystica glandularis. The latter lesion is superficial and shows very regular with rounded epithelial-stromal borders. The glands of cystitis cystica are often lined by attenuated cuboidal cells rather than urothelial-type cells. Nephrogenic adenoma sometimes has a microcystic appearance and enters the differential diagnosis with microcystic urothelial carcinoma, however, nephrogenic adenoma typically displays other patterns as well. In problematic cases, a racemase and Pax 2 or 8 stains maybe useful since it strongly decorates nephrogenic adenoma.

Additionally, primary vesicular adenocarcinoma and secondary adenocarcinoma is sometimes in the differential diagnosis. Immunohistochemical studies may be required to resolve the differential diagnosis [170].

g) Ancillary Studies: Microcystic urothelial carcinomas stain in a similar fashion to other urothelial carcinomas [143,177-179].

h) Prognosis: Due to the limited number of cases, very little is known about the prognosis of this variant, however, in reported cases, the prognosis has been similar to usual invasive urothelial carcinoma [143].

7. LYMPHOEPITHELIOMA-LIKE CARCINOMA

a) Definition: Lymphoepithelioma-like carcinoma of the urinary bladder is a variant of urothelial carcinoma in which there is a dense inflammatory infiltrate surrounding nests of poorly differentiated carcinoma cells, imparting a close resemblance to the well-known lymphoepitheliomas of the head and neck.

b) Incidence: Although lymphoepithelioma-like carcinoma was first recognized two decades ago in 1991, the largest series is 28 cases and the next three largest series encompass only 13, 11, and 9 cases so lymphoepithelioma-like carcinoma of the bladder appears rare [180-184].

c) Clinical: In the 4 largest series, 70% of the patients have been men. Ages ranged from 44 to 90 years with a median age of 70 years. The age distribution for women appears to be the same as for men. The age distribution for patients with pure lymphoepithelioma-like carcinoma does not appear to be different from that for patients with mixed tumors. Macroscopic hematuria is the most common presenting complaint. Urgency, burning sensation at micturition, increased frequency of micturition, and difficulty in micturition have also been reported, although the last two may be symptoms of concurrent prostatic hyperplasia. Little information is available about the cystoscopic appearances of these tumors.

d) Microscopic Features: As the name indicates, the essence of the histology of these tumors is a resemblance to the lymphoepitheliomas of the nasopharynx: syncytial-looking nests sheets and cords of large poorly differentiated carcinoma cells in a stroma heavily infiltrated by lymphocytes.

Figure 34. Microcystic urothelial carcinoma.
(Figure 35). The carcinoma cells have large vesicular nuclei with prominent nucleoli and mitotic figures are usually numerous. Rarely, the nuclei may be dramatically pleomorphic [185]. The lymphoid infiltrate may include populations of plasma cells, histiocytes, and granulocytes. While some lymphoepithelioma-like carcinomas are tumors composed entirely of this element, many times the diagnosis is applied when areas of lymphoepithelioma-like carcinoma are found in tumors which also contain garden-variety urothelial carcinoma, with or without other variants of urothelial carcinoma. With no well-defined lower limit for the amount of lymphoepithelioma-like carcinoma needed to support the diagnosis, it is possible that this variant is underdiagnosed. Amin et al stratified their cases into those composed purely of lymphoepithelioma-like carcinoma, those composed predominantly of lymphoepithelioma-like carcinoma, and those with only focal lymphoepithelioma-like carcinoma [180]. Tamas et al simplified this approach by stratifying their cases into those composed purely of lymphoepithelioma-like carcinoma and those in which other elements were present. This distinction appears to have prognostic implications (vide infra) [183].

**e) Ancillary Diagnostic Tests:** In most cases, no ancillary tests should be required to make the diagnosis. However, if lymphoma is a consideration on routine sections, immunohistochemistry to detect markers of epithelial differentiation will quickly clarify the situation because the carcinoma cells mark strongly with antibodies to a variety of markers of epithelial differentiation. Cytokeratin AE1/3, epithelial membrane antigen, cytokeratin 7, and cytokeratin 8 are some of the most frequently detected epitopes. Tumor protein p53 is also frequently detectable in lymphoepithelioma-like carcinoma of the urinary bladder. Epstein-Barr virus is found in nasopharyngeal carcinomas but is not found in lymphoepithelioma-like carcinoma of the urinary bladder [186,187].

**f) Prognosis:** For 28 patients from the major series with pure lymphoepithelioma-like carcinoma of the urinary bladder with follow up of 4 months to 216 months (median 29 months) only one is recorded as having died of the carcinoma and only 2 more are recorded as having spread or recurrence but had not died at the time of the report. The outlook for those with mixtures of other elements may be less favorable. For 10 patients with focal lymphoepithelioma-like carcinoma of the urinary bladder, 9 died of the carcinoma and 1 died shortly after diagnosis of other causes. For 29 patients with “predominant” or “mixed” lymphoepithelioma-like carcinoma of the urinary bladder, 10 died of the carcinoma and 3 had major progression of the carcinoma at the time of the report. While the numbers are small, the differences in reported outcomes between pure lymphoepithelioma-like carcinoma and tumors with other components seems likely to matter. In pathology reports, it would be appropriate to state whether or not the tumor is pure lymphoepithelioma-like carcinoma.

### 8. LIPOID-RICH VARIANT OF UROTHELIAL CARCINOMA

**a) Definition:** Lipid-rich (lipoid) variant is defined by the presence of large carcinoma cells with multiple large, clear cytoplasmic vacuoles, morphologically similar to lipoblasts [188].

**b) Incidence:** This is a rare variant of urothelial carcinoma. Following the initial description [189], two published series included a total of 32 patients [148,190].

**c) Clinical:** Patients have typical symptoms of urothelial cancer; all studied cases had hematuria but other symptoms included pain, irritation and obstruction. There is a striking (>90%) predominance of males with most patients in the 7th decade of life.

**d) Gross Appearance:** Cystoscopically and grossly these tumors show no distinctive features. Most cases of the lipid-rich variant of urothelial carcinoma arise in the bladder.

**e) Microscopic Features:** The low power appearance is that of high-grade urothelial carcinoma admixed with large, multi-vacuolated cells that constitute 10-50% of the lesion [148]. At high-power, the diagnostic cells have optically clear vacuoles which often indent an eccentric nucleus (Figure 36). Some cases may also exhibit other subtypes of urothelial carcinoma [148,191,192]. Histochemistry and electron microscopy indicate that the vacuoles contain lipid rather than mucin [117,148]. The lipidized cells are carcinoma cells and have similar immunoprofile to urothelial carcinoma and stain with EMA, cytokeratins (including cytokeratin 7 in all cases and cytokeratin 20 and 34BE12 in most.
cases) and more specific urothelial markers such as thrombomodulin. They are negative for S100 [148].

**Figure 36. Lipoid-rich variant of urothelial carcinoma. Solid sheets of high-grade urothelial carcinoma with abundant vacuolated clear cells, many of which have a multivacuolated, ‘lipoblast-like’ appearance (arrows).**

**f) Differential Diagnosis:** The main differential diagnosis includes sarcomatoid carcinoma with heterologous liposarcomatous differentiation and signet ring cell carcinoma. As both tumors can be either primary or secondary [193,194], this may be of importance.

**g) Ancillary Diagnostic Tests:** Lipid rich cells are negative for mucin histochemical stains and S100 immunostain. As these cells are immunopositive for cytokeratin, a panel of mucin stains, S100 immunostain and cytokeratin immunostain may be useful to rule out sarcomatoid and signet ring cell carcinoma [121,148,195]. Tumors retain the immunoprofile of usual type urothelial carcinoma (positive for cytokeratin 7, and focally positive for thrombomodulin, cytokeratin 20 and high-molecular weight cytokeratins) [121,170].

**h) Prognosis:** The outcome for this variant is poor. In two series [148,190] that included 32 cases, 27 (84%) were muscle-invasive or beyond (and all of those not diagnosed as muscle-invasive were staged based on transurethral tumor resection). The vast majority of patients (94%) had progressive (local or metastatic) disease and death occurred in almost two thirds of patients.

9. **CLEAR CELL (GLYCOGEN RICH) VARIANT OF UROTHELIAL CARCINOMA**

**a) Definition:** Cytoplasmic clearing is focally present in many, otherwise typical, urothelial carcinomas [124] as well as in occasional cases of urothelial dysplasia [196]. In rare instances, clear cell change is the predominant pattern in which case the term clear cell variant of urothelial carcinoma is used [197].

**b) Incidence:** Rare with less than 20 documented cases in the English literature [198-203] and has so far not detailed in any large-scale series.

**c) Clinical:** Patients present with typical symptoms of urothelial carcinoma, mainly hematuria. Mean age is 64 (41-82) years.

**d) Gross Appearance:** Most cases occur in bladder but ureter/renal pelvis and urethral origin are also described [198,200,201]. There is no information available to suggest that gross appearance of tumors differ from usual type.

**e) Microscopic Features:** Tumors are typically high-grade and invasive with papillary and/or solid growth pattern similar to usual type urothelial carcinoma. In the majority of cases, more typical urothelial carcinoma is recognized elsewhere [117] and tumors may also display other variant types [199]. Tumor cells are large with abundant clear cytoplasm and well defined cell membranes and centrally placed pleomorphic nuclei (Figure 37).

**Figure 37. Clear cell (glycogen-rich) variant of urothelial carcinoma. Expansile, invasive nests sheets of high-grade urothelial carcinoma showing clear cytoplasm.**

**f) Differential Diagnosis:** It is important to recognize that clear cell variant urothelial carcinoma can be confused histologically with other clear cell neoplasms. Clear cell adenocarcinoma [204-206] and metastatic renal cell carcinoma [207-211] both enter into the differential diagnosis as may on occasion prostatic adenocarcinoma and paraganglioma [212]. Finally, urothelial carcinomas of usual type frequently exhibit artifactual cytoplasmic clearing, especially in TURBT specimens where diathermy was used.

**g) Ancillary Tests:** Immunohistochemistry is similar to that of usual type urothelial carcinoma, i.e. positive for high-molecular weight cytokeratins, cytokeratin 7, p63, GATA-3, thrombomodulin and variably positive for cytokeratin 20 [117,170,202,203,213]. Negativity for renal, prostatic and neuroendocrine markers may be of help in above differentials.
h) Prognosis: The prognostic and therapeutic implication of clear cell variant histology remains uncertain given lack of large series. Tumors are typically muscle invasive [198-203] and have been associated with a high (50%) frequency of nodal metastases [198-203]. See Table 9.

Table 9. Clear cell variant. Small series and case reports. Gender, age and stage

<table>
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<th>Reference</th>
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<tr>
<td>Braslis et al, 1997</td>
<td>2</td>
<td>T4</td>
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</tr>
<tr>
<td>Braslis et al, 1997</td>
<td></td>
<td>T3+</td>
<td>6 months AWOT</td>
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<td>Braslis et al, 1997</td>
<td></td>
<td>T3+</td>
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<td>T3</td>
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<td>T3+</td>
<td>7 months AWOT</td>
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<td>T3+</td>
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AWOT, alive without evidence of tumor.

10. UROTHELIAL CARCINOMA WITH RHABDOID FEATURES

a) Definition: Urothelial carcinoma with rhabdoid differentiation is a rare, aggressive tumor. Typically, in adults, rhabdoid features are seen within an otherwise poorly differentiated conventional urothelial carcinoma [214]. “Pure” rhabdoid tumors of the bladder (extra-renal malignant rhabdoid tumor) are even rarer, and those reported have occurred in pediatric patients [215-217].

b) Incidence: A specific incidence is unknown, given the rarity of these tumors in the bladder. Approximately 6 cases have been reported in adults, all associated with other morphologies including conventional urothelial carcinoma, malignant fibrous histiocytoma, and small cell, sarcomatoid, and myxoid histologies [218-220]. One case of urothelial carcinoma with sarcomatoid growth and rhabdoid differentiation in a 2 year old girl has also been reported [221]. “Pure” rhabdoid tumors of the urinary bladder are exceedingly rare with only 3 possible cases reported to have occurred in pediatric patients [215-217].

c) Clinical: In adults, most of the tumors have occurred in men with an age range of 53-86 years (mean 68.7 years). In the pediatric cases, all patients have been girls; at presentation, one patient was 2 years old, two were 4 years of age and one was six years old. Hematuria appears to be the most common presenting sign.

d) Gross: These tumors do not have a specific gross appearance; some have been described as a polyoid or submucosal mass [216,217].

e) Microscopic Features: Tumors with rhabdoid differentiation have a very distinct microscopic appearance. They are characterized by large discohesive tumor cells that have distinct cell borders, abundant cytoplasm with a perinuclear eosinophilic inclusion, and a large nucleus, sometimes eccentrically located within the cell, with a prominent nucleolus (Figure 38). The tumor cells may be arranged singly, in small clusters or in more diffuse sheets. Ultrastructural studies have shown that the cytoplasmic inclusion consists of whorls of intermediate filaments.

f) Differential Diagnosis: Given that most bladder tumors with rhabdoid features, at least in adults, are poorly differentiated urothelial carcinomas morphologically, diagnoses should not be too problematic. If, however, the entire tumor consists of rhabdoid cells, the main differential diagnosis would be an extra-renal malignant rhabdoid tumor. Much less likely would be other tumors with dense eosinophilic cytoplasm, including adrenal cortical carcinoma, hepatocellular carcinoma, rhabdomyosarcoma, and epithelioid angiomyolipoma.

g) Ancillary Diagnostic Tests: Malignant rhabdoid tumors have a deletion or mutation of the hSNF5/INI1 gene on chromosome 22q11.2 [222,223]. For bladder tumors that consist entirely of rhabdoid cells, some advocate that molecular analysis should be performed to determine if the tumor is a primary extra-renal malignant rhabdoid tumor or a urothelial carcinoma with rhabdoid differentiation [214]. Loss
of nuclear INI1 immunohistochemical expression has been demonstrated to be useful in distinguishing malignant rhabdoid tumors from other tumors that may demonstrate rhabdoid features [224] and, therefore, this test could also be performed.

**h) Prognosis:** In general, bladder urothelial carcinomas with rhabdoid differentiation are aggressive high grade, high stage neoplasms and the patient prognosis is poor [214,219,220]. For the pediatric patients diagnosed with "pure" rhabdoid bladder tumors, two were alive without evidence of disease at follow-up of 2 years and 9 years [216,217]. Given the behavior of these tumors, at least in adults, radical resection seems prudent. Some pediatric patients received chemotherapy and/or partial cystectomy or transurethral resection.

11. **PLASMACYTOID UROTHELIAL CARCINOMA**

**a) Definition:** Plasmacytoid urothelial carcinoma is a rare variant of urothelial carcinoma characterized by tumor cells that morphologically resemble plasma cells. This malignant tumor has been recognized by the most recent World Health Organization classification as a distinct variant of urothelial carcinoma [225].

**b) Incidence:** This tumor is not common; the literature contains individual cases reports and relatively small series [150,184,192,226-239]. To date, less than 100 cases have been reported. In one series of 720 high grade urothelial carcinomas of the bladder, the incidence of the plasmacytoid urothelial carcinoma was less than 1% [228], and in another series of 260 invasive urothelial carcinomas, the plasmacytoid variant accounted for 2.7% of cases [231].

**c) Clinical:** The majority of patients with plasmacytoid urothelial carcinoma are men [150,184,192,226-239]. The age range at presentation is broad (46-89 years). In some of the larger series, the mean age at presentation was 64.3 years [235], 66.2 years [227], 67 years [150] and 70 years [233]. Most patients present with hematuria, with fewer complaints related to irritative voiding symptoms [150,192,226,227,230,231,233,235,238,239].

**d) Gross Appearance:** The gross findings are non-specific and little information is provided in the literature. Only a few reports provide a description of the tumors appearance which includes sessile [192] and ulcerated, firm mass or masses [227].

**e) Microscopic Features:** The tumor is characterized by discohesive round to oval tumor cells with dense eosinophilic cytoplasm which may occasionally contain small vacuoles [150,235]. The nuclei are round to oval and hyperchromatic and are located eccentrically within the cell (Figure 39). Typically the degree of nuclear pleomorphism is low to moderate. Binucleation may be present [150,233]. Nucleoli may be present. The tumors cells are often in a stroma that appears edematous or myxoid and can be arranged in cords, small nests, sheet-like or scattered discohesive cells [214,233,235]. The plasmacytoid tumor cells usually co-exist with conventional urothelial carcinoma, sarcomatoid carcinoma, nested or micropapillary urothelial carcinoma, glandular morphology, urothelial carcinoma in situ or high grade papillary urothelial carcinoma [150,228,233,235].

**f) Differential Diagnosis:** At cystectomy, plasmacytoid carcinoma is usually associated with conventional urothelial carcinoma. In the setting of a small bladder biopsy or metastatic tumor containing only plasmacytoid cells and the absence of a precursor urothelial neoplasm (in situ carcinoma or papillary urothelial carcinoma) in a bladder biopsy, the differential diagnosis of plasmacytoid urothelial carcinoma is broad and includes lymphoma/plasmacytoma, malignant melanoma, rhabdomyosarcoma, lobular breast carcinoma, gastric adenocarcinoma, neuroendocrine carcinoma, paraganglioma [214,235].

**g) Ancillary Diagnostic Tests:** Plasmacytoid urothelial carcinomas are positive for pancytokeratin, CK7, CK20 and uroplakin III [150,233,235,240]. CD138 is a marker expressed in normal and malignant plasma cells and is also expressed in plasmacytoid urothelial carcinoma [150,232-234,240]; therefore, it cannot be used alone to diagnose plasmacytoid urothelial carcinoma. In one of the largest and most recent studies, 78% of the tumor cells were positive for CD138 [240]. In this same study, 64.5% of the tumors had loss of membranous E-cadherin expression and the authors propose that loss of this expression is a feature of plasmacytoid urothelial carcinoma. Depending on the specific differential diagnosis, other immunohistochemical markers can be performed as necessary.

**h) Prognosis:** Plasmacytoid urothelial carcinoma typically presents at an advanced stage and, in

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Figure 39. Plasmacytoid urothelial carcinoma.
general, the prognosis is poor [150,214,233,235,240]. Treatment options are variable. Some patients receive neoadjuvant or adjuvant chemotherapy and resection may consist of a transurethral resection or cystectomy.

12. SARCOMATOID CARCINOMA OF THE URINARY BLADDER

a) Definition: A malignant urothelial-derived carcinoma that displays both spindle cell and epithelial elements (formerly “carcinosarcoma”).

b) Incidence: Sarcomatoid carcinoma accounts for approximately 0.6% of all bladder cancers [241,242].

c) Clinical: The mean patient age is 66 years and the male to female ratio is 3:1. Similar to other bladder carcinomas, patients with sarcomatoid carcinoma typically present with hematuria [243-251].

d) Gross Appearance: The majority of lesions appear as a solitary, polypoid mass that may involve any portion of the bladder.

e) Microscopic Features: The spindle cell component usually shows high-grade morphology with nondescript architecture that often resembles malignant fibrous histiocytoma. (Figure 40) Heterologous differentiation is often present that may contain - in decreasing order of frequency - areas that resemble osteosarcoma, chondrosarcoma, rhabdomyosarcoma, liposarcoma, angiosarcoma or a mixture of sarcomatoid histologies [245,247]. Despite the morphologic resemblance to sarcoma, it is currently recognized that these spindle cell areas are derived from an underlying epithelial malignancy, hence the revised terminology of “sarcomatoid carcinoma.” Often associated with areas of sarcomatoid morphology may be foci of overlying flat urothelial carcinoma in situ or adjacent invasive high grade urothelial carcinoma, squamous cell carcinoma, adenocarcinoma, or small cell carcinoma.

f) Differential Diagnosis: The differential diagnosis includes benign conditions such as pseudosarcomatous myofibroblastic proliferations (including postoperative spindle cell nodules and inflammatory myofibroblastic tumors) or more aggressive lesions such as urothelial carcinoma with chondroid or osseous metaplasia, and leiomyosarcoma [252,253].

g) Ancillary Diagnostic Tests: The immunohistochemical profile of sarcomatoid carcinoma includes immunoreactivity for pancytokeratin, high molecular weight cytokeratin, CK5/6 and p63. Smooth muscle actin is only variably positive at best and Alk-1 is negative – these markers are frequently expressed in inflammatory myofibroblastic tumors/pseudosarcomatous myofibroblastic proliferations and leiomyosarcomas [254,255].

h) Prognosis: An estimated 70% of patients die within 2 years of diagnosis. Compared with patients with pure urothelial carcinoma, patients with sarcomatoid carcinoma are at a greater risk for death even after adjusting for the stage at presentation.

13. UNDIFFERENTIATED UROTHELIAL CARCINOMA WITH TROPHOBLASTIC GIANT CELLS

a) Definition: Trophoblastic differentiation may be seen in several settings in urothelial carcinoma: 1) Serologically and/or immunohistochemically in otherwise typical urothelial carcinoma; or 2) Morphological evidence of trophoblastic differentiation either with scattered trophoblastic giant cells in urothelial carcinoma or with a biphasic tumor indistinguishable from choriocarcinoma [256-260]. It is considered that this phenomenon represents either morphologic and/or functional trophoblastic differentiation from reactivation of embryonal cellular programs in tumor cells.

b) Incidence: 1) Human chorionic gonadotropin (HCG) and to a lesser extent human placental lactogen (HPL) and pregnancy-specific beta-1-glycoprotein (SP-1) immunoreactive cells have been found in a minority of urothelial carcinomas, typically high grade. Although different grading systems have been used, the incidence for high grade tumors has been 19%, 21%, 40%, and 55% in various studies. Most studies have found no immunohistochemical HCG production in low grade tumors, although one study found 26% [229,256,261-263]. Serum HCG levels have also been shown to be elevated in some of the cases with immunohistochemical evidence of HCG expression.

c) Clinical: In patients with usual urothelial carcinoma expressing HCG immunohistochemically or by the presence of scattered syncytiotrophoblastic giant cells, there is no endocrinologic manifestations related to HCG. Tumors with pure choriocarcinoma or choriocarcinoma associated with poorly differentiated urothelial carcinoma have in some cases been associated with gynecomastia.

Figure 40. Sarcomatoid urothelial carcinoma.
d) **Gross Appearance:** High grade tumors associated immunohistochemical evidence of HCG or those with choriocarcinoma usually have been described as large, exophytic, or fungating, often with hemorrhage and necrosis.

e) **Microscopic Features:** Areas of high grade pleomorphic urothelial carcinoma, whether non-invasive papillary, CIS, or invasive are the most likely to immunohistochemically express HCG. The HCG positive cells morphologically look indistinguishable to adjacent HCG negative cancer cells. Morphological evidence of trophoblastic differentiation shows either scattered syncytiotrophoblastic giant cells or choriocarcinoma with both syncytiotrophoblastic giant cells admixed with cytotrophoblasts indistinguishable from choriocarcinoma. Scattered syncytiotrophoblastic giant cells can be seen in a wide spectrum of urothelial carcinomas including noninvasive papillary low and high grade urothelial carcinoma, as well as invasive carcinoma. Many cases reported as choriocarcinoma are not classic choriocarcinomas and when their photomicrographs are evaluated they represent undifferentiated urothelial carcinoma with scattered tumor giant cells. Cases which appear histologically identical to choriocarcinoma typically are admixed with high grade urothelial carcinoma. Even rarer cases appear to be typical choriocarcinoma from inception without associated urothelial carcinoma (Figure 41).

f) **Differential Diagnosis:** Urothelial carcinoma with trophoblastic differentiation can be confused with choriocarcinoma, whereby inappropriate chemotherapy may be utilized or there could be a delay in treatment while looking for a primary elsewhere. In the setting of a primary choriocarcinoma of the bladder, spread should be excluded from a gynecological or testicular primary, in women and men, respectively.

g) **Ancillary Diagnostic Tests:** Comparative genomic hybridization showed that both the urothelial carcinoma and choriocarcinoma shared losses of chromosomes 9 and 17, similar to the genetic findings previously reported for urothelial carcinoma [264]. The less well-differentiated choriocarcinomatous component showed more genetic alterations than the papillary urothelial carcinoma component. In a case of micropapillary urothelial carcinoma and choriocarcinoma, the trophoblastic component was positive for high molecular weight cytokeratin, which typically is not seen in trophoblasts yet can be seen in urothelial carcinoma. One case of pure choriocarcinoma has been shown to have an isochromosome 12p, as seen in germ cell tumors [265]. All of the above findings support that choriocarcinoma is of urothelial origin and “acquires” varying degrees of trophoblastic differentiation.

h) **Prognosis:** HCG immunoreactivity in pretreatment in some studies has been a strong predictor of treatment response (22 of 29 patients with HCG-positive specimens did not respond to treatment versus 29 of 71 patients with HCG-negative specimens. Of the few patients with choriocarcinoma, most have died of disease. Although there has been anecdotal treatment specifically directed at trophoblastic tissue, it has failed to influence the course of the disease. Falling levels of βHCG is not invariably associated with tumor response to chemotherapy.

14. **UNDIFFERENTIATED UROTHELIAL CARCINOMA WITH OSTEOCLASTIC GIANT CELLS**

a) **Definition:** Tumors closely recapitulating the morphology of osteoclastic giant-cell tumors of bone or soft parts, with a biphasic tumor composed of both mononuclear cells and osteoclast-like giant cells. Tumors are considered a variant of urothelial carcinoma based on their association with usual urothelial carcinoma and various ancillary studies (see below).

b) **Incidence:** Rare with the largest series composed of 6 cases from a consult service [266-271]. As of 2006, there were 20 reported cases with a few case reports reported subsequently.

c) **Clinical:** Approximately two-thirds of patients are male with most in their 7th decade. The presenting symptoms are nonspecific and typical for urothelial neoplasms in general with gross hematuria as the most common manifestation. Other complaints reported in the literature are flank pain, renal colic, and dysuria.

d) **Gross Appearance:** Approximately 50% are located in the renal pelvis and involve the kidney.

e) **Microscopic Features:** Neoplasms closely recapitulate giant-cell tumors of bone and soft tissues.
They are composed of a mixture of oval to plump mononuclear cells and multinucleated osteoclast-like giant cells, which form sheets and nodules (Figure 42). The stroma is richly vascularized with frequent areas of erythrocyte extravasation, occasionally forming large blood filled lakes. Large areas of necrosis are seen in a minority of cases. Osteoclast-like giant cells exhibit phagocytic features with erythrocytes, hemosiderin, mononuclear cells, or debris readily found within their cytoplasm. Neoplasms are unencapsulated and demonstrated a tongue-like infiltrative growth pattern. Lymphovascular invasion is present in many cases. The vast majority of cases are associated with either CIS or non-invasive high grade papillary urothelial carcinoma.

Figure 42. Undifferentiated urothelial carcinoma with numerous osteoclastic giant cells.

**Differential Diagnosis:** One of the differential diagnoses would be a sarcomatoid urothelial carcinoma, if associated with a conventional urothelial carcinoma component. If conventional urothelial carcinoma was not identified, the tumor might not be recognized as a variant of urothelial carcinoma. It may be misdiagnosed as a sarcoma, either primary in the bladder or spread to the bladder from an occult primary.

**Ancillary Diagnostic Tests:** In most but not all cases, the mononuclear cells immunohistochemically demonstrate epithelial differentiation with focal positivity for various keratins or epithelial membrane antigen. Ultrastructurally, the mononuclear cells display few desmosomes, microvilli, and intracytoplasmic keratin. The multinucleated cells have identical morphological and immunohistochemical properties of osteoclasts; positive for CD-68, LCA, CD51 and CD54, and primarily negative for cytokeratins and EMA. Varying percentages of mononuclear cells express alpha-smooth muscle actin, desmin, S-100, and CD68. The mononuclear cells have a relatively high proliferation index of between 20-50%. Based on these findings the mononuclear cells are regarded as undifferentiated urothelial carcinoma with the osteoclast-like giant cells representing reactive histiocytes.

**Prognosis:** Renal pelvis tumors are often high stage at presentation (pT3) with invasion of the renal parenchyma, hilar adipose tissue, and thick walled veins. Bladder tumors have been of variable stage from T1 to T3. In many cases, the disease-free follow-up is too short to be useful. Of cases with more meaningful yet still short follow-up, about 50% of patients have been without evidence of disease for 1.5-3.5 years. The remaining approximately 50% of patients have died of disease within a short time with pulmonary metastases the most common site of distant disease. Death typically occurs less than 1 year following radical surgery. Extensive surgical excision appears to be the common consensus for primary or recurrent lesions until the treatment benefits of adjuvant chemotherapy or radiotherapy can be established.

**15. UNDIFFERENTIATED CARCINOMA (INCLUDING GIANT CELL CARCINOMA)**

**Definition:** Carcinomas of the urinary bladder with a phenotype composed of sheets or isolated undifferentiated cells that do not fit into urothelial, squamous, adenocarcinoma or any other recognized category of bladder carcinoma [117,118,120,121,149,188,199,272,273]. Some authorities would classify these cases as large-cell undifferentiated carcinoma [120,149,273]. Others may prefer to denote these lesions as high-grade urothelial carcinoma, given that this is the most common cancer within the bladder and that this pattern of tumor most likely represents the most poorly differentiated manifestation of conventional urothelial carcinoma (Figure 43) [120,149,273]. Giant cell carcinoma is an undifferentiated carcinoma of the bladder that occasionally may be composed predominantly or purely of poorly differentiated, pleomorphic, multinucleated, and multinucleated anaplastic cells with abundant eosinophilic or amphophilic cytoplasm [117,118,120,121,149,273]. The tumor cells often contain multiple nucleoli and are similar to giant cell carcinomas seen in the lung and in other parts of the body (Figure 44) [274].

**Incidence:** Rare with the largest series composed of 8 cases of large cell undifferentiated carcinoma, five of them seen in consultation, and an additional series of 8 cases of giant cell carcinoma [149,273].

**Clinical:** The presenting symptoms are nonspecific and typical for urothelial neoplasms in general with gross hematuria as the most common manifestation. Approximately two-thirds of patients are male with most in their 6th or 7th decade. Large cell undifferentiated and giant cell carcinomas present at an advanced stage [149,273].

**Gross Appearance:** No information available.

**Microscopic Features:** Neoplasms closely recapitulate large-cell undifferentiated or giant-
cell carcinoma seen in the lung and in other parts of the body [274]. They are composed of sheets of large polygonal or round cells with moderate to abundant cytoplasm and distinct cell borders [117,118,120,121,149,188,199,272-274]. The architectural pattern of the tumor varies from infiltrating tumor to solid expansile nests of undifferentiated cells. Pleomorphic giant cells are prominent in the giant cell variant. Typical or atypical mitotic figures are common. Rarely, the stroma is hypocellular and desmoplastic. The vast majority of cases are associated with invasive high grade conventional urothelial carcinoma [149,273]. Lymphovascular invasion is present in many cases.

f) **Differential Diagnosis:** If present in a metastatic site, the histology of undifferentiated carcinoma would not suggest an urothelial primary [117,118,120,121,149,188,199,272-274]. The high degree of nuclear anaplasia helps differentiate giant cell carcinoma from the osteoclast-type giant cells that may be seen in urothelial carcinoma [267]. Other giant cells that may be seen with urothelial carcinoma include syncytiotrophoblastic giant cells or foreign body giant cells secondary to previous biopsy or resection. In limited samples, undifferentiated carcinoma may be misdiagnosed as secondary carcinoma or sarcoma, a pitfall of paramount importance for its clinical management [117,118,120,121,149,188,199,267,272-274].

g) **Ancillary diagnostic tests:** Immunohistochemical staining demonstrated that large –cell undifferentiated carcinoma cases were positive for cytokeratins AE1/AE3 and 7; CAM 5.2, CK20, thrombomodulin and Uroplakin III were positive in 6, 3, 3 and 2 cases, respectively.2 Both pleomorphic giant cell and associated conventional urothelial carcinoma were positive for cytokeratins 7, CAM 5.2 and AE1/ AE3, and epithelial membrane antigen; P63, thrombomodulin and Uroplakin III were positive in 6, 3 and 2 cases, respectively. 1 Other immunohistochemical markers performed in the differential diagnosis context included α-Feto-protein, βHCG, PSA, Vimentin, synaptophysin and chromogranin and all were negative [149].

h) **Prognosis:** Large-cell undifferentiated bladder carcinoma is an aggressive variant of urothelial carcinoma [117,118,120,121,149,188,199,267, 272-274]. All patients had advanced stage cancer (≥ pT3); and 87.5 % had lymph node metastases. 20 On follow up 75% of patients died of disease from 5 to 26 months and 2 patients were alive with metastases at 6 and 14 months. The prognosis of large-cell undifferentiated bladder carcinoma was compared with conventional urothelial carcinoma of similar stages showing survival differences (P=0.0004). Five (62%) of patients with giant cell carcinoma died of disease from 6 to 17 months and 2 patients were alive with metastases at 11 and 19 months. One patient had no evidence of disease at 74 months [149]. Extensive surgical excision appears to be the common consensus for primary or recurrent lesions until the treatment benefits of adjuvant chemotherapy or radiotherapy can be established.

Figure 43. Giant cell carcinoma of urinary bladder.

Figure 44. Giant cell carcinoma of urinary bladder.

II. SQUAMOUS CELL CARCINOMA

1. SQUAMOUS CELL CARCINOMA, NON-SCHISTOSOMAL

a) **Definition:** Urinary bladder squamous cell carcinoma is a primary malignancy of urothelial origin that consists almost entirely of keratin-forming squamous carcinoma.

b) **Incidence:** Squamous cell carcinoma comprises approximately 5% of all bladder cancers in the Western world [275]. Excluded from this category are urothelial carcinomas with extensive squamous differentiation (“urothelial carcinoma with divergent differentiation”), although the distinction of these two entities on histological review may be challenging, especially on small tissue samples. Risk factors are associated with long standing inflammation and include long-term indwelling catheters, chronic infection, chronic bladder neck obstruction and bladder calculi [13,14,276,277]. Human papillomavirus (HPV)
is generally not associated with squamous cell carcinoma except in extremely rare cases [13,278-281].

c) Clinical Features: Squamous cell carcinoma occurs most frequently in the seventh decade [275]. The male to female ratio is approximately 2:1 and African-Americans are twice as likely to be affected [281]. Clinical presentation is similar to patients with urothelial carcinoma and includes hematuria and irritative voiding symptoms.

d) Gross Appearance: At cystoscopy, squamous cell carcinoma is frequently sessile, solid and often demonstrates a white, flaky surface secondary to keratin formation. Ulceration may occur in up to half of all carcinomas [279]. Lesions are predominantly solitary, may involve any aspect of the bladder wall, although the posterior and lateral walls are most commonly affected, and range in size from 0.8-6.4 cm (average 3.8 cm) [279].

e) Histologic Features: Squamous cell carcinoma shows nests of invasive squamous carcinoma cells with glassy, pink cells and variable keratin formation, often described as “keratin pearls.” (Figure 45) Other classic histologic features include intercellular bridges and sloughed keratin debris. All squamous cell carcinomas are considered to be high-grade. Associated mucosal findings include keratinizing squamous metaplasia (62%), nonkeratinizing squamous metaplasia (44%), squamous cell carcinoma in situ (36%), flat urothelial carcinoma in situ (16%), squamous metaplasia with dysplasia (9%), verrucous squamous hyperplasia (7%) and - rarely - condyloma accuminata (2%) [279].

f) Ancillary Diagnostic Tests: Immunohistochemical staining is similar to squamous cell carcinoma arising at other locations and includes positive immunoreactivity to p63, high-molecular weight cytokeratin and pancytokeratin. Recent studies are evaluating markers that may distinguish between squamous cell carcinoma and urothelial carcinoma with extensive squamous differentiation, which will be of high utility on biopsy or transurethral resection specimens.

g) Differential Diagnosis: The differential diagnosis of bladder squamous cell carcinoma includes urothelial carcinoma with extensive squamous differentiation (divergent differentiation) or squamous cell carcinoma secondarily involving the bladder from sites such as the cervix or anus.

h) Prognosis: There are few studies available on pure non-Schistosomal squamous cell carcinoma of the bladder. Five-year disease-free survival following radical cystectomy ranges from 43 to 57% [130,279,282]. The poor outcomes associated with this disease may be attributed to the high stage at initial presentation and relative frequency of regional lymph node metastases in 24% of patients at the time of cystectomy [279]. However, when compared to urothelial carcinoma on a stage-by-stage basis, outcomes appear similar, with a 5-year disease specific survival rate of 57% [130,283]. Squamous cell carcinoma has been associated with limited responsiveness to chemotherapy and radiation treatment.

A key challenge is in the management of patients who present with squamous cell carcinoma on initial biopsy or transurethral resection. Due to sampling, the exclusion of a high-grade urothelial carcinoma with squamous differentiation is challenging and this distinction can be made primarily on radical cystectomy when the entire lesion is available for histologic analysis. A second challenge is the management of in situ squamous lesions found on biopsy. The most concerning of all associated mucosal lesions is squamous cell carcinoma in situ, which has a high likelihood of progression to invasive carcinoma in patients and one study that followed up on these in situ lesions found that 5/7 patients with squamous cell carcinoma in situ on initial sampling developed subsequent invasive carcinoma [13].

2. VERRUCOUS CARCINOMA

a) Definition: Verrucous carcinoma, a tumor much more common in the upper aerodigestive tract, anus and genitalia than the urinary bladder, is a rare subtype of squamous cell carcinoma that is most often related to urinary schistosomiasis infection [284-287], but may also rarely occur in its absence [288-294]. It is a well-differentiated invasive squamous neoplasm with a broad deep border that “pushes” into the underlying stroma rather than demonstrating frank stromal invasion typical of a conventional squamous cell carcinoma.

b) Incidence: In areas with endemic urinary schistosomiasis, verrucous carcinoma accounts for up to 3.4% of all bladder carcinomas [285-287] and 4.6-6.5% of squamous cell carcinomas [286,287].

c) Clinical: The tumor occurs more frequently in men than women [285-287], and in regions with endemic urinary schistosomiasis, tends to occur at a younger age (mean age 44-46 years) in those with
the parasitic infection than in those without the infection (mean age 53 years) and those with bladder cancer in general, who typically present in the sixth and seventh decades of life [284-287]. In non-endemic regions of the world, a few cases of verrucous carcinoma have been reported to be related to condyloma acuminatum [288,293], chronic urinary tract infection [288,289,294] and bladder diverticula [290]. In some patients, the tumors are not associated with other genitourinary diseases [291,292]. Patients usually have irritative bladder symptoms at presentation and urine analysis may reveal white cellular debris, consistent with keratin [284,290,292]. Patients have also reported seeing white material in their urine [286,287,292]. Hematuria is not common [286,287].

d) Gross Appearance: Most tumors are solitary [287,294]. While the tumor may occur anywhere within the urinary bladder, one series reported that 80% occurred on the posterior wall or dome [287]. The tumor is typically exophytic, firm, white, and "wart-like".

e) Microscopic Features: Verrucous carcinoma is a well-differentiated neoplasm, with both exophytic and endophytic growth, characterized by hyperplastic, parakeratotic squamous epithelium that has minimal cytologic atypia and few mitoses (Figure 46). The surface of the neoplasm projects as epithelial papillae above the bladder mucosa. The thickened squamous epithelium invaginates into the underlying stroma; the deep border consists of a round, wide base of epithelium that "pushes," rather than frankly invades, into the stroma. A chronic inflammatory infiltrate may be present in the lamina propria, adjacent to the base of the tumor. Parasite ova may be present in the bladder tissue. Within the bladder, verrucous carcinoma arises from areas of squamous metaplasia; the metaplastic change develops secondary to chronic irritation most often caused by the parasite [284,295].

f) Differential Diagnosis: A definitive diagnosis of verrucous carcinoma, without its complete intact resection, can be very difficult to make. Superficial biopsy samples may not include the base of the lesion, and may consist only of thickened, well-differentiated, almost benign-appearing, squamous epithelium. Transurethral resections may not be particularly useful either, as they may be maloriented and muscularis propria, useful to evaluate for invasion, may not be present. The main differential diagnosis includes: verrucous squamous hyperplasia, squamous papilloma, pseudoepitheliomatous hyperplasia, condyloma acuminatum and a conventional invasive squamous cell carcinoma that contains foci morphologically resembling a verrucous carcinoma.

g) Ancillary Diagnostic Tests: None available.

h) Prognosis: For tumors that are not associated with urinary schistosomiasis, the patient follow-up is relatively short (3 months-3 years) [288-290,292,294]. Nevertheless, while some of the patients experienced tumor recurrence in the bladder due to lack of radical resection initially [290,292,294], all did well after total cystectomy. In larger series of verrucous carcinoma that occurred in areas with endemic schistosomiasis, specific outcomes are not provided [285,286]. However, if these tumors are diagnosed with strict adherence to histologic criteria, given that these neoplasms are low grade neoplasms without a propensity for lymph node metastases, the implication from these studies is that patients do well. If, however, an invasive component typical of a conventional squamous cell carcinoma is present, the possibility for more aggressive behavior exists. Therefore, in the latter situation, the World Health Organization [225] has recommended that such tumors not be diagnosed as "verrucous carcinoma." Due to the tendency for tumor recurrence and potential to be associated with a conventional squamous cell carcinoma, the treatment of choice is complete resection, usually by total rather than partial cystectomy. Radiation treatment is not advocated because of the possibility of development of anaplasia within the tumor and risk of more aggressive behavior, as documented in these tumors that occur at other sites [286,289,296-298].

3. SQUAMOUS CELL CARCINOMA, SCHISTOSOMAL

a) Definition: Urinary bladder squamous cell carcinoma that consists almost entirely of keratin-forming squamous carcinoma and is associated with a precedent or concurrent infection with schistosomal species.

b) Incidence: This form of squamous cell carcinoma occurs most frequently in the Middle East and Africa and - until recently - represented the most common form of bladder cancer in Egypt [299-301]. Risk factors include infection with Schistosoma hematobium [276, 277], exposure to nitrate-based fertilizers, pesticides, and smoking. Schistosomal eggs deposited within
III. ADENOCARCINOMA VARIANTS

1. PRIMARY ADENOCARCINOMA OF BLADDER

a) Definition: Urinary bladder adenocarcinoma is a primary malignancy that shows glandular differentiation, with features of enteric, mucinous or signet ring cell carcinoma.

b) Incidence: Population based studies on the incidence of bladder adenocarcinoma are limited by the rarity of these tumors. In larger series, adenocarcinomas constituted 0.55% to 2.6% of all urinary bladder malignancies [302-306], although these data are hampered by the inclusion of cases of urachal carcinoma. Lack of histological review is also likely to have a confounding effect, as in one series 58.7% reported cases of bladder adenocarcinoma were found, on review, to be other forms of malignancy [307]. In particular this included urachal adenocarcinomas, urethelial carcinomas with focal glandular differentiation and metastatic extravesical adenocarcinomas.

There is an association between schistosomiasis and bladder adenocarcinoma and in cases from Egypt, 5.2% to 11.4% of bladder tumors were found to be adenocarcinomas [308-310]. An increased incidence of these tumors is also seen in individuals with bladder extrophy [310,311].

c) Clinical Features: Adenocarcinoma of the bladder occurs most frequently in the fifth to seventh decades, although rare pediatric cases have been reported [312]. In registry-based studies that focus on adults and in larger clinical series, patients ranged in age from 15 to 93 years with mean ages of 60 to 64 years [303-305,307]. In these series the male:female ratio was 1.7:1 to 3:2:1. In schistosoma endemic areas, patients present at a younger age (mean age 46 to 50.4 years) with a male to female ratio of 2.18:1 to 2.25:1[308-310,313].

Adenocarcinoma is the most common malignancy associated with bladder extrophy and occurs in approximately 10% of cases [314,315]. In these patients tumor development is usually a late phenomenon and may occur in individuals who have undergone surgical repair at a young age [311,316,317].Although adenocarcinomas have been reported in association with neurogenic bladder and chronic in-dwelling catheters, these conditions do not appear to be predisposing factors for these tumors [318]. There is evidence that non-urothelial bladder malignancies occur more frequently in bladder diverticula although, due to small sample size, it remains uncertain if this is specific for primary adenocarcinoma [319].

Hematuria is the most common presenting symptom for bladder adenocarcinoma with other presenting features being irritative bladder symptoms, flank pain secondary to outflow obstruction, suprapubic pain, urinary frequency, dysuria and mucosuria [302,304,305,307,315,320,321].

d) Gross Appearance: At cystoscopy primary bladder adenocarcinoma is more frequently solid or sessile than papillary, and there is usually extensive ulceration [312,315,322]. Tumors may be mucinous and hemorrhage is frequently seen. There may be associated inflammation with the tumor forming an ill-defined mass [315]. Adenocarcinomas are solitary...
in >50% of cases and while the trigone is the most common primary site, all parts of the bladder may be involved [302,305,307,312,315,322,323]. Infiltration of the bladder wall and beyond is frequently detected by physical examination at presentation and at cystoscopy.

Signet ring cell carcinomas are almost always invasive at diagnosis. Features of linitis plastica with diffuse thickening of the bladder wall are commonly present and the mucosa is frequently ulcerated [312,320,324].

e) Histologic Features: Urinary bladder adenocarcinomas show a morphologic spectrum similar to that of colonic adenocarcinoma (Figure 47) and five specific morphotypes have been described [307,325]. 1. Enteric tumors are acinar, cribriform, villous or solid. Occasionally these tumors may contain cells that show neuroendocrine differentiation [325]. 2. Mucinous or colloid carcinomas consist of individual cells and cell nests within lakes of mucin. These tumors may also contain mucin filled acini and occasional signet ring cells may also be seen[320]. 3. Signet ring cell carcinoma (Figure 48) is restricted to those tumors that show a diffuse signet ring morphology with varying amounts of mucin and without foci of glandular, urothelial or squamous differentiation [195,320,323,326]. 4. Adenocarcinoma not otherwise specified (NOS) is applied to tumors where the architectural pattern does not conform to the preceding three morphotypes. 5. Mixed forms showing two or more morphologic patterns. (Figure 49) It has been suggested that to be included in this category, a tumor should not exhibit >75% of one tumor morphotype [325] Rare hepatoid forms have also been described [327].

In some series clear cell adenocarcinoma of apparent Müllerian origin are included as variants of bladder adenocarcinoma, while in other series they are considered to be a separate entity [307]. The features of these tumors are considered elsewhere in this work.

Of the five morphological variants of bladder adenocarcinoma, enteric and colloid carcinoma are the most commonly encountered morphotypes, although in one series 42% of tumors were classified as adenocarcinomas NOS, while only 25% of tumors had the features of enteric/mucinous adenocarcinoma. Signet ring cell carcinomas are rare and with less than 100 cases reported to date these tumors constitute approximately 5% of cases of bladder adenocarcinoma [307,323].

Various grading systems, including that of the World Health Organization, have been employed for these tumors. In general signet ring cell adenocarcinomas are considered to be high grade [322,326].

Bladder adenocarcinoma is often found in association with cystitis glandularis and urothelial intestinal metaplasia [20,325]. Although both metaplastic conditions result from chronic urothelial irritation/inflammation, more recent studies have suggested that these have no associated risk for the development of adenocarcinoma [20,21]. It has, however, been noted that the epithelium adjacent to foci of adenocarcinoma may show atypia or in situ carcinoma, and in one report this was present in 17% of cases [323,325].
f) Ancillary Diagnostic Tests: Immunohistochemical staining may assist in the diagnosis of primary urinary bladder adenocarcinoma of non-urachal origin [170,328-331]. These tumors show variable expression of cytokeratin 20, E48, carcinoembryonic antigen, LeuM1 and β-catenin. Positive staining for cytokeratin 7, OC125 and Her-2/neu may occasionally be present [320,330,331]. Tumors are usually negative for thrombomodulin, monoclonal prostatespecific antigen, prostate specific acid phosphatase and vimentin, although occasional tumors show positive staining for prostate antigen P501S [329], prostate specific membrane antigen[329] and polyclonal prostate specific antigen. In bladder adenocarcinomas, bcl-2 expression has been shown to decrease, while p53 expression increased, with increasing grade[332], and this may have prognostic significance.

g) Differential Diagnosis: The differential diagnosis of bladder adenocarcinoma includes other forms of bladder neoplasia and secondary adenocarcinoma of the stomach, appendix, large bowel, breast, endometrium and prostate gland. Rare villous adenomas of the bladder may resemble enteric type adenocarcinomas, although they lack the degree of atypia seen in carcinoma and do not infiltrate the bladder wall. Villous adenomas show membranous expression of prostatic specific membrane antigen and while this may also be seen in mucinous and signet ring cell adenocarcinomas, enteric adenocarcinomas usually show cytoplasmic staining [329]. Urothelial carcinomas may show cystic change with gland-like lumens, however, some tumors more typical areas of urothelial carcinoma may be identified.

Infiltration of the bladder by prostatic adenocarcinoma may be differentiated from primary bladder adenocarcinoma by immunohistochemistry as bladder tumors are negative for monoclonal prostate specific antigen and prostate specific acid phosphatase [333]. Colonic adenocarcinoma infiltrating or metastatic to the bladder may mimic bladder adenocarcinoma although careful examination will confirm that colonic metastases do not have any in situ component. Immunohistochemical expression may also be helpful as positive staining for cytokeratin 7 and negative staining for cytokeratin 20 is seen in 41% of bladder tumors but is not a feature of colonic adenocarcinoma [170]. Additionally bladder adenocarcinomas often show positivity for thrombomodulin, while colon adenocarcinomas are negative and unlike bladder tumors, often show nuclear staining for β-catenin [331].

Signet ring cell adenocarcinoma of the bladder may resemble metastatic gastrointestinal tumors. These tumors have an immunexpression similar to enteric-type bladder adenocarcinoma and further they are likely to have less of a mucinous component when compared to tumors of gastrointestinal origin.

Signet ring cell adenocarcinoma may occasionally mimic lobular carcinoma of the breast; however, immunostaining for ER, PR and GCDFP-15 should lead to the correct diagnosis.

h) Prognosis: Most studies relating to the outcome of primary adenocarcinomas of the urinary bladder are hampered by small sample size. Further confounding factors are that in many series urachal and non-urachal carcinomas, are admixed [304-306]. In further series adenocarcinomas, which contained areas of typical urothelial carcinoma were included [307]. Bladder adenocarcinomas are often of advanced stage at presentation. On imaging studies 75% of primary non-urachal adenocarcinoma were found to have diffuse thickening of the bladder wall on computerized tomography, while 88% had stranding of perivesical fat. Lymphadenopathy was visible in 25% of cases and in 25% there was direct invasion of the rectus muscle [334]. These results are reflected in cystoscopic and gross pathological findings, with most tumors showing infiltration into the bladder wall at diagnosis [302,307,312,322,335]. Metastases are present in approximately 25% of cases with secondary sites in descending order of frequency being liver, bone, regional lymph nodes, adrenals, peritoneum and skin [302,307,312,322,335]. Bladder adenocarcinoma has a poor prognosis with 5-year survivals of 11% to 55% being reported [242]. In various studies tumor stage at diagnosis has been shown to be an important prognostic feature [307,315,322,325]. In a recent registry-based study of 306 patients with bladder adenocarcinomas [303], the distribution of cases according to pT staging category was pTis/a 0.3%, pT1 7.8%, pT2 30.4%, pT3 28.4% and pT4 33%, and cancer specific 5-year survival rates for organ-confined and extravesical disease were 82.5% and 43.3% respectively. Comparison showed that adenocarcinomas had the same natural history as urothelial carcinoma following radical cystectomy, but that patients with adenocarcinoma were usually of a more advanced stage at the time of treatment. In a separate study the median survival for patients with localized tumors was 64 months, while median survivals for patients with tumors showing regional and distant spread were 29 and 8 months respectively [242].

Morphology has been associated with outcome, with 5-year survival rates being 64% for tumors showing mixed morphology, 55% for mucinous adenocarcinomas, 51% for adenocarcinoma NOS, and 27% for signet ring cell adenocarcinomas, although these data did not achieve statistical significance[326]. Signet ring cell carcinoma are usually of an advanced stage at diagnosis, with mean survivals of 9 to 12 months, and a 5-year survival of <11% being reported [195,326,336].
Other features also shown to be of prognostic significance are tumor size, histological grade and method of treatment. It is, however, evident that the prognostic significance of treatment modality is stage dependent as this determines treatment selection [322,325].

It has been suggested that for localized tumor observed poor outcomes following cystectomy relate to occult spread of tumor [322,325]. This may explain the significantly improved 5-year survival rates (58% versus 44%) for patients treated with neoadjuvant radiotherapy, four to ten weeks post-operatively [337].

2. URACHAL CARCINOMA

a) Definition: Urachal carcinomas are malignant tumors arising in urachal remnants. While the great majority of these tumors are adenocarcinomas originating from vestigial urachal epithelium, squamous cell carcinoma, urothelial carcinoma, neuroendocrine carcinoma and sarcomas have also been reported, albeit rarely [338].

b) Incidence: Although urachal remnants are seen in up to one third of post mortems [339], urachal malignancies are rare tumors with many reports consisting of single cases and small series [340,341]. In population based studies from the Swedish Cancer Registry, the annual incidence was 1 in 5 x 10^6 [342], while in Massachusetts these tumors comprised 0.01% of all malignant tumors [343]. Urachal carcinomas have been shown to constitute 0.07% - 0.7% of bladder carcinomas in North America and Europe and 0.55% - 1.2% of bladder carcinomas in Japan [344]. In a separate study these tumors were shown to comprise 0.17% - 0.34% of bladder neoplasms and 20% - 39% of all bladder adenocarcinomas [345]. More recently urachal cancer was found to account for <0.1% of all bladder cancers reported to the Ontario Cancer Registry [346].

c) Clinical Features: There is a male predominance for all types of urachal cancers with male to female ratios of 1.8:1 to 3:1 being reported [338,341,347]. In various series, patients ranged in age from 16 to 87 years and the mean age ranged from 50 to 60.7 years [338,340,341,345,347-349]. Approximately 70% of patients were aged between 41 and 70 years at diagnosis [338,345].

For urachal adenocarcinomas the male to female ratio ranged from 1.35:1 to 3:1 [338,346]. Greater than 70% of patients were aged 41 to 70 years, while 20% of patients were less than 40 years of age at diagnosis [338,345]. In a further series 20% of patients who presented with urachal adenocarcinoma were greater than 70 years of age [346].

Hematuria is the most common presenting feature in 55% to 80% of cases [340,344,345,347]. Other presenting signs and symptoms are abdominal mass or pain, suprapubic mass, umbilical mass or discharge, recurrent urinary tract infections, irritative voiding symptoms, or urinary outflow obstruction, while mucinuria is seen in 25% of urachal adenocarcinomas [338,340,347].

d) Gross Appearances: During fetal development, the urachus contains the allantois and connects the umbilicus to dome of the bladder. Following birth the urachus undergoes involution to form the median umbilical ligament [350]. In one third of individuals the epithelial-lined urachal lumen persists as urothelium or mucinous columnar epithelium, resulting in patent urachus, cysts or tubular canals of varying size and complexity within the median umbilical ligament or bladder wall [339]. The embryogenesis of the urachus accounts for the observation that urachal carcinomas are seen as a mass at the bladder dome or on the anterior surface of the bladder. There is usually infiltration into the bladder wall although occasionally this may be absent, with the tumor having a pushing margin and being clearly demarcated from adjacent bladder tissue. Tumors are usually bulky at diagnosis with extension beyond the bladder within the space of Retzius or through to the anterior abdominal wall in the midline [323]. Less frequently urachal carcinomas infiltrate the bladder mucosa [340] and may appear grossly as ulcerated, mucinous or papillary masses [338].

Imaging studies suggest a diagnosis of urachal carcinoma when tumors are seen in the bladder dome or extending to the anterior abdominal wall in the midline [349,351]. Calcification is frequently present within the tumor and is seen on computerized tomography in approximately 70% of cases [349,352].

e) Histological Features: Because of the morphologic overlap of vesical and urachal adenocarcinoma, several diagnostic criteria for urachal tumors have been proposed (Table 10). It is considered that the Wheeler and Hill [353] and Mostofi [323] criteria are too restrictive and likely to exclude cases of true urachal adenocarcinoma. For this reason the criteria of Gopalan et al. (2009) [340] are preferred.

The majority of urachal carcinoma are adenocarcinoma [325,341,347] and closely resemble colonic adenocarcinoma. Many of the tumors have a pronounced mucinous component and this has been considered as a separate subtype consisting of single tumor cells or cell nests within lakes of extracellular mucin [325]. Less frequently the tumor has a signet ring cell morphology [325,341,347].

Rare carcinomas have features other than those of typical adenocarcinoma and cases of squamous cell carcinoma [341,347,354,355], urothelial carcinoma [347,355], lymphoepithelial-like...
carcinoma, clear cell carcinoma and small cell/neuroendocrine carcinoma have been described. On occasion more typical urachal adenocarcinomas may contain focal areas of these rare forms of carcinoma. Several cases of urachal sarcoma with features resembling leiomyosarcoma, rhabdomyosarcoma and hemangiopericytoma have also been reported.

In larger series tumor grading is reported, although no formal grading system for these tumors has been established. In these series tumors are subjectively graded as well differentiated/poorly differentiated or well/moderately/poorly differentiated.

f) Ancillary Diagnostic Tests: Studies on the immunohistochemical expression of urachal carcinomas are limited. These tumors are usually positive for carcinoembryonic antigen, 7E12H12 IgM isotype, CDX2 and Leu-M1, while focal positivity has been reported for cytokeratin 7, cytokeratin 20, 34βE12 and E48 antibody. Stains for vimentin, Her-2/neu and prostate specific antigen are negative. Cytoplasmic β-catenin and CA19-9 positivity is seen in the majority of urachal adenocarcinomas, while CA125 positivity is only rarely present.

g) Differential Diagnosis: The differential diagnosis includes primary adenocarcinoma of the bladder and metastatic colonic, ovarian and prostatic carcinomas.

Table 10. Criteria for diagnosis of urachal adenocarcinoma

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<tr>
<td></td>
<td>2. Absence of cystitis cystica or cystitis glandularis.</td>
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<td>3. Predominant involvement of muscularis rather than submucosa, with intact or ulcerative bladder epithelium.</td>
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<td>4. Urachal remnant connected to neoplasm.</td>
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<td>5. Suprapubic neoplastic mass.</td>
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<tr>
<th>Mostofi et al, 1955</th>
<th>Criteria additional to Wheeler and Hill</th>
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<tr>
<td>1. Location in anterior wall of bladder.</td>
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<td>2. Sharp demarcation of tumor and surface epithelium.</td>
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<tr>
<td>3. Extension to space of Retzius, to umbilicus or anterior abdominal wall.</td>
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<tr>
<td>2. Sharp demarcation between tumor and bladder epithelium.</td>
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<tr>
<td>3. Exclusion of another primary (non-urachal) adenocarcinoma.</td>
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<tr>
<td>2. Epicenter of carcinoma in bladder.</td>
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<tr>
<td>3. Absence of widespread cystitis cystica/glandularis beyond the dome/anterior bladder.</td>
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<tr>
<td>4. No known primary elsewhere.</td>
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Extravesical genital tract carcinomas may be differentiated from urachal adenocarcinomas by prostate specific antigen, vimentin and CA125 immunohistochemistry. Vesical urothelial carcinomas are usually negative for carcinoembryonic antigen.

There is often an overlap in the morphologic features of vesical, colonic and urachal adenocarcinoma and clinicopathologic correlation, with application of the defining criteria for urachal carcinoma (Table 10), usually leads to the correct diagnosis. Each of these primary tumors may show positive staining with carcinoembryonic antigen, however, diffuse expression favors a urachal origin. Unlike urachal adenocarcinoma, colonic tumors are likely to show diffuse cytokeratin 20 staining and are cytokeratin 7 negative.

h) Prognosis: In earlier series the prognosis of urachal carcinoma was found to be poor with overall survivals of 22.7% and 31%, and a 5 year survival of 61% being reported. In more recent studies mean overall survival was 122 months and a meta-analysis of 312 patients showed 5 year post-operative cancer free survivals to range from 43% to 70%.[325,341,345-348,363-367].

A staging system for urachal carcinoma was established by Sheldon et al. This was hampered by a relatively large number of categories and a simplified staging classification has been proposed (Table 11). Advanced tumor
stage is associated with a less favorable outcome, with reported 5 year survivals of 93\% for patients with tumor confined to the urachus and bladder, 69\% for extra-vesical and peri-urachal tumors and 0\% for tumors within the peritoneal cavity [341,347]. In a further series all patients who developed local recurrence or metastases were Sheldon stage T3 or higher [340]. Other features associated with poor survival are high tumor grade and positive surgical margins [341,346,347].

Successful management of urachal carcinoma is dependent on complete surgical excision of tumor. This involves partial or radical cystectomy, removal of the medial umbilical ligament/urachus and resection of the umbilicus, and in recent years laparoscopic surgical techniques have been described [368-370]. Recurrence are more likely following partial cystectomy [347,371,372] and common metastatic sites are liver, lung, bone and peritoneum [340,341,343-347], while metastasis to the brain and skin are less common [347,373,374]. For patients who developed local recurrence or metastases, time to relapse is usually short, ranging from 10 to 22 months [340,341]. Salvage surgery has been shown to result in a long term cure for 50\% of patients with local recurrence [347].

Adjuvant chemotherapy currently has a limited efficacy for urachal adenocarcinoma. Although tumor regression has been reported following chemotherapy for a few cases [339,340,346,351,375], it has been noted that this does not alter survival interval for patients with metastatic disease [347]. Despite this, it has recently been suggested that 5-fluorouracil-based chemotherapy may have some efficacy [376].

3. CLEAR CELL ADENOCARCINOMA

a) **Definition:** This designation should be reserved for tumors resembling to a significant degree clear cell adenocarcinoma of müllerian type as encountered in the female genital tract and should have one or more of the typical tubulocystic, solid and papillary patterns as well as one or more of the typical cell types including clear cell, non-specific cuboidal and hobnail [205,377].

b) **Incidence:** These are rare neoplasms and are of two fundamental types. Those that arise in females from endometriosis and accordingly histogenetically as well as morphologically are identical to müllerian clear cell carcinoma. The second group includes neoplasms without a proven association with endometriosis but with morphologic similarity to tumors having such an association. Even when both subsets are combined this is amongst the rarest of all bladder cancers accounting for no more than 0.01\% of cases.

c) **Clinical:** The great majority (approximately 80\%) of these tumors have occurred in females. There is a wide age distribution in adult life from the early twenties to late years but the majority occur in a somewhat old population (mean 57 years). There is no unique aspect to the clinical presentation amongst the reported cases although it is conceivable that an association in a female of symptoms with the menstrual cycle could indicate an endometriosis associated carcinoma.

d) **Gross Appearance:** Most of the reported tumors have been polyoid to papillary. An entirely mural neoplasm, although not reported, could be encountered due to the origin of some cases in endometriosis within the muscularis propria of the

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**Table 11. Staging systems for urachal carcinoma.**

<table>
<thead>
<tr>
<th>1. Sheldon staging classification</th>
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<tbody>
<tr>
<td>Stage I</td>
<td>Confined to urachal mucosa.</td>
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<tr>
<td>Stage II</td>
<td>Confined to urachus.</td>
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<tr>
<td>Stage III</td>
<td>Extension to bladder.</td>
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<tr>
<td>IIIA</td>
<td>Peri-urachal and vesical fat invasion.</td>
</tr>
<tr>
<td>IIIB</td>
<td>Extension to peritoneum.</td>
</tr>
<tr>
<td>IIIC</td>
<td>Extension to viscera other than bladder</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Metastases to regional lymph nodes.</td>
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<tr>
<td>IVA</td>
<td>Metastases to other organs.</td>
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<td>IV</td>
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<th>2. Mayo staging classification</th>
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<tbody>
<tr>
<td>Stage I</td>
<td>Confined to urachus and bladder.</td>
</tr>
<tr>
<td>Stage II</td>
<td>Beyond muscular layer of urachus and/or bladder.</td>
</tr>
<tr>
<td>Stage III</td>
<td>Infiltration of regional lymph nodes.</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Infiltration of non-regional lymph nodes or distant sites.</td>
</tr>
</tbody>
</table>
e) Microscopic Features: The typical triad is that of tubulocystic, papillary and diffuse (solid) arrangements. The commonest is tubulocystic, the lumens of these formations often containing basophilic or eosinophilic secretion that may be mucin positive (Figure 50). The papillae are generally small and rounded but may be large and delicately filiform. Rarely they are hyalinized. In tumors with a diffuse growth the cells may have conspicuous clear cytoplasm and appreciable clear cytoplasm may be a feature of the cells lining tubules and cysts or forming papillae although generally the cells of these structures have non-specific lightly eosinophilic cytoplasm of modest amount. A variety of other rare patterns may be encountered including solid tubular formations. Some of the cells lining tubules and cysts may have the features of hobnail cells but they are generally predominantly non-specific and cuboidal in nature [205,377].

Figure 50. Clear cell variant urothelial carcinoma, tubulocystic pattern. This neoplasm, from a female, was associated with endometriosis.

g) Ancillary Diagnostic Tests: These are rarely needed to establish the diagnosis but some information potentially of benefit has accrued, albeit overall knowledge on this aspect is limited. Most of the reported tumors have stained immunohistochemically for CA-125 and CK7. CK20 has usually been only focally and weakly positive although it was strongly positive in one tumor.

h) Prognosis: The prognostic parameters are similar to those of conventional carcinoma of the bladder and standard parameters such as invasion of the lamina propria, and its extent, and even more so invasion of the muscularis propria are guides to both therapy and prognosis. There is no evidence that the behavior, stage for stage, is different from usual bladder cancer.

IV. NEUROENDOCRINE NEOPLASMS

1. NEUROENDOCRINE CARCINOMA OF THE BLADDER

a) Definition: A group of tumors comprising small cell carcinoma and large cell neuroendocrine carcinoma and mixed patterns [378].

b) Incidence: Large cell neuroendocrine carcinoma of the urinary bladder is extremely rare with less than ten cases reported in the literature [379]. Small cell carcinoma of the urinary bladder, although relatively much more common than both carcinoid and large cell neuroendocrine carcinoma, is an extremely rare primary bladder malignancy, accounting for less than 1% of urinary bladder cancers [120,380-382].

c) Clinical: Although there are no more than single cases of primary large cell neuroendocrine carcinoma of the urinary bladder, the age at diagnosis ranges from 32 to 82 years, and patients may present with...
symptoms similar to those of carcinoid tumor [383-385]. Small cell carcinomas mostly occur in the sixth to seventh decade of life, the mean age being 66 years at the time of diagnosis (range 36 to 85 years), and have a male preponderance [386]. Patients usually present with hematuria, which may be accompanied by dysuria, frequency, nocturia, urinary obstructive symptoms, or localized abdominal/pelvic pain [380,386]. Small cell carcinomas arise most frequently in the lateral walls and dome of the bladder, and rarely in bladder diverticula [119,120].

d) Gross Appearance: The few reported cases of large cell neuroendocrine carcinomas have not been associated with any one single modality of growth. Small cell carcinoma may manifest as a single large, solid, polypoid, sessile or ulcerated mass, which may be infiltrative at presentation [119,120,387].

e) Microscopic Features: Large cell neuroendocrine carcinoma is poorly differentiated and high-grade. At low magnification, it demonstrates a noticeable histologic pattern of growth in the form of nests and trabeculae. Tumor cells have irregular angular nuclear outlines and prominent nucleoli. Pure small cell carcinomas have a “patternless” pattern of growth, meaning at low magnification, the tumor cells grow in a diffuse fashion with no clear organization. As an exception however, one may find focal nesting pattern. Tumor cells have very little cytoplasm; as a result, they show nuclear crowding and molding as though being pushed in to one another (Figure 51). Nucleoli are inconspicuous and the chromatin is evenly dispersed. Small cell carcinomas carry a high proliferation rate, as evidenced by frequent mitoses, crush artifact, geographic necrosis, and the subsequent Azzopardi effect, whereby blood vessel walls undergo encrustation by excess liberated DNA.

f) Differential Diagnosis: Large cell neuroendocrine carcinoma, also due to its exquisite rarity, ought not be confused with a metastatic deposit of its pulmonary counterpart. Small cell carcinoma may be mistaken for malignant lymphoma, poorly differentiated urothelial carcinoma, and even exuberant inflammation in the background of crush or cautery thermal artifact, especially in a superficial or scant specimen. Pulmonary metastasis or extension from adjacent viscera must be ruled out by clinicoradiologic correlation, as immunohistochemistry offers limited assistance in this setting. An additional rare but significant consideration is alveolar rhabdomyosarcoma, a subset of which can impart a primitive round cell appearance, imparting a histology reminiscent of small cell carcinoma [120].

g) Ancillary Diagnostic Tests: Tumor cells of large cell neuroendocrine carcinoma are immunopositive for neuroendocrine markers chromogranin A, synaptophysin, CD56, and neuron-specific enolase, and for cytookeratins CAM 5.2 and AE1/AE3, and epithelial membrane antigen. Small cell carcinoma tumor cells are immunopositive for chromogranin A and synaptophysin (greater than 60% of cases) and frequently demonstrate a dot-like immunopositivity for pan-cytokeratin. TTF-1 may be immunopositive in up to 40% of cases [388]. Unlike neuroendocrine tumors, lymphomas are immunopositive for leukocyte common antigen and negative for keratin and neuroendocrine markers. Poorly differentiated urothelial carcinoma does not express neuroendocrine markers such as chromogranin or synaptophysin, thereby differentiating it from small cell carcinoma. Prostatic adenocarcinoma, unlike small cell carcinoma, would be immunopositive for prostate-specific markers, prostate specific antigen and prostatic acid phosphatase. Lastly, alveolar rhabdomyosarcoma with small cell differentiation would be immunopositive for desmin, myogenin and Myo D1 and negative for keratin. Interestingly, this tumor is associated with immunopositivity for the neuroendocrine marker synaptophysin, necessitating the employment of a panel of immunohistochemical markers.

h) Prognosis: Large cell neuroendocrine carcinoma appears to behave by way of small cell carcinoma, being aggressive with high metastatic potential, with most reported cases having a fatal outcome [383,384]. As with primary pure carcinoid tumors of the urinary bladder, large studies have not been possible due to the limited number of reported cases. Small cell carcinoma of the urinary bladder often presents at an advanced stage, with up to 94% of cases having muscularis propria invasion or extravesical extension. Metastasis at time of presentation is not uncommon, to sites that include regional lymph nodes, liver, bone, and lung. Treatment recommendations for small cell carcinoma of the urinary bladder have been based on case reports and small retrospective series. Cisplatin and etoposide-based chemotherapy in conjunction with surgery has been associated with significantly improved survival, including reports of long-term survivors. Various clini-
cal studies have addressed patient management by way of different combinations and modalities of surgery, chemotherapy and radiation therapy, making it exceedingly difficult to correlate outcome between the different series. Mean survival ranges from 6 to 34.9 months and the reported 5-year survival rate ranges from 8 to 40%. Organ-confined disease is more amenable to therapy and is associated with more favorable patient survival. In sum, prognosis is influenced by disease extent at diagnosis, employment of chemotherapy, and the patient’s performance status [386,387,389].

2. CARCINOID TUMOR

a) **Definition:** A well-differentiated neuroendocrine tumor similar to that seen in other organs which is part of a very broad spectrum neuroendocrine tumors in the bladder [378].

b) **Incidence:** Pure carcinoid tumor of the urinary bladder are extremely rare. By way of criteria applied to their more common pulmonary counterparts, less than ten cases have been reported in the literature [390,391].

c) **Clinical:** Carcinoid tumors of the urinary bladder have been reported to occur solely in adults ranging from 29 to 75 years of age, with a slight male preponderance. These patients may present with hematuria and irritative voiding symptoms.

d) **Gross Appearance:** Carcinoid tumors usually present as small polypoid masses at the bladder neck/trigone[390].

e) **Microscopic Features:** Microscopically, carcinoid tumors are submucosal and confined within the lamina propria, often associated with adjacent cystitis cystica et glandularis. The tumors are composed of uniform, cuboidal, or columnar cells with finely stippled chromatin and inconspicuous nucleoli in a prominent pseudoglandular pattern composed of acinar and cribriform structures (Figure 52).

f) **Differential Diagnosis:** Carcinoid tumors can be histologically confused with nested variant of urothelial carcinoma, inverted urothelial papilloma, and metastatic tumors arising in the prostate, gastrointestinal tract and lung. The rarity of carcinoid tumors of the urinary bladder coupled with the prognostic significance of its differentials makes it paramount to employ ancillary studies and clinicoradiologic correlation as part of case work-up.

g) **Ancillary Diagnostic Tests:** Carcinoid tumor cells are immunopositive for neuroendocrine markers chromogranin, synaptophysin, serotonin, and neuron-specific enolase, and for cytokeratin AE1/AE3.

h) **Prognosis:** In the largest series to date, all 6 pure carcinoid tumors with similar morphology had excellent prognosis [390]. However, the number of cases reported is still relatively small and the tumors likely had been completely removed by biopsies. Pure primary carcinoid tumor of the bladder and prostatic urethra, when presenting as small polypoid nodules in the bladder is associated with a very favorable outcome. However, there are reports of larger more invasive lesion with regional lymph node or distant metastases [119,392]. Some of the early reported cases with aggressive behavior were found to be mixed tumors with associated small cell carcinoma or adenocarcinoma components.

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**E. ROLE OF IMMUNOHISTOCHEMISTRY AND ANCILLARY DIAGNOSTICS IN HE DIAGNOSIS, STAGING, PROGNOSTICATION AND PREDICTION OF BLADDER CANCER IN CONTEMPORARY CLINICAL PRACTICE**

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**I. IMMUNOHISTOCHEMICAL MARKERS FOR STAGING OF BLADDER CANCER**

1. **INTRODUCTION**

Pathologic staging of bladder cancer identified in transurethral resections or biopsies is the clinically most powerful determinant with regard to treatment decision, in addition to grading[393]. Although grading is the strongest prognosticator for progression of bladder cancer in the subset of non-invasive (pTa) bladder cancers, grading tends to lose its independent prognostic value in invasive bladder cancers[115]. Pathologic staging depends on the morphologic recognition of invasion beyond the basement membrane into the lamina propria,
while invasion of the detrusor muscle serves as a landmark for T2 bladder cancer.[393] The diagnosis of muscularis propria invasion generally leads to the clinical decision to perform a major surgery, including cystectomy or nephroureterectomy. Histopathological assessment of invasion of the lamina propria may be hampered by several factors, which include artefacts related to the procurement of the tissue and the morphologic variation of bladder cancers.[393] Indeed, sometimes it is impossible for a pathologist to determine whether a bladder cancer is invasive. Artifactual confounders are the occurrence of severe cauter and crush effects related to the urological procedure and the lack of spatial orientation due to the random embedding of the bladder tissue chips. If the biopsy or transurethral resection is very superficial, underlying stroma may be too scarce or even absent, again precluding the staging of the tumour sample. Biological tumor-associated factors that may preclude a proper assessment of pathological stage are the presence of an inverted growth pattern, which is more commonly associated with a trabecular or even pushing invasive growth pattern, and the occurrence of a florid desmoplastic reaction, which in particular could hamper the identification of the detrusor muscle. Further, the variation in thickness of the muscularis mucosae, which are normally represented by thin wisps of smooth muscle fibers may lead to an erroneous assignment of T2 bladder cancer, particularly when this layer becomes hypertrophic in appearance. At various sites in the bladder (e.g. the trigone, the bladder neck, or the renal calyces), the detrusor muscle may be located superficial, and as a consequence, its invasion may spuriously be deemed as invasion of the muscularis mucosae, resulting in under-staging of the bladder cancer. Finally, in resected cancers of bladder diverticula (in fact pseudo-diverticula) it is generally impossible to distinguish pT1 from pT2 or even pT3 stages as this site generally lacks the landmark detrusor muscle.

A few studies have demonstrated a substantial level of inter-observer variation among pathologists for staging of bladder cancers (Table 12).[33,394,395]. For this reason, several attempts have been made to identify easily applicable histological markers that would increase the accuracy of pathological staging of cancers of the urinary tract.

2. DETERMINATION OF INVASIVENESS OF BLADDER CANCER

The identification of invasive bladder cancer cells can be challenging, especially when the number of invading cells is small or in the presence of cautery or mechanical artefacts. In addition, some tumours may show pushing growth deep in the lamina propria without an obvious invasive pattern. Although no formal studies have been reported in the literature, it is well-established that immunostaining with anti-cytokeratin antibodies can facilitate the diagnosis of invasion in cases with prominent inflammation obscuring the interface between epithelium and stroma. The most commonly employed antibodies for this purpose are pan-keratins, like AE1 / AE3 and antibodies against cytokeratins 8 and 18[396]. (Table 13) Also, in case of cautery artefacts or as a sequel to a previous urological procedure, cytokeratin staining may allow the identification of carcinoma cells infiltrating the (cauterized) stroma[393,397]. A potential pitfall, particularly in the setting of a previous urological procedure such as a transurethral resection, is the positive staining for cytokeratins of myofibroblasts and smooth muscle cells[397]. Both myofibroblasts and smooth muscle cells generally express only low-molecular weight cytokeratins, while epithelial cells will show immunoreativity to high molecular weight forms. Most importantly, a correlation of the cytologic appearance of the cytokeratin positive cells is essential in order to obtain a correct diagnostic interpretation.

Table 12. Interobserver variation for staging of bladder cancers.

<table>
<thead>
<tr>
<th>Author (reference)</th>
<th>Down staging pT1 -- pTa</th>
<th>Upstaging pT1 – pT2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abel, 1988</td>
<td>13%</td>
<td>1%</td>
</tr>
<tr>
<td>Van der Meiiden, 2000</td>
<td>53%</td>
<td>10%</td>
</tr>
<tr>
<td>Bol, 2003</td>
<td>56%</td>
<td>13%</td>
</tr>
<tr>
<td>Tosoni et al, 2000</td>
<td>35%</td>
<td>3%</td>
</tr>
</tbody>
</table>

Experimental studies have shown that tumour invasion is associated with dysregulation of both adhesion molecules, involved in cell-cell interactions and cell-basement membrane structures like hemidesmosomes, and endopeptidases with the capacity to de-grade extracellular matrix proteins [398]. Cadherins are a family of cell-cell adhesion molecules whose expression is altered during the epithelial mesenchymal transition which is characteristic of tumour invasion [399,400]. Whereas carcinoma in situ of the urothelium expresses high levels of E-cadherin, its expression is reduced during the epithelial mesenchymal transition which is characteristic of tumour invasion [399,400]. Whereas carcinoma in situ of the urothelium expresses high levels of E-cadherin, its expression is reduced, and a switch to N-cadherin and in particular P-cadherin expression has been reported in invasive bladder cancers [399]. Negative markers such as E-cadherin are obviously not suitable for diagnostic use to detect invasion, but markers which are selectively up-regulated in invasive cells may hold diagnostic promise. P-cadherin expression was shown to be elevated in particular in the invading edge, but this molecule is also predominantly expressed in the
basal layers of the non-invasive bladder cancers [398], precluding its use as a diagnostic adjunct for invasion.

Among the extracellular matrix degrading endopeptidases, collagenase-3 (matrix metalloproteinase-13) and stromelysin-3 have been studied in relatively small series of bladder cancers for their diagnostic and prognostic use [401-403]. MMP-13 was expressed predominantly at the invading edge and invasive nests of about 60% of the invasive carcinomas. Further, a weak expression was also noted in the stromal fibroblasts of some of the invading cancers [403]. Given the low sensitivity of MMP-13, this marker does not seem useful in diagnostics of bladder cancer invasiveness. Stromelysin expression was particularly noted in the stromal fibroblasts adjacent to the invasive carcinoma nests of about 70% of carcinomas, but not in the carcinoma cells. However, a small proportion of non-invasive bladder cancers were also positive for this marker, diminishing its diagnostic significance [401,402]. Of interest, stromelysin expression showed a statistically significant correlation with lymphatic vessel invasion.

Further, some studies addressed the potential of immunostaining for basement membrane proteins as an adjunct to the morphologic detection of invasive cells in bladder cancer. Laminins are glycoproteins which represent a major component of the basement membrane and they consist of three subunits, i.e. an α, β and γ chain. The LN-5 γ chain is a specific target of MMP-2, and this cleavage is critical for tumor invasion and tissue remodeling. It was reported that expression of LN-5 γ2 is increased in the carcinoma cells at the invasive edge of the bladder cancers [404,405]. Although LN-5 γ2 was strongly and independently associated with unfavourable prognosis, only about one third of the invasive carcinomas expressed this marker as compared to 7% of the non-invasive bladder cancers, which renders LN-5 γ2 unsuitable as a diagnostic marker.

3. IMMUNOHISTOCHEMICAL MARKERS FOR SUBSTAGING pT1 BLADDER CANCERS

Stage pT1 bladder cancers are clinically heterogeneous, particularly with regard to risk of progression and death of disease during follow-up. Several attempts have been made to substage T1 bladder cancers. The most often employed substaging system employs the muscularis mucosae and the associated plexus venosus in the lamina propria as reference point, distinguishing a substage pT1a, pT1b and pT1c [44]. pT1a cancers are the most superficial bladder cancers, with invasion above the muscularis mucosae, while pT1c cancers would invade beyond the plexus venosus. A condensed and probably more robust substaging system aggregates pT1a and pT1b cancers in the substage of minimally invasive bladder cancers [40]. Several studies reported a considerable inter-observer variation for this substaging system, while it was also noted that in a variable proportion of cases pathologists were not able to assign a substage due to absence of the muscularis mucosae / plexus venosus and poor orientation. As a consequence, pT1 substaging has not been included in the WHO 2010 classification of bladder cancers. One attempt was made to use immunohistochemistry for improvement in the accuracy of pT1 substaging (18), using antibodies against desmin and pan-keratin; in a series of 93 consecutive pT1 bladder cancers, they observed that in a small proportion of cases immunostaining could eliminate the disagreement with regard to pT1 substage among two pathologists when reviewing H&E stained slides [406]. Thus, it was concluded that the use of desmin and cytokeratin immunostaining could be of help to improve the precision of substaging pT1 bladder cancers; however, there is no data to show that using immunohistochemistry for substaging improves the prediction of recurrent or progressive disease and therefore it is not recommended for routine application.

4. IMMUNOHISTOCHEMICAL MARKERS FOR IDENTIFICATION OF DETRUSOR MUSCLE

Particularly in transurethral resections of the bladder, the distinction between T1 and T2 bladder cancer may be challenging. For this reason immunohistochemical markers have been employed to help discriminate muscularis mucosae from muscularis propria.
Initially, the utility of desmin and/or smooth muscle type actin in the identification of the detrusor muscle was evaluated, but these markers do not allow a differential staining of the muscularis mucosae and muscularis propria. Histochemical stains such as hematoxylin-phloxine-saffron or Mallory trichrome have been used to identify muscle fibers in areas of desmoplastic stroma or cautery artifact. Although many pathologists do utilize such stains, there are no published series reporting on use of any of these markers in a routine pathology setting. There is no good data on the value or the validity of this approach; therefore, these cannot be recommended for routine use.

Smoothelin was identified in 1996 as a marker for smooth muscle tissue, and two isoforms, smoothelin-A (59kDa) and smoothelin-B (110-kDa) have been described [407]. Their function is related to the contractility of smooth muscle and its expression is absent in non-contractile or proliferative smooth muscle cells. (Table 13) Smoothelins are actin-binding proteins that are expressed abundantly in terminally differentiated visceral (smoothelin-A) and vascular (smoothelin-B) smooth muscle and both types can be visualized by monoclonal antibody R4A. The latter antibody is the most commonly employed antibody for the immunohistochemical detection of smoothelin in a diagnostic setting. Recently, Paner et al. reported the differential staining of detrusor muscle and muscularis mucosae by this anti-smoothelin antibody to help distinguish muscularis mucosae versus detrusor muscle invasion of bladder cancer [408]. Similarly, in the gastro-intestinal tract smoothelin is now being studied to distinguish between pT1 and pT2 adenocarcinomas of Barrett esophagus [409]. After a second confirmatory study by Paner et al.[410] on a larger series of 70 TUR samples, a subsequent study by Council et al. compared the diagnostic value of smoothelin with that of smooth muscle actin, desmin, caldesmon, and vimentin on a series of 15 cystectomies [411]. In contrast to the similar intense expression levels of muscularis mucosae and detrusor muscle for smooth muscle actin, desmin, and the variable expression levels of caldesmon, smoothelin and vimentin displayed a differential expression pattern. Smoothelin was intensely positive for all detrusor muscle samples and negative or weakly positive for muscularis mucosae, whereas vimentin was rarely expressed in the detrusor muscle and positive in 9 of 11 specimens with muscularis mucosae. Council et al. also noted that antibodies specific for caldesmon and desmin were able to selectively stain smooth muscle cells as compared to reactive myofibroblasts [411]. These authors recommended the use of caldesmon and desmin immunohistochemistry to distinguish reactive myofibroblasts, e.g. in desmoplasia from smooth muscle cells, while a combination of smoothelin and vimentin could help distinguish detrusor muscle from muscularis mucosae. Two subsequent studies addressed the question of whether immunohistochemistry with smoothelin would help resolve pathologic staging difficulty in problematic transurethral resection specimens [412,413]. Both studies confirmed the diagnostic utility of this marker. In the first study, 4 cases with equivocal muscularis propria on standard H&E stains were examined and in the latter a series of 34 specimens submitted for consultation because of questions relating to pathological stage were stained for smoothelin. This publication mentioned that the staining intensity of blood vessel wall was similar to that of the detrusor muscle, implying that the vessel wall musculature could be used as an internal reference [412]. The latter publication noted occasional overlap in intensity of smoothelin staining for the two muscle layers, which might lead to spurious pathological staging results [413]. Since all studies to date have demonstrated that immunostaining for smoothelin with clone R4A monoclonal antibody can help differentiate between muscularis mucosae and detrusor muscle, this marker may be employed in controversial cases as a diagnostic tool. Since a minority of samples displayed a similar intensity of staining in both muscle types, the immunostaining should always be used in conjunction with the H&E findings. Further, vimentin immunostaining may be of additional help in distinguishing muscularis mucosae from detrusor muscle [411].

5. CONCLUSIONS

Although these markers have been shown to have promise, the studies are limited and from only a few institutions. Substantially more data is needed before these could be recommended for routine application.

Level of evidence: 4
Recommendation: C

II. SUMMARY OF MOLECULAR/GENETIC ALTERATIONS IN UROTHELIAL CARCINOMA

1. INTRODUCTION

Despite the extensive new information and knowledge on bladder cancer genetics, epigenetics and gene expression, much is needed to satisfy several unanswered questions.

Much of the work is following, and pointing toward, two distinct pathways that correspond to two main groups of tumors: superficial (papillary and flat) and muscularis propria-invasive urothelial carcinoma. A major question is whether the existing molecular information can explain tumorigenesis along the
proposed two major tumor groups in regard to the molecular events and of the biochemical signaling pathways involved. Another equally important question is whether currently available information, or future knowledge, can predict which superficial bladder tumors will later progress to become invasive. Similarly, will there be any marker that can have prognostic significance within any given stage of the tumor. Despite this being a goal of many molecular studies, to date molecular information has failed to provide robust or reliable predictive markers. Possibly, key markers still remain to be identified.

2. MOLECULAR ALTERATIONS IN UROTHELIAL CARCINOMA

Molecular, genetic and epigenetic aberrations commonly involved in urothelial carcinoma are listed in Tables 15 and 16. Briefly, most studies of low-grade papillary urothelial carcinoma show few molecular alterations apart from deletions involving chromosome 9 and mutations of FGFR3 and HRAS. These tumors are often near-diploid with loss of chromosome 9 by far the most common cytogenetic finding (refer to Tables 15 and 16 for more details).

In invasive urothelial carcinoma, many genetic alterations have been reported in addition to frequent chromosome, which involve dysregulations of several oncogenes and tumor suppressor genes. It has been recently shown that tumors with aberrations in p53/MDM2, RB1 and E2F3 are associated with more genomic instability.

3. SIGNALLING PATHWAYS IN UROTHELIAL CARCINOMA

There seems to be distinct signaling pathways in two groups of urothelial carcinoma. The association of FGFR3 or HRAS mutations in the majority of superficial tumors suggests that they share changes in pathway activation, whereas, the common inactivation of RB1 and TP53 pathways in invasive tumors may indicate a distinct signaling status.

Activation of the PI3K/Akt pathway in urothelial carcinoma could occur via the known mutation
of PTEN and TSC1. A number of therapeutic applications targeting molecules in these pathways have been developed and are being tested for potential roles in treating urothelial carcinoma.

4. BIOMARKERS WITH DIAGNOSTIC/PROGNOSTIC VALUES IN URINE SAMPLES

a) BTA tests

This test is based on the detection of the human complement factor H-related protein, which is reported to be expressed only in bladder tumor cells. The sensitivity of the BTA stat is reported to be 50% for low grade urothelial carcinomas, which is higher than cytology. Conversely, the specificity of BTA stat is reportedly lower than cytology.

b) Nuclear Matrix Protein 22 (NMP22)

This test is based on the detection of NMP22, which is a member of a family of proteins that is part of the structural framework of the nucleus and provide support for the nuclear shape and also involved in DNA replication, in RNA transcription and in regulation of gene expression. This protein is reported to have a concentration as high as 25 times in urothelial carcinoma as compared to normal urothelial cells. This assay is approved for both the detection of new cancers and the follow-up of patients with a prior history of urothelial carcinoma. The reported sensitivity ranges are 34.6%–100%, and 49.5%–65.0%, but false positive results have been reported.

c) Bladder Cancer Immunofluorescence Assay

This is an immunofluorescence assay designed to improve the sensitivity of urine cytology. It employs a cocktail of three monoclonal antibodies; M344, LDQ10 and 19A211. The first two detect a mucin-like antigen, while the third one recognizes a high molecular weight glycosylated form of carcinoembryonic antigen in exfoliated tumour cells. This assay is approved only for use as a

Table 15. Common aberrations in urothelial carcinoma as detected by loss of heterozygosity (LOH) and comparative genomic hybridization (CGH) analyses

<table>
<thead>
<tr>
<th>LOH</th>
<th>CGH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td>Clinical Association</td>
</tr>
<tr>
<td>3p</td>
<td>high grade/high stage</td>
</tr>
<tr>
<td>4p</td>
<td>high grade/high stage</td>
</tr>
<tr>
<td>4q</td>
<td>high grade/high stage</td>
</tr>
<tr>
<td>8p</td>
<td>high grade/high stage</td>
</tr>
<tr>
<td>9q</td>
<td>all stages/grades</td>
</tr>
<tr>
<td>11p</td>
<td>high grade/high stage</td>
</tr>
<tr>
<td>14q</td>
<td>recurrence</td>
</tr>
</tbody>
</table>

Table 16. Established clinicopathologic prognostic parameters in superficial and muscle invasive urothelial carcinoma of bladder.

<table>
<thead>
<tr>
<th>Clinicopathologic Prognostic Parameters</th>
<th>Superficial urothelial carcinoma</th>
<th>Muscle invasive urothelial carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO/ISUP Grade</td>
<td>pTNM</td>
<td></td>
</tr>
<tr>
<td>pT stage</td>
<td>Resistance to neoadjuvant chemotherapy</td>
<td></td>
</tr>
<tr>
<td>Presence of associated CIS/Dysplasia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease duration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to and frequency of recurrences</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multifocality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor Size (&gt;3 cm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Failure of prior BCG Rx</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence of LVI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depth of Lamina propria Invasion</td>
<td></td>
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</tbody>
</table>
surveillance test if used in conjunction with cytology. The overall sensitivity of the combined Bladder Cancer Immunofluorescence Assay and cytology is approximately 84%, which is better than either test alone and it performs better at the detection of low grade urothelial carcinoma.

**d) UroVysion®**

This is a fluorescent in situ hybridization (FISH) probe set with FDA approval for use in monitoring tumor recurrence and primary detection of urothelial carcinoma in voided urine specimens from patients with gross or microscopic hematuria, but no previous history of urothelial carcinoma. The UroVysion® test probe set contains a mixture of four fluorescent labeled DNA probes; a locus specific probe to the 9p21 band on chromosome 9 and to the centromere of chromosomes 3, 7 and 17. The individual sensitivity of the centromeric probes for chromosome 3, 7, 17 is reported to be 73.7%, 76.2% and 61.9%, respectively, while the sensitivity of homozygous 9p21 deletion for urothelial carcinoma has been reported as 28.6%. The UroVysion® test is based on combination of these probes and the sensitivity and specificity has been reported to be 72% and 83%, respectively. This test, however, is not free of false positive and false negative results.

**Level of evidence: 4**

**Recommendation: C**

### III. PROGNOSTIC AND PREDICTIVE BIOMARKERS IN UROTHELIAL CARCINOMA

**1. INTRODUCTION**

Molecular diagnostics applications are now an integral part of the management algorithms of several solid tumors such as breast, colon, and lung. In stark contrast, the current clinical management of urologic malignancies is lagging behind. Clinically robust molecular tests that can identify patients that are more likely to respond to a given targeted agent or even those in need of a more aggressive treatment based on well-validated molecular prognosticators are still lacking. Table 17 and 18 outline traditional and potential molecular markers in bladder cancer. Several promising biomarkers for detection, prognosis, and targeted therapeutics are now under evaluation. The following is a discussion of some candidate biomarkers that may soon make their transition to clinical assays in urothelial carcinoma patients.

**2. DIVERGENT MOLECULAR PATHOGENESIS IN UROTHELIAL CARCINOMA**

Superficial and muscle invasive bladder urothelial carcinoma (BC) display two distinct clinical phenotypes in regards to biologic behavior and prognosis. Increasingly, molecular evidence supporting two divergent pathways of pathogenesis for superficial and invasive disease is accumulating. Superficial BC is thought to originate from benign urothelium through hyperplasia with only a small contribution (10-15%) to the pool of high grade non-invasive and subsequently invasive BC. The majority of invasive tumors appear to originate through progression from dysplasia to flat CIS and high grade non invasive BC where genetic instability lead to accumulation of genetic alterations promoting progression to invasive lesions [414-417].

Clinically, a significant proportion of superficial tumors (pTa and pT1) are deemed to recur following transurethral resection (TURB) with only a relative minority of cases enduring progression to higher-grade, deeply invasive aggressive tumors.

The superficial BC pathogenesis pathway appears to be primarily based on alterations in the tyrosine kinase receptor FGFR-3 and H-RAS[418] and PIK3-CA-Akt in a subset of cases [414,419,420]. The RAS-MAPK and PI3K-Akt pathways are potentially the most important pathways promoting cell growth in urothelial neoplasia. RAS genes activating mutations lead to activation of Mitogen-activated protein kinases (MAPK) and PI3K pathways. Activating mutations in upstream tyrosine kinase receptor FGFR3 seems to be mutually exclusive with RAS mutations given that both signal through a common downstream pathway in urothelial oncogenesis. On the other hand, PIK3CA mutations generally co-occur with FGFR3 mutations suggesting an additive oncogenic effect of PIK3CA to FGFR3 mutations.

The pathogenic pathway for muscle invasive BC primarily involves alterations in tumor suppressor genes p53, p16 and Rb [416,417,421].

As illustrated in figure 53, subsequent p53 and Rb alterations are also needed for the progression of a subset of superficial lesions into a higher grade muscle invasive BC.

**3. PROGNOSTIC BIOMARKERS IN SUPERFICIAL NON-MUSCLE INVASIVE (NMI-BC) AND MUSCLE INVASIVE UROTHELIAL CARCINOMA (MI-BC)**

The currently established clinicopathologic prognostic parameters in superficial lesions include: pTNM stage, WHO/ISUP grade, size of tumor, disease multifocality, presence of CIS and frequency and rate of prior recurrences [422]. Prognostic parameters that can accurately predict the subset of superficial tumors that will progress are actively sought in order to identify patients in need for vigilant surveillance and aggressive treatment plan [423,424]. Equally needed are markers that will improve prognostication in muscle invasive disease given the current poor
### Emerging Molecular Prognostic Markers

<table>
<thead>
<tr>
<th>Superficial Non Muscle Invasive Urothelial Carcinoma (NMI-BC)</th>
<th>Muscle Invasive Urothelial Carcinoma (MI-BC)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proliferation index (Ki67, MIB1, S phase)</strong></td>
<td>p53 inactivation/accumulation</td>
</tr>
<tr>
<td><strong>FGFR3 Mutation/Overexpression (protective)</strong></td>
<td>Alterations of Rb expression</td>
</tr>
<tr>
<td><strong>mG (FGFR3/MIB1)</strong></td>
<td>Loss of p21 expression</td>
</tr>
<tr>
<td><strong>p53 inactivation/accumulation</strong></td>
<td>Alteration of p16 expression</td>
</tr>
<tr>
<td><strong>DNA Ploidy Status</strong></td>
<td>Loss of E Cadherin</td>
</tr>
<tr>
<td>Multi Traget FISH</td>
<td><strong>RTK:</strong></td>
</tr>
<tr>
<td>HRAS</td>
<td>EGFR overexpression</td>
</tr>
<tr>
<td>ERBB3, ERBB4 overexpression (protective)</td>
<td>HER2 overexpression/amplification</td>
</tr>
<tr>
<td>Loss of E Cadherin</td>
<td></td>
</tr>
<tr>
<td><strong>Cell Cycle Control:</strong></td>
<td></td>
</tr>
<tr>
<td>Downregulation of Rb expression</td>
<td></td>
</tr>
<tr>
<td>Downregulation of p21 expression</td>
<td></td>
</tr>
<tr>
<td>Downregulation of p27 expression</td>
<td></td>
</tr>
<tr>
<td>Cyclin D3 overexpression</td>
<td></td>
</tr>
<tr>
<td>Cyclin D1 overexpression</td>
<td></td>
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<tr>
<td><strong>Multimarker Immunexpression Analysis:</strong></td>
<td></td>
</tr>
<tr>
<td>(p53,p27,Ki67,Rb,p21)</td>
<td></td>
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<tr>
<td><strong>Angiogenesis Markers:</strong></td>
<td></td>
</tr>
<tr>
<td>VEGF overexpression</td>
<td></td>
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<tr>
<td>HIF 1A overexpression</td>
<td></td>
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<tr>
<td>TSP1 Overexpression</td>
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<tr>
<td><strong>mTOR-Akt Pathway:</strong></td>
<td></td>
</tr>
<tr>
<td>mTOR</td>
<td></td>
</tr>
<tr>
<td>Phos S6 expression (protective)</td>
<td></td>
</tr>
<tr>
<td><strong>Genomic and Gene Expression Array Panels</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Epigenetic Alterations:</strong></td>
<td></td>
</tr>
<tr>
<td>RASSF1 promotor hypermethylation</td>
<td></td>
</tr>
<tr>
<td>DAPK promotor hypermethylation</td>
<td></td>
</tr>
<tr>
<td>APC promotor hypermethylation</td>
<td></td>
</tr>
<tr>
<td>E Cad promotor hypermethylation</td>
<td></td>
</tr>
<tr>
<td>EDNRB promotor hypermethylation</td>
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</tbody>
</table>
outcome (60% or less overall survival rate) in this group of patients [425-427].

The current increasingly detailed understanding of the molecular pathways involved in urothelial bladder cancer (BC) development and progression has fueled the field of molecular prognostication, theranostics and targeted therapy in this disease [73,424,428-444]. Incorporating molecular biomarkers in clinical management can only be done after rigorous and extensive validation process. Initial retrospective discovery studies need to be confirmed and validated in large independent cohorts. The crucial subsequent step in developing a prognostic or predictive biomarker is validating the robustnest of the proposed biomarker in well controlled multi-institutional randomized prospective study. Such prospective study should support a additive role for the inclusion of the new biomarker in existing management algorithm(s) [445,446]. It is the lack of the latter crucial steps in biomarkers development that had hindered the streamlining of clinical utilization of several promising markers in BC patient management.

a) Chromosomal Numerical Alteration

Chromosome 9 alterations are the earliest genetic alterations in both of the above described divergent pathways of BC development. They are responsible for providing the necessary milieu of genetic instability that in turn allows for the accumulation of subsequent genetic defects. Several additional structural/numeral somatic chromosomal alterations are also a common occurrence in BC. Among these, gains of chromosomes 3q, 7p, and 17q and 9p21 deletions (p16 locus) are of special interest given their potential diagnostic and prognostic value [447,448]. A multtarget interphase FISH based urine cytogenetic assay was developed (39) based on the above numerical chromosomal alterations and is now commercially available and commonly used in clinical management. Initially FDA approved for surveillance of recurrence in previously diagnosed BC patients, the test subsequently became approved for screening in high risk (smoking exposure) patients with hematuria. The multicolor FISH assay appears to enhance the sensitivity of routine urine cytology analysis and can be used in combination with routine cytology as a reflex testing in cases with atypical cytology. A sensitivity range of 69-87% and a specificity range of 89-96% have been reported with the multitarget interphase FISH assay [449]. With the exception of one study [450], the multitarget FISH urine assay has been shown to be more sensitive than routine cytology. An additional advantage of urine based FISH testing could be the anticipatory positive category of patients identified by such assay. This refers to patients where FISH assay detects molecular alteration of BC in urine cells several months prior to cancer detection by cystoscopy or routine cytology. In the study by Yoder et al [451], two thirds of the 27% of patients categorized as “anticipatory positive” developed BC that was detected by cystoscopy up to 29 months later. Such encouraging results point to the great potential of molecular testing in early detection and allocation of vigorous/frequent follow-up cystoscopy in at risk patients [452-455].

Finally, several recent studies have pointed to the potential prognostic role for multitarget FISH analysis [447,448,456-458]. Maffezini et al. were able to demonstrate that low-risk FISH-positive patients, defined as 9p21 loss/Ch3 abnormalities, had a higher rate of recurrence as compared to FISH-negative patients [456]. The recurrence rate was even greater in patients with a high-risk positive FISH (Ch7/Ch17 abnormality). Both Kawauuchi et al., using bladder washings and Kruger et al., using

Table 18. Recommended Nomenclature for Urine Cytology

I. Adequacy Statement (Optional)
Satisfactory for evaluation
List any quality factors affecting specimen
Unsatisfactory for evaluation (give reason)

II. General Categorization
Negative for epithelial cell abnormality (see Descriptive Diagnosis)
Epithelial cell abnormality present (see Descriptive diagnosis)

III. Descriptive Diagnosis
Negative for epithelial cell abnormality
Infectious agents
Bacterial organisms
Fungal organisms
Viral changes (CMV, herpes, adenvirus, polyomavirus)
Nonspecific inflammatory changes
Acute inflammation
Chronic inflammation
Changes consistent with xanthogranulomatous pyelonephritis
Cellular changes associated with:
Chemotherapeutic agents
Radiation

Epithelial Cell Abnormalities
Atypical urothelial cells (*see comment)
Low-grade urothelial carcinoma
High-grade urothelial carcinoma (invasive carcinoma vs. carcinoma in situ)
Squamous cell carcinoma
Adenocarcinoma
Other malignant neoplasms (specify type)

IV. Other
A comment section should be available and used at the discretion of the cytopathologist in which additional findings can be listed and/or further clarification of findings within one or more of the above diagnostic categories make. At the discretion of the cytopathologist, ancillary studies may be included in the report.
formalin fixed paraffin embedded transurethral biopsy samples, independently found loss of 9p21 to predict recurrence but not progression in superficial BC [447,448]. Furthermore, both Savic et al [457] and Whitson et al [458] found urine cytology and FISH in post-BCG bladder washings to be predictive of failure to BCG therapy in patients with non muscle invasive disease. Such promising prognostic role for multitarget FISH awaits prospective randomized trial before clinical integration into practice algorithm. Clear guidelines for interpretation and test performance parameters in terms of interobserver reproducibility is also needed [459].

b) Receptor Tyrosine Kinases

Recent studies have pointed to the potential prognostic value of evaluating the expression of receptor tyrosine kinases (RTK) such as FGFR-3, EGFR and other ERB family members (HER2/neu and ERBB3) [89,417,429,460-467] in superficial and muscle invasive bladder cancer disease.

FGFR3 mutations are a common occurrence in NMIB and can theoretically be used alone or combined with RAS and PIK3CA oncogenes as markers of early recurrence during surveillance. Both Zuiverloon et al [468] and Miyake et al [469] independently developed sensitive PCR assays for detecting FGFR3 mutations in voided urine. A positive urine sample by the assay developed by Zuiverloon group was associated with concomitant or future recurrence in 81% of NMI-BC cases [468]. An even higher positive predictive value of 90% was achieved in patients with consecutive FGFR3 positive urine samples. Similarly, Miyake et al. were able to detect FGFR3 mutation in 53% of their 45 patients and found their assay to be superior to cytology (78% vs 0) in detecting post TURB recurrence in NMI-BC harboring FGFR3 mutations in primary tumors [469].

Kompier et al. were recently able to develop multiplex PCR assay for mutational analysis detecting the most frequent mutations hot spots of HRAS, KRAS, NRAS, FGFR3 and PIK3CA in formalin fixed paraffin embedded (FFPE) TURB samples [419]. They demonstrated evidence of at least one mutation in up to 88% of low grade NMI-BC samples. Hernandez et al revealed that FGFR3 mutations were more common among low malignant potential neoplasms (LMPN; 77%) and TaG1/TaG2 tumors (61%/58%) than among TaG3 tumors (34%) and T1G3 tumors (17%) [470]. On multivariable analysis, mutations were associated with increased risk of recurrence in NMI-BC.

Van Rhijn et al previously proposed a molecular grade parameter (mG) based on a combination of FGFR3 gene mutation status and MIB-1 index as an alternative to pathologic grade in NMI-BC [471]. Recently, the same group elegantly validated their previously proposed mG parameter[89] and compared it to the European Organization for Research and Treatment of Cancer (EORTC) NMI-BC calculator [472] (weighted score of six variables including WHO 1973 grade, stage, presence of CIS, multiplicity, size, and prior recurrence rate). The mG (89%) was more reproducible than the pathologic grade (41-74%). FGFR3 mutations significantly correlated with favorable disease parameters, whereas increased MIB-1 was frequently seen with pT1, high grade, and high EORTC risk scores. EORTC risk score remained significant in multivariable analyses for recurrence and progression. Importantly, mG also maintained independent significance for progression and disease-specific survival and the addition of mG to the multivariable model for progression increased the predictive accuracy from 74.9% to 81.7%.

Several studies have suggested a negative prognostic role for HER2/neu amplification/overexpression in MI-BC [446,473-475]. Most recently, Bolenz et al. found HER2/neu positive MI-BC patients to be at twice increased risk for recurrence and cancer specific mortality on multivariable analyses adjusted for pathological stage, grade, LVI, lymph node metastasis and adjuvant chemotherapy [461].

c) P53, Cell Cycle Regulators and Proliferation Index Markers:

Early studies by Sarkis et al revealed p53 alterations to be a strong independent predictor of disease progression in BC (superficial, muscle invasive as well as CIS) [476-478]. P53 has also been shown to be predictive of increased sensitivity to chemotherapeutic agents that damage DNA [479-481]. Recent studies have further supported the prognostic role of p53 in pT1-pT2 patients following cystectomy showing an independent role for p53 alteration in predicting disease free survival (DFS) and disease specific survival (DSS) [482].

Among other G1-S phase cell cycle regulators, Cyclin D3 and Cyclin D1, p16, p21 and p27 have also been evaluated as prognosticators in NMI-BC [480,483-488]. Lopez-Beltran et al [485], confirmed their initial finding of the independent prognostic role of cyclin D3 and cyclin D1 overexpression in predicting progression in pTa and pT1 tumors [480]. Their findings however are in contrast to subsequent findings by Shariat et al. emphasizing the need for further validation in multi-institutional large cohorts of patients [487].

A synergistic prognostic role for combining p53 evaluation with other cell cycle control elements such as pRb, cyclin E1, p21 and p27 is emerging both in NMI-BC and MI-BC [424,435,479,489,490]. In a study by Shariat et al [424], NMI-BC patients with TURB demonstrating synchronous immunohistochemical alterations in all four tested markers (p53, p21, pRb and p27) were at significantly lower likelihood of sustaining disease free survival (DFS) compared
algorithms were 89% accurate for tumor staging, nodal metastases, and overall survival. Predictive algorithms were used to stratify bladder tumors based on stage, hierarchical clustering and supervised algorithms profiles of 105 cases of NMI-BC and MI-BC.433,443,444,496-501.

The superiority of multimarkers approach compared to prior single marker approach certainly merits further assessment [476-478,491]. Such multimarker approach of prognostication could soon be integrated in the standard of care in BC management once additional multi-institutional, prospective, trials confirm the above promising findings. Tumor proliferation index measured immunohistochemically by either Ki-67 or MiB-1 has been consistently shown to be a prognosticator in bladder cancer [89,471,480,484,492-495]. As mentioned above, tumor proliferation index (MiB1) in NMI-BC plays a prognostic role as one of the elements of the mG parameter forwarded by Van Rijn et al [471]. The independent prognostic role of proliferation index measured by Ki-67 has also been shown. In the study by Quintero et al. Ki67 index in NMI-BC TURB biopsy was predictive of PFS and DSS [494].

A similar role for proliferation index assessment as prognosticator is established in MI-BC. Building on initial findings of significance in an organ confined subset of MI-BC by Margulis et al a recent report of the bladder consortium multi-institutional trial (7 institutions and 713 patients) confirmed the role of proliferation index, measured in cystectomy specimens [492]. In the later study, Ki-67 improved prediction of both PFS and DSS when added to standard prediction models supporting a role for proliferation index assessment in stratifying patients for peri-operative systemic chemotherapy. This has certainly taken Ki-67 assessment a step closer to clinical applicability in MI-BC.

d) Gene Expression and Genomic Analysis

Several recent gene expression studies have highlighted sets of differentially expressed genes that may play a role in diagnosis and in predicting recurrence and progression in BC [73,102,416,430-433,443,444,496-501].

In a landmark study by Sanchez- Carbayo et al oligonucleotide arrays were used to analyze transcript profiles of 105 cases of NMI-BC and MI-BC.433 Hierarchical clustering and supervised algorithms were used to stratify bladder tumors based on stage, nodal metastases, and overall survival. Predictive algorithms were 89% accurate for tumor staging using genes differentially expressed in superficial Vs muscle invasive tumors. Accuracies of 82% (entire cohort) and 90% (MI-BC) were also obtained for predicting overall survival. A genetic profile consisting of 174 probes was identified in patients with positive lymph nodes and poor survival.

Recently, Birkhahn et al attempted to identify genes predictive for recurrence and progression in Ta using a quantitative pathway-specific approach in a set of 24 key genes by real-time PCR in tumor biopsies at initial presentation 73. They found CCND3 expression to be highly sensitive and specific for recurrence (97% and 63%, respectively). While HRAS, E2F1, BIRC5/Survivin and VEGFR2 were predictive for progression by univariate analysis, on multivariable analysis the combination of HRAS, VEGFR2, and VEGF expression status predicted progression with an impressive 81% sensitivity and 94% specificity.

In a recent landmark study, Lindgren et al suggested that a combined molecular and histopathologic classification of BC may prove more powerful in predicting outcome and stratifying treatment [497]. The authors combined gene expression analysis, whole genome array-CGH analysis and mutational analysis of FGFR3, PIK3CA, KRAS, HRAS, NRAS, TP53, CDKN2A, and TSC1 to identify two intrinsic molecular signatures (MS1 and MS2). Genomic instability was the most distinguishing genomic feature of MS2 signature, independent of TP53/MDM2 alterations. Their genetic signatures were validated in two independent data sets that successfully classified urothelial carcinomas into low-grade and high-grade tumors as well NMI-BC and MI-BC with high precisions and sensitivities. Furthermore, a gene expression signature that independently predicts metastasis and disease-specific survival was also defined. This clearly supports the role of molecular grading as a complement to standard pathologic grading.

Mengual et al performed gene expression analysis in 341 urine samples from NMI-BC and MI-BC patients and 235 controls by TaqMan Arrays [444]. A 12+2 gene expression signature demonstrated a staggering 98% sensitivity and 99% specificity in discriminating between BC and control and 79% sensitivity and 92% specificity in predicting tumor aggressiveness (NMI-BC vs MI-BC). The signature was then validated in voided urine samples and maintained accuracy. In an integrated genetic/epigenetic approach, Serizawa et al. performed a comprehensive study of the expression of 24 key genes by real-time PCR in tumor biopsies at initial presentation. They found CCND3 expression to be highly sensitive and specific for recurrence (97% and 63%, respectively). While HRAS, E2F1, BIRC5/Survivin and VEGFR2 were predictive for progression by univariate analysis, on multivariable analysis the combination of HRAS, VEGFR2, and VEGF expression status predicted progression with an impressive 81% sensitivity and 94% specificity.
and 189 hypermethylation events were detected. The total panel of markers provided a sensitivity of 93% and 70% in biopsies and urine samples respectively. FGFR3 mutations in combination with three methylation markers (APC, RASSF1A and SFRP2) provided a sensitivity of 90% in tumors and 62% in urine with 100% specificity.

With the impending cost and turn around time advantages of next generation sequencing technology, the power of genomic approach in providing a non-invasive diagnostic and predictive tool should be heavily pursued in a prospective large cohort.

e) Epigenetic Alterations

Epigenetic analysis is also gaining momentum in BC as a non invasive diagnostic tool for screening and surveillance. As a prognostic tool, epigenetic analysis has similarly shown promising potential in BC patients [501-514].

In an early study by Catto et al hypermethylation analysis at 11 CpG promoters islands was performed by MSP PCR in 116 bladder and 164 upper-tract tumors [503]. Promoter methylation was found in 86% of all tumors and the incidence was relatively higher in upper tract tumors compared to BC. Methylation was associated with advanced tumor stage and higher tumor progression and mortality rates. Most importantly, on multivariate analysis methylation rates at the RASSF1A and DAPK genes promoters was associated with disease progression independent of tumor stage and grade.

The same group, using quantitative methylation-specific PCR (MSP) at 17 candidate gene promoters, found five loci to be associated with progression (RASSF1a, E-cadherin, TNFSR25, EDNRB, and APC) [513]. Multivariate analysis revealed that the overall degree of methylation was more significantly associated with subsequent progression and death than tumor stage. An epigenetic predictive models developed using artificial intelligence techniques identified likelihood and timing of progression with 97% specificity and 75% sensitivity.

Among the studies on the diagnostic role of promoter methylation, the study by Lin et al used MSP assay in 4 genes (E-cadherin, p16, p14, and RASSF1A) in primary tumor DNA and urine sediment DNA from 57 bladder cancer patients 508. MSP detected hypermethylation in the urine of 80% of tested patients. Hypermethylation analysis of E-cadherin, p14 or RASSF1A in urine sediment DNA detected 85% of superficial and low grade BC and 79% of high grade and 75% of invasive bladder cancers. The study highlighted the great potential of such test in detecting NMI-BC. Similar diagnostic role was also found by Cabello et al. using a novel technology, methylation-specific multiplex ligation-dependent probe amplification assay (MS-MLAP), to analyze 25 tumor suppressor genes (TSG) that have been thought to play a role in BC oncogenes.502. The TSG included PTEN, CD44, WT1, GSTP1, BRCA2, RB1, TP53, BRCA1, TP73, RARB, VHL, ESR1, PAX5A, CDKN2A, and PAX6. The authors found BRCA1, WT1, and RARB to be the most frequently methylated TSGs with receiver operating characteristic curve analyses revealing significant diagnostic accuracies in two additional validation sets.

Finally, assessment of promoter methylation is giving additional insights on BC oncogenesis. Promoter methylation of CpG Islands and “shores” controlling miRNA expression is one such example [505].

f) Ploidy and Morphometric Analysis

Several studies have pointed to the independent prognostic role of ploidy and S phase analysis in NMI-BC [495,515-521]. Ploidy analysis can be performed by flow cytometry or automated image cytometry (ICM) and is applicable to urine cytology specimens as well as biopsy supernatant [521] and disaggregated TURB FFPE specimens [516].

In one of the largest studies assessing DNA ploidy in NMI-BC (377 test set; 156 validation set); Ali-Et-Dein et al. found stage, DNA ploidy, tumor multiplicity, history of recurrence, tumor configuration and type of adjuvant therapy to independently predict recurrence [515]. Recurrence at 3-month, grade and DNA ploidy were the only predictors of progression to muscle-invasion. The constructed “Predictive – Index” model successfully stratified patients in a second validation set into three risk groups. Likewise, Baak et al were able to show ploidy status and S phase measured by an automated image cytometry platform (ICM) to be strong independent predictors of recurrence and progression in pTa and pT1 patients [516].

Despite all the above encouraging data, ploidy analysis still await a prospective randomized trial to bring ICM or flowcytometry technique into current standard management algorithms for NMI-BC.

g) Emerging Potential Biomarkers:

Other biomarkers with encouraging but less robust data on their potential prognostic role in BC include tumor microenvironment markers such as cell adhesion E Cadherin and N Cadherin [439,522] and angiogenesis modulators such as HIF 1a, HIF 2, VEGF, CA IX and Thrombospondin-1 [438,523-528]. In addition, our group and others have demonstrated a potential prognostic role for mTOR-Akt pathway markers [439,522,529-532]. Other markers such as Aurora-A have also been investigated in this setting [533,534]. Finally, miRNA profile alterations will certainly be a new area of heavy investigation as a non invasive diagnostic and as a prognostic tool in BC patients [505,535-537].
The current clinicopathologic based prognostic approach to predicting progression in superficial BC [102,494,538-540] will potentially be supplemented in the not so distant future by a molecular guided approach based on markers among those listed in *table 16 and 17*, [422,427,435,503,513,524,525, 53,532,541-544].

Finally, from a targeted therapy perspective, RTK-HRAS-MAPK (superficial disease) and p53-pRb (muscle-invasive disease) pathogenic pathways as well as angiogenesis pathway of the tumor microenvironment offer tremendous new opportunities for future management of BC. Phase II trials evaluating the role of tyrosine receptor kinase inhibitors (TKI) targeting EGFR with small molecules such as Gefitinib and Sorafenib or monoclonal antibodies (MoAb) such as Cetuximab are underway. Other Phase II trials are addressing the role of Herceptin (anti HER2 MoAb) and Bevacizumab (anti VEGF MoAb) in BC. Phase I trials testing the safety of p53 or Rb intravesical gene therapy are being evaluated. One strategy example is the intravesical introduction of a wild type p53 loaded replication deficient Adenovirus (AdSCMV-TP53) in an ambitious attempt to compensate for the loss of p53 function in invasive BC [545-549].

### h) Conclusion:

At present, there are no prognostic or predictive biomarkers for urothelial carcinoma that significantly improve on pathologic grade and stage information; therefore, none of these evaluations are currently recommended for routine clinical practice.

**Level of evidence: 4**

**Recommendation: C**

### IV. THE UTILITY OF IMMUNOHISTOCHEMISTRY IN THE DIFFERENTIAL DIAGNOSIS OF PRIMARY VERSUS METASTATIC TUMORS TO THE URINARY BLADDER

#### 1. INTRODUCTION

Tumors metastatic to the urinary bladder are relatively uncommon accounting for 2 to 14% of all bladder malignancies [193,194,550,551]. Secondary neoplasms may affect the urinary bladder by either direct extension from adjacent anatomic sites or, less frequently, by lymphovascular spread [552]. Tumors that may extend directly to the urinary bladder include colon (21%), prostate (19%), rectum (12%), and uterine cervix (11%). Distant sites include stomach, skin, lung, breast, kidney, and testis [193,550,553-555]. These tumor deposits are almost always solitary lesions, often (more than half) are located in the neck or trigone, and the vast majority correspond to adenocarcinomas [193]. It is important to separate metastases from primary urinary bladder tumors as they are associated with different managerial approaches and ominous prognoses. However, this distinction may represent an important challenge for urologists and pathologists. In this section we will be discussing specific immunohistochemical markers used in distinguishing primary from secondary tumors of the urinary bladder.

#### 2. PROSTATIC ADENOCARCINOMA

Direct invasion is the most frequent mechanism of bladder involvement by prostatic adenocarcinoma. The latter can be morphologically indistinguishable from poorly differentiated urothelial carcinoma, especially when glandular differentiation or clear cell features are exhibited by urothelial carcinomas. This distinction is critical given the staging, therapeutic, and prognostic implications. Several immunohistochemical markers have been reported to reliably differentiate poorly differentiated urothelial carcinoma from prostatic adenocarcinoma. However, none of them is sufficiently sensitive and/or specific to be used alone, and therefore immunohistochemical panels are recommended. Kunju et al [556] evaluated the joint utility of prostatic specific antigen (PSA), prostate acid phosphatase (PAP), high-molecular weight cytokeratin (HMWCK) (clone 34BE12), CK7, CK20, p63 and α-methylacylcoenzyme (P504s) in this differential diagnosis. They found that 95% of documented prostatic adenocarcinomas demonstrated a PSA+, HMWCK/p63- immunohistochemical profile whereas 97% of urothelial carcinomas tested were PSA-, HMWCK/p63+. Negative PSA associated with HMWCK and/or p63 positivity may also establish a diagnosis of urothelial carcinoma. Even though PSA and PAP are reliable markers of prostatic adenocarcinoma [556-561], their expression can be absent or only focally and weakly seen in high-grade tumors. PSA expression is frequently heterogeneous and consequently, immunostains may need to be performed on multiple blocks containing tumor [562]. Additionally, PAP is slightly less specific for prostatic origin as a minority of urothelial carcinomas (approximately 10%), may be focally positive for this marker [562]. Although the majority of prostatic adenocarcinomas are CK7-/CK20-, while urothelial carcinomas are CK7+/CK20+ or CK7+/CK 20-[556,557,559,563-565], results frequently overlap making these markers less sensitive and specific when used in isolation. However, the coordinate expression patterns of CK7 and CK20 in conjunction with PAP may be very helpful in differentiating prostatic carcinoma (PAP+/CK7+/CK20–) from urothelial carcinoma (PAP+/CK7+/CK20+ or PAP+/ CK7+/CK20–), especially when the results of the preliminary panel of PSA, HMWCK, and p63 are all negative. Furthermore, in the occasion where
the primary panel demonstrates negative results, addition of uroplakin III and thrombomodulin may help as both markers are negative in adenocarcinomas of prostatic origin. Alphamethylacyl-CoA-racemase (P504s) is not a useful marker to distinguish prostatic from urothelial carcinomas since it is also expressed in approximately one third of urothelial carcinomas [556,566-568].

Newer prostate restricted markers such as prostate specific membrane antigen (PSMA) and protein (P501S) have been proposed to be a useful adjunct in the diagnosis of prostate adenocarcinoma as they have a high sensitivity [569-576] and can be used in the differential diagnosis between prostatic and urothelial carcinoma.

A novel marker NKX3.1, an androgen regulated homeodomain gene whose expression in prostate epithelium has been extensively studied, has been established as part of the immunohistochemical panel to distinguish metastatic prostatic adenocarcinoma and high grade urothelial carcinoma [333,577]. The sensitivity of NKX3.1 in prostatic adenocarcinoma (Gleason scores 8 to 10) ranges from 92% to 94%. Specificity for prostate versus urothelial origin has been reported to be 100%, as all urothelial carcinomas are NKX3 negative [577]. The predominant NKX3 nuclear staining in primary and metastatic prostatic adenocarcinomas is useful when compared to other prostate specific markers (e.g. PSA, PAP, and P501s) that exhibit cytoplasmic staining. This staining pattern can be of additional diagnostic benefit when there is only weak and focal cytoplasmic staining of other prostate markers.

Glutamate decarboxylase 1 (GAD1) is also a sensitive and specific for prostate tissue, whereas bladder neoplasms are entirely negative [578]. When compared to the sensitivity and specificity profile of PSA and PSMA, GAD1 has been found to as reliable as PSA and to show higher specificity than PSMA. GAD1 shows consistent strong expression in both benign and malignant prostate tissues, while cancers from the urinary bladder, rectum, and lung are almost entirely negative [578].

In an attempt to find better markers for urothelial carcinoma, Higgins et al identified S100P and GATA3 as two distinct genes showing consistently high and uniform expression in urothelial carcinoma when compared to prostatic adenocarcinoma[213] In an immunohistochemical analysis on tissue microarrays, polyclonal antiserum against S100P protein stained 86% of urothelial carcinomas but only 3% of prostatic adenocarcinomas and monoclonal antibody against GATA3 stained 67% urothelial carcinomas but none of the prostate carcinomas.

3. COLORECTAL CARCINOMA

The morphologic appearance of poorly differentiated rectal or colonic carcinoma, which may secondarily invade the urinary bladder, may have significant morphologic overlap with high-grade urothelial carcinoma with glandular differentiation (either with mucinous, enteric, or signet ring cell features) or pure urinary bladder adenocarcinoma. Even though clinical history is essential and the findings of cystitis glandularis of intestinal type, carcinoma in situ, or tumor centered in the inner half of the bladder wall would favor a primary urothelial origin, in small specimens these findings may not be seen and immunohistochemistry may be needed in elucidating the origin of the tumor [193]. Urothelial carcinoma with glandular differentiation may be separated from secondary involvement by colonic carcinoma as it is positive for CK7 and CK20, but negative for villin. Colonic adenocarcinoma is typically CK7 negative and CK20/villin positive [579,580]. However, it is important to keep in mind that colonic carcinomas, although uncommonly, can express CK7 along with CK20 [581]. Although bladder carcinomas generally lack of villin and CDX2 staining, primary vesical carcinomas with gland formation may take on an enteric immunophenotype [579,582,583]. Other markers that may be used as part of a panel include thrombomodulin, uroplakin III and β-catenin. Thrombomodulin is expressed in urothelial carcinomas, but it is negative in colorectal carcinomas, and it appears to be a more sensitive marker than CEA in this differential diagnosis [584]. Up to date, uroplakin III has only been demonstrated in urothelial carcinomas [557,585,586]. β-catenin is highly expressed in colonic carcinoma cells as a result of mutated adenomatous polyposis coli gene [331], but its expression is minimal to absent in tumors of urothelial origin including adenocarcinomas [331,587]. CEA and P504s are not helpful in either differential diagnosis [193,582]. The latter is observed in approximately 30% of urothelial carcinomas [566,588] and up to 65% of urinary bladder adenocarcinomas [582]. In difficult cases, colonoscopy should serve as the gold-standard in this distinction.

4. CERVICAL/VAGINAL CARCINOMA

Squamous cell carcinoma of the cervix or vagina can secondarily involve the urinary bladder and mimic a primary squamous cell or high-grade urothelial carcinoma with or without squamous differentiation [118]. Likewise, adenocarcinomas of the cervix with or without intestinal differentiation and transitional cell carcinoma of the cervix or corpus (the latter very rare) or vagina, may simulate a primary adenocarcinoma or urothelial carcinoma of the urinary bladder [589-595].

In general, all squamous cell carcinomas, independent of site of origin, are CK7, CK5/6, cytokeratin 34BE12, and p63 positive; therefore, these markers are not helpful in establishing the site
of origin [596-598]. Even though p16, a surrogate marker of human papilloma virus (HPV), is widely expressed in squamous cell carcinomas of the cervix and vagina,[599,600] it has also been reported in one third of squamous cell carcinomas of the urinary bladder in both males and female patients [601] and in high-grade urothelial carcinomas [313]. The use of in situ hybridization for HPV DNA can be helpful as this is positive in most squamous cell carcinomas of the cervix, but not of the bladder (Figure 54A,B) [602].

Urothelial carcinomas of the urinary bladder are typically positive for CK7, CK20, uroplakin, and thrombomodulin with the latter two having 100% and 96% specificity and 57% and 69% sensitivity, respectively [585,603]. They are also typically p63 positive [255]. Squamotransitional cell carcinomas of the uterus have been shown to be CK7 and p63 positive and uroplakin negative, but experience is very limited [604]. Transitional cell carcinomas of the uterus and vagina as well as those arising from the urinary bladder are both positive for CA19.9 and CEA [603]. No experience has been reported with thrombomodulin in squamotransitional carcinomas of the uterus, although Ordoñez reported negative staining on 7 squamous cell carcinomas of the cervix and 35 adenocarcinomas of the endometrium [605]. Two relatively new markers proposed by some investigators to be highly expressed in urothelial carcinomas of the bladder, namely S100p and GATA3, have been shown to be also positive in transitional cell proliferations/tumors of the ovary [213], but no experience is reported in transitional cell proliferations of the lower female genital tract.

Cervical adenocarcinomas of the usual or intestinal type, or even those with signet ring cells, are typically CK7 positive. Intestinal type adenocarcinomas are also often positive for CK20 and CDX2, in contrast to usual cervical adenocarcinomas, which rarely stain for these markers [590]. However, cervical carcinomas with signet ring morphology have been reported to be CK20 and CDX2 negative [590]. Thus, these markers are not useful in distinguishing secondary involvement by cervical adenocarcinoma from urinary bladder adenocarcinoma, especially when the tumor has intestinal morphology. CEA is not helpful in this differential diagnosis either, while thrombomodulin expression in urinary bladder adenocarcinomas is much lower (approximately 17%) when compared to conventional urothelial carcinomas. Thus, if positive, thrombomodulin is helpful in favoring a urinary bladder origin of the adenocarcinoma [584]. Uroplakin expression has been reported in 50 to 60% of all urothelial carcinomas [557], but results on urothelial carcinomas with glandular differentiation or pure adenocarcinomas are lacking. p16, as discussed in the differential diagnosis of squamous cell carcinomas, is typically positive in cervical adenocarcinomas (related to HPV infection); however, it has not been studied in primary adenocarcinomas of the urinary bladder and should be used with caution as it has been shown to be expressed in endometrial and colorectal carcinomas [606,607].

Clear cell carcinoma can arise in the uterine cervix or vagina and may secondary involve the urinary bladder. In such cases, the differential diagnosis includes a clear cell carcinoma of the urinary bladder or a urothelial carcinoma with clear cytoplasm [205,608]. A prior clinical history of diethylstilbestrol or finding areas of typical urothelial neoplasia would favor a primary cervical or urinary bladder origin, respectively. Clear cell carcinomas of the urinary bladder express low-molecular weight keratins, CK7 and CK20, but are negative for estrogen and progesterone receptors [114,204,609-611], an immunohistochemical profile that overlaps with that seen in clear cell tumors of the female genital tract. Primary urinary clear cell carcinomas are also typically positive for CD10, P504s, and they can be positive for PAX2 [608]. In contrast, clear cell carcinoma of the cervix and vagina has been reported to be CD10 negative, although experience with this marker is limited [612]. Up to date, PAX2 and P504s have not been studied in clear cell carcinomas of the

Figure 54. A) Cervical squamous cell carcinoma involving the urinary bladder shows B) positivity by HPV in situ hybridization.
female genital tract. PAX8, another positive marker of clear cell carcinoma of the urinary bladder [613] is expressed in tumors arising from the ovary [614], but no experience is reported in clear cell carcinomas of the uterus or vagina.

5. GASTRIC CARCINOMA

Advanced gastric carcinoma, especially if poorly differentiated or signet ring cell type, may secondarily involve the urinary bladder. The morphologic appearance may overlap with that seen in poorly differentiated or plasmacytoid urothelial carcinoma. These tumors typically show a CK7+/CK20+ immunohistochemical profile that overlaps with that observed in urothelial carcinoma. Uroplakin may be helpful in separating a poorly differentiated urothelial carcinoma from a poorly differentiated gastric carcinoma, but is not helpful in the differential diagnosis with plasmacytoid carcinoma, as the latter is frequently negative or shows minimal positivity [233]. Thrombomodulin, another useful marker in the diagnosis of urothelial carcinoma, has not been reported in gastric carcinoma, but in some pancreatic carcinomas [170].

6. MALIGNANT MELANOMA

Melanoma can be primary [615,616] or involve secondarily (more commonly) the urinary bladder [194]. In most cases a prior history of melanoma, the finding of typical histologic patterns and the presence of melanin pigment are helpful in the diagnosis of melanoma. Specifically, the finding of an in situ component may be helpful in establishing a primary origin in the urinary bladder. However, it is well known that malignant melanoma in the urinary tract may closely mimic the appearance of a urothelial carcinoma, as it can have a papillary, nested, sarcomatoid, plasmacytoid and even pagetoid growths as described in urothelial carcinomas [617]. When separating melanoma from urothelial carcinoma, it is important to remember that the latter is frequently positive for S-100 [213] and melanomas may rarely be positive for pankeratins [150], and thus a panel of antibodies including HMB45, melan-A and cytokeratins should be used to establish the nature of the tumor.

7. LUNG CARCINOMA

Lung adenocarcinoma is the most frequent type of pulmonary neoplasm and therefore is the most frequent type found in a metastatic setting, followed by small cell and squamous cell carcinoma. When glandular morphology is the predominant pattern in a bladder neoplasm in a patient with a known lung carcinoma or lung mass, the differential diagnosis between a primary and a secondary neoplasm should be entertained. The use of a limited immunohistochemical panel including napsin A, GATA3, and S100P may be extremely helpful in this setting [618]. Thyroid transcription factor-1 (TTF-1) plays a role in the development and physiology of the thyroid gland and lungs, and it is used as a marker of carcinomas originating in these organs. Commercially available clones of TTF-1 monoclonal antibodies, 8G7G3/1 and SPT24, have been reported to have different sensitivities for the detection of neoplasms of different origins. SPT24 clone detects a significant number of non-pulmonary primary tumors, especially invasive urothelial carcinoma (5%) [619]. Therefore, if SPT24 is used, results should be interpreted with caution.

Even though small cell carcinoma of the urinary bladder accounts for less than 1% of all bladder tumors, the urinary bladder is the most frequent location of extrapulmonary small cell carcinoma [620]. Morphologically, this tumor is identical to its lung counterpart. The finding of associated conventional urothelial neoplasia or its variants would favor a primary origin from the urinary bladder, as one third of small cell carcinomas are admixed with conventional urothelial carcinoma. Both pulmonary and urinary bladder small cell carcinomas share a dot-like positive staining with pan-keratin and have variable expression of neuroendocrine markers (chromogranin, synaptophysin and CD56). Although TTF-1 was initially proposed as a useful marker to confirm the lung as the origin of a metastatic adenocarcinoma, its expression has been increasingly reported in tumors from other origins including small cell carcinomas of the urinary bladder [621].

When squamous differentiation is the predominant pattern in a urinary bladder neoplasm in a patient with a known lung squamous cell carcinoma, the differential diagnosis between a primary and a secondary neoplasm may be difficult. A panel including TTF-1, napsin A and p16 may be helpful, with TTF-1 and/or napsin A positivity favoring a lung primary, while p16 positivity typically would favor an extrapulmonary site [597].

8. BREAST CARCINOMA

Breast carcinoma metastatic to the urinary bladder is a rare event [622]. For the most part, the morphologic appearance of typical ductal carcinoma (which metastasizes to the urinary bladder less commonly than lobular carcinoma) does not create problems in differential diagnosis; however, when tumors have a micropapillary architecture or are composed of signet ring cells (either ductal or lobular), the histologic appearance overlaps with primary urothelial neoplasms [233,623,624]. When using immunohistochemistry, it is important to keep in mind that CK7 expression is seen in both breast and urothelial carcinomas,[563] although primary and metastatic ductal carcinoma show important differences in CK7 expression [625]. Cytokeratin 5/6 positivity can be detected in about half of urothelial
carcinomas, but can also be seen in one third of breast ductal but not lobular carcinomas [626]. Estrogen receptor (ER) expression is typically seen in breast carcinomas [627], but urothelial carcinomas can also express ER, especially when invasive, higher grade and high stage [628-630]. It is primarily β form that is expressed with expression of the α form being much less frequent (95). CK20 is rarely expressed in ductal and lobular carcinoma in contrast to 30% of transitional carcinomas [563]. Thus, a CK7+/CK20- profile would favor a breast carcinoma while a CK7+/CK20+ profile would support the diagnosis of urothelial carcinoma [564]. However, unusual subtypes of breast carcinomas including mucinous and papillary can be CK20 positive [627,631]. Gross cystic disease protein 15 (GCDP-15), a fairly specific marker for breast carcinoma, is only expressed in approximately 60% of these tumors. Thus, a positive stain supports a diagnosis of metastatic breast carcinoma, but a negative stain does not exclude it [632]. Other markers including EMA, CEA are not helpful in this differential diagnosis as both tumors may stain for these markers [558,633]. Thrombomodulin and CK34BE12, reported to be positive in up to 70% and 100% of urothelial carcinomas, can be expressed also in breast carcinoma [170].

9) RENAL CELL CARCINOMA

Renal cell carcinoma is an uncommon source of bladder metastasis with fewer than forty reported cases [208,554,634-637]. When metastatic renal cell carcinoma is encountered, immunohistochemistry may be very helpful as: a) either metastatic renal cell carcinoma may precede the primary tumor or in patients with a known prior history of renal carcinoma, metastatic foci may develop after a prolonged period of time and slides from the primary neoplasm may not be available for review; and b) metastatic renal cell carcinoma may look morphologically different from the primary tumor. Furthermore, in patients with a prior history of renal carcinoma and a “new” bladder tumor, it is extremely important to know if the tumor is a new primary versus metastases. Typically, patients with renal cell carcinoma metastatic to the bladder present with gross hematuria demonstrating sessile bladder lesions [554]. Histological evaluation is usually straightforward, however, on occasions, the differential diagnosis between a metastatic renal cell carcinoma and urothelial carcinoma is difficult as both may show overlapping morphologies, particularly if urothelial carcinoma has clear [202] or lipid-type cells [148]. A large variety of markers have been proposed for the diagnosis of primary renal cell carcinoma, however, studies on the immunoprofile of metastatic tumors are scarce. Metastatic renal cell carcinoma usually retains an immunoprofile that is similar to the one seen in primary neoplasms; however, intensity and proportion of staining tends to decrease.

CD10 membranous immunoreactivity is frequently used in the diagnosis of renal cell carcinoma, clear cell type [638]. However, there is a growing list of neoplasms that can be CD10 positive, including urothelial carcinomas. Bahadir et al [639] demonstrated that this marker is positive in more than 40% of urothelial carcinomas and its expression is strongly correlated with high tumor grade and stage. Therefore, in a setting where metastatic renal cell carcinoma is in the differential diagnosis, CD10 should be interpreted with caution. CK7 and P504s are sensitive markers for papillary renal cell carcinoma [613]; however, they also can be expressed in carcinomas of urothelial origin [556]. Although PAX2 and PAX8 are sensitive and relatively specific markers for renal neoplasms, regardless of subtype [638], these two markers have recently been also found in clear cell adenocarcinoma of the lower urinary tract limiting its value in this setting as discussed earlier [613]. C-kit is expressed in most chromophobe renal cell carcinomas and oncocytomas, however, clear and papillary renal cell carcinomas are negative for this marker as are urothelial carcinomas, except small cell carcinomas of the urinary bladder (approximately one third are immunoreactive) [640]; therefore, this marker may have limited utility in the differential diagnosis of renal versus urothelial carcinoma. In conclusion, it is suggested that a panel which includes PAX2 or PAX8 and CD10, supplemented by a urothelial marker would reliably differentiate the majority of metastatic renal cell carcinomas from urothelial carcinoma [638].

When renal carcinoma originates from the collecting ducts (collecting duct carcinoma) and metastasizes to urinary bladder, the differential diagnosis with urothelial carcinoma with glandular differentiation can be extremely challenging. High–molecular-weight cytokeratin is expressed in most collecting duct and urothelial carcinomas [638,641]. Adding urothelial markers like p63 can be useful in this differential diagnosis [638,641]. Finally, renal pelvic urothelial carcinomas are generally morphologically and immunophenotypically indistinguishable for their bladder counterpart; however, strong PAX8 expression is seen in a subset of renal pelvic urothelial carcinomas (unpublished data).

10. TESTICULAR NEOPLASMS

Metastatic testicular germ cell tumor to the urinary bladder is extremely rare with few reported cases in the literature [553,642]. Still, distinguishing metastatic germ cell from a non germ cell tumor has important clinical managerial implications. Markers used in the diagnosis of testicular germ cell tumors have included placental-like alkaline phosphatase (PLAP), CD30, CD117(C-KIT), and a-fetoprotein (AFP). Although these markers are useful, they
show only moderate sensitivity/specifcity and significant immunophenotypic overlap with somatic malignancies that may show PLAP and CD30 expression [643]. Furthermore, as their expression can be lost in metastatic foci, other markers have been recently investigated. Glypican 3 has been proposed as a new marker for yolk sac tumor, but its staining is typically focal and is not highly specific [644]; it has been shown to be positive in urothelial carcinomas with myxoid stroma [645]. Also, novel embryonic stem cell markers have been identified as being sensitive and specific for testicular germ cell tumors. Cheng et al established the sensitivity and specificity of OCT4 in detecting metastatic germ cell tumors in retroperitoneal lymph nodes and found that all embryonal carcinomas and seminomas showed diffuse and strong OCT4 nuclear staining. In contrast, yolk sac tumors, choriocarcinoma, mature teratomas, primitive neuroectodermal tumors, malignant lymphomas, melanomas and carcinomas from other sites including prostate, urinary bladder, pancreas, lung, colon, and kidney, were negative for this marker [646]. SALL4 has also been reported as a marker of seminoma and embryonal carcinoma, but unlike OCT4, SALL4 is also strongly expressed in yolk sac tumors [647,648].

11. CONCLUSIONS

Immunohistochemistry is commonly employed, and sometimes essential, in routine diagnostic practice for the distinction between a primary bladder carcinoma and secondary involvement form another anatomic site. The exact immunohistochemical panel required, if any, depends on the histologic features of a given case.

Level of evidence: 4
Recommendation: C

V. THE USE OF IMMUNOHISTOCHEMISTRY IN FLAT UROTHELIAL LESIONS WITH ATYPIA

1. INTRODUCTION

The histologic classification of flat urothelial lesions with atypia (i.e. reactive urothelial atypia, urothelial atypia of uncertain significance, urothelial dysplasia, and urothelial carcinoma in situ) can be one of the most difficult diagnostic challenges in genitourinary pathology. Numerous studies have investigated the potential utility of adjunctive immunohistochemistry in the diagnosis of these flat urothelial lesions.

The ability of a given immunophenotype to predict disease progression, independent of histology, has not been adequately studied. We, therefore, do not endorse using immunohistochemistry to distinguish urothelial atypia of uncertain significance from urothelial dysplasia, which would require clinical outcome studies to be of any value to clinical management. Studies of adjunctive methods of classification in the urothelial atypia of uncertain significance/urothelial dysplasia histologic spectrum have underscored the problems with immunohistochemistry in that specific diagnostic setting [649]. We discuss the use of adjunctive immunohistochemistry to distinguish between urothelial carcinoma in situ and benign reactive lesions in routine diagnostic practice.

2. P53

Urothelial carcinoma in situ may show strong, diffuse nuclear immunoreactivity for p53 [650-654]; however, the sensitivity has been reported to be as low as 57%. It is important to acknowledge that the evaluation of p53 by immunohistochemistry can be difficult [655]. The intensity of the antibody staining may fluctuate significantly with small variations in titer and inter-laboratory variation is not uncommon. Normal or reactive urothelium, therefore, may show numerous cells with weak to moderate nuclear staining. It is critical that one use a high threshold for a positive result when evaluating p53 in flat urothelial lesions. Only diffuse 3+ nuclear immunoreactivity in the neoplastic cell population should be regarded as positive.

3. CYTOKERATIN 20

CK20 expression has been studied by numerous groups that have all verified the typically strong and diffuse cytoplasmic immunoreactivity in urothelial carcinoma in situ cells (Figure 55 A,B) [649-651,656-658]. The reported sensitivity of CK20 for carcinoma in situ has ranged from 72-89%, while the specificity is over 90%. The extent of staining depends on the pattern of the urothelial carcinoma in situ being evaluated. Carcinoma in situ shows full thickness staining when the neoplastic cells comprise the full thickness of the urothelium; however, in cases of pagetoid carcinoma in situ, this staining is restricted to the individual neoplastic cells without reactivity in the surrounding benign urothelial cells. In normal urothelium and in reactive urothelial atypia, cytokertatin 20 expression is restricted to the superficial umbrella cell layer. In our experience, the CK20 expression in carcinoma in situ is preserved after both intravesical and radiation therapy (unpublished data).

4. CD44S

The CD44s antibody has been suggested as a useful comparative immunostain to use in conjunction with CK20 because it has the reverse staining pattern [651]. In normal urothelium, the basal cell layer shows membranous reactivity for CD44s, occasionally with some extension to the intermediate cell levels. In reactive urothelial atypia, the full thickness of the urothelium often shows this basal-like membranous
staining pattern. In contrast, the neoplastic cells of urothelial carcinoma in situ do not express CD44s, and the normal basal cell population is frequently absent.

5. **P16**

A few groups have evaluated the staining pattern of p16 in urothelial carcinoma in situ [488, 649]. Strong and diffuse cytoplasmic expression of p16 is reported in urothelial carcinoma in situ, while normal and reactive urothelium both show uniform weak expression. As with the use of p16 in cervical dysplasia, the interpretation of varying levels of intensity may present problems, and one must maintain a high threshold for a positive result. There are very few studies with this antibody, and we have not had similar success with its use.

6. **Kl-67**

Proliferation markers have also been evaluated as adjuncts to the diagnosis of carcinoma in situ. [650, 652, 657, 658] The proliferation rate of carcinoma in situ, as defined by Kl-67 immunohistochemistry, has significant overlap with florid reactive atypia, particularly when inflammatory infiltrates are present. [657] Therefore, proliferation markers have little role as diagnostic markers in this setting.

7. **CONCLUSIONS**

Despite the reported prototypical immunostaining profiles of flat urothelial lesions with atypia, the authors of this document have anecdotaly seen cases of both morphologically obvious carcinoma in situ and benign reactive urothelium with unexpected immunophenotypes. Any adjunctive immunohistochemistry must be carefully correlated with the morphologic features of the urothelial lesion being evaluated. Currently, routine morphologic evaluation should remain as the gold-standard for the diagnosis of flat urothelial lesions with atypia. As stated, we do not endorse the use of immunohistochemistry in the distinction of dysplasia and atypia of uncertain significance. Of the immunostains that might be used as confirmatory adjuncts for carcinoma in situ or reactive atypia in select difficult cases, CK20, CD44s, and p53 currently offer the most potential utility.

**Level of evidence: 4**

**Recommendation: C**

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**F. RECOMMENDED NOMENCLATURE FOR URINE CYTOLOGY**

**I. NOMENCLATURE AND REPORTING**

The Papanicolaou Society of Cytopathology Practice and Guidelines Task Force recommends a diagnostic format that mimics the Bethesda 2001 System for reporting cervical cytology format. (Table 18) The diagnostic section for urinary cytology should include a statement as to the site of origin of the urinary tract specimen (urethra, urinary bladder, or ureter/renal pelvis) and also state the technique used for obtaining the specimen when known (voided urine, washing, brushing, etc.) [659].

This classification nomenclature raises few issues in urine cytology diagnosis, particularly in the atypical and low grade urothelial carcinoma categories. The diagnosis of low grade urothelial carcinoma is rarely used due to the lack of specific criteria; therefore, most low grade urothelial carcinomas are included in the atypical category. Regarding the atypical urothelial cells terminology, there is little consensus in the literature on the criteria for inclusion in this category. Nonetheless, it has been suggested that this atypical category can be subdivided into 2 subcategories, atypical urothelial cells of undetermined significance (AUC-US) and atypical urothelial cell, cannot rule out high grade urothelial carcinoma or favor neoplasm. The rationale for this subclassification is that specimens diagnosed in the latter category should be referred to cystoscopy while...
the ones diagnosed as AUC-US could be followed with repeat urines [660-662].

**Level of evidence: 4**  
**Recommendation: C**

## II. ROLE OF URINE CYTOLOGY IN SCREENING AND MONITORING PATIENTS WITH BLADDER CANCER

Urinary cytology is a simple, noninvasive, and relatively inexpensive method for detecting UC [663]. It has consistently shown to have high specificity, especially in detecting carcinoma in situ and high-grade, flat lesions (Fig 56) [664,665]. However, it is also accepted that urine cytology has low sensitivity that varies particularly for low grade urothelial carcinoma [449,450,666-674]. Factors leading to the low sensitivity of urine cytology include minimal atypia seen in low grade UC, paucity of tumor cells in an inflammatory background, instrumentation effect, lithiasis, reactive changes, post BCG treatment, degenerative changes and viral cytopathic effect [675,676]. Diagnostic accuracy is also dependent on diagnostic expertise [677].

**Level of evidence: 3C**  
**Recommendation: B**

![Figure 56. High grade urothelial carcinoma in urine cytology](image)

## III. ROLE OF FISH IN SCREENING AND MONITORING OF BLADDER CARCINOMA

Urovysion has been approved by the US Food and Drug Administration for screening of urothelial carcinoma in patients with hematuria and monitoring for tumor recurrence in patients with a prior history of urothelial carcinoma [449,678].

The overall sensitivity and specificity of Urovysion is 72 and 83%[679], UroVysion FISH has a sensitivity of 90–100% for the detection of invasive bladder cancer (pT1–4) and a carcinoma specificity of 95% while for low-grade non-invasive the sensitivity increases from 25 to 60–75% when compared to cytology [680]. Use of Urovysion has been advocated in equivocal urine specimens, either suspicious or atypical [455,457,681-684] due to its increased sensitivity. Skacel et al [685] retrospectively evaluated the UroVysion FISH assay in 120 urine specimens and found a sensitivity of 100 and 89% in patients with suspicious and atypical urine cytology specimens, respectively, while the overall specificity was 97%. A negative FISH result in case of a negative or atypical cytology does not exclude low-grade urothelial neoplasia, since up to 30% of these tumors are negative with the FISH assay.

A positive Urovysion test (Figure 57) has been associated with higher rate of recurrence in patients treated with intravesical bacillus Calmette-Guerin (BCG) for high-grade non-muscle invasive urothelial carcinoma [453,457,458,686,687]. A higher rate of recurrence has also been noted in patients with positive Urovysion test and negative cystoscopy and cytology [455,678,688,689] although this was not confirmed in all studies [454,690]. Pitfalls of Urovysion have been associated with overinterpretation of benign tetraploid cells [691], or chromosomal aberrations following pelvic irradiation [692], except deletion of 9p21.

The wide application of UroVysion in routine practice is still controversial due to its high cost [693-695]. Although there is higher accuracy in the detection of high-grade lesions, the benefit achieved from better diagnosis of clinically harmless low-grade lesions by Urovysion is minor and it is achieved at a much higher cost [661]. The low cost efficiency is also cited as a problem when Urovysion is used in a population of patients with hematuria but no increased risk for urothelial carcinoma [680,693,694].

**Level of evidence: 3C**  
**Recommendation: B**

![Figure 57. Positive Urovysion in a urine specimen](image)
Providing the best management for patients with bladder neoplasia relies on close cooperation and teamwork among urologists, oncologists, radiologists and pathologists. The pathologist is involved in the diagnosis and assessment of prognostic and therapeutic variables in surgical specimens such as bladder biopsies, transurethral resection (TUR) and cystectomy specimens. Pathologists must report accurately and with minimal variability the key pathologic parameters using terminologies that are well understood by clinicians [696]. The most common tissue specimens encountered are biopsy and TUR, which provide the main information essential in tailoring the patient subsequent therapy that includes more aggressive treatment options. Additional information on curative-intent resections (e.g. cystectomy) determines the adequacy of therapy and appropriate surveillance or further need for surgery or adjuvant chemotherapy and/or radiotherapy [697]. The recent literature is not short of satisfactory checklists and commentaries for handling and reporting of genitourinary pathology specimens [174,393,698,699]. Organizations such as the College of American Pathologists (CAP) recommend reporting in a checklist/synoptic format and have outlined “essential” elements for reporting specimens resected for invasive bladder cancer [698]. However changes remain in flux as recent advancements, shift to multidisciplinary care, and regular introductions of updated clinical guidelines in bladder cancer diagnosis and management diversify the nature of specimens and impact the manner of handling and assessment. For example, other than the usual cystectomy for muscle invasive cancer, contemporary cystectomies include “early” (non-muscle invasive tumors), post neo-adjuvant chemotherapy, salvage, or palliative resections. Eventual pT0 or pTis cystectomies that contain no invasive cancer are becoming much more common. Segmental cystectomy for solitary lesions without pTis lesions amenable to resection with adequate margin is now considered a feasible surgical option. Second TUR procedures can be received for prior inadequate initial TUR staging or deep muscle sampling, prior incomplete tumor resection, or bladder-preservation treatment. The differences in indications and characteristics of tumor content in these specimens evoke re-appraisal instead of being uniformly processed in the traditional manner.

With some updates in select topics, this proposed guideline aim at standardizing descriptions of diagnosis and reporting of urothelial carcinoma of the bladder and to help optimize uniformity between individual pathology practices and institutions (Grade C). This protocol may assist pathologists in providing clinically useful and relevant reporting information in a multidisciplinary care setting.

The ability to have an open communication is essential for pathologists, urologists and oncologists in the decision-making process for diagnosis and management. Adequate clinical information is important to pathologists in deciding the best approach in handling and processing the surgical specimens and directing the most essential information which to be reported. The pathology specimen requisition form must be filled with relevant and sufficient information the clinicians can provide. With the high degree of accuracy of cystoscopy, the pathologists should also take extreme measures of reviewing cystoscopic impressions before diagnosing a tumor in biopsy or TUR samples [700,701]. With differing implications for non-invasive papillary versus flat (carcinoma in situ) tumors and advent of enhanced cystoscopic (e.g. fluoroscopic) visualization, urologist’s impression provides helpful information to the pathologist in difficult situations, such as when the entire lesion architecture is not obvious on the slides (e.g. fragmented or superficial sections). Indications of the surgical procedure, such as for surveillance or post intravesical therapy biopsies, initial or second TUR (e.g. for deep muscle assessment or completion of resection), “early” or salvage cystectomy, among others, are important for pathologists in specimen handling and reporting. Other relevant information includes history of bladder cancer and prior intravesical or neoadjuvant chemotherapy. Presence of calculi, catheterization or infection may explain reactive changes (versus dysplasia) when under consideration.

Tissue preservation is required and samples should be handled the minimum way possible. Ideally, tissue container with fixatives for biopsy or TUR specimens should be readily available in the operating rooms. In situations where patients are part of study protocols or clinical trials requiring fresh tissue preservation, the specimen should be sent without any delay to pathology gross room for immediate processing. In TUR, a deeper bite for assessment of MP involvement is preferably submitted separately in another container especially in situations of larger
tumors. This will facilitate search for muscle invasive component of the tumor. Biopsy or TUR of multifocal tumors should also be submitted separately according to site. Cold cup mapping biopsies of visually normal mucosa and prostatic urethra are needed to exclude flat lesions and should also be submitted separately per site. This provides a better picture of the extent of the lesions in the bladder. Any erythematous or velvety area should be sampled. In cystectomy, ureter margins submitted separately should have proper labelling of the distal end (true margin). In partial or segmental cystectomy, the bladder wall resection margins should be marked with identifiers such as suture to facilitate identification.

IV. PATHOLOGIST HANDLING OF BIOPSY SPECIMENS

All biopsy-sampled tissues should be submitted for processing. Effort should be made to identify the mucosal aspect of tissue fragments to allow embedding on edge and better visualization of the surface urothelium, although this may not always be possible. For histologic evaluation, at least 3 levels of tissue sections for each biopsy should be prepared. Deeper levels into the block are recommended if the surface urothelium is deemed not entirely visible or in situations of denuded samples, particularly with known risk for CIS, to exclude the possibility of denuded CIS (clinging type) (Grade C).

V. PATHOLOGIST HANDLING OF TRANSCURETHRAL RESECTIONS

The conventional way of processing TUR specimens is to submit the tissue entirely. In large tumors exceeding 10 cm, one approach is to submit 1 section per cm of tumor diameter (up to 10 cassettes), and additional selective sampling until MP invasion is identified, or submitting the rest of the sample if no MP invasion is recognized after the first selective sampling. The second TURs for deep muscle staging are typically low volume samples, which can be processed entirely. Large bulk completion TUR for incompletely resected tumors may have an option to submit less if the initial TUR has already established the diagnosis and attributed risk (e.g. pT2 stage). Follow-up TUR for bladder-preservation treatment after chemotherapy and/or radiotherapy however should be processed the conventional way. (Table 19)

VI. PATHOLOGIST HANDLING OF CYSTECTOMY SPECIMENS

The bladder must be opened and after adequate fixation samples must be taken from representative areas of the tumor, normal-appearing bladder, the prostate, seminal vesicles, or other organs included in the surgical specimen. Minimum sections of the bladder should include at least the tumor/s including its deepest penetration, and representative sections of the dome, trigone, anterior, posterior and lateral walls. In potential cystectomy with no residual tumor (pT0), prior surgical sites or mucosal ulcerations should be submitted entirely for any possible residual tumor. Adequate mapping of different regions of the bladder should be performed, as well as in “early” cystectomy or in setting of post-neoadjuvant chemotherapy with less visible or no gross residual tumors. Any suspicious-looking areas of reddening and mucosal induration (for CIS) need to be sampled. Grossly visible tumour in perivesical fat (pT3b) or at resection margins (R2) must be stated in the gross examination. For tumor grossly invading the bladder wall, multiple full thickness sections including the area grossly suspicious for deepest penetration should be included in the sections to assess pT2a/b vs. pT3a. The underlying soft tissue margin should be examined, inked and sampled. Unless submitted separately for frozen section, ureter and urethral margins should be sampled, preferably taken as shave cross sections so that the entire mucosal circumference can be visualized. In case of segmental cystectomy, bladder wall margins of resection should be identified for tumor involvement. In cystoprostatectomy specimens, right and left prostate should be inked differently and representative sections from both sides are to be taken including perpendicular sections of the apical margins, to secure assessment of important variables in case of concomitant prostate cancer, which is not uncommon to occur. Sections of the prostate should include the prostatic urethra to identify possible tumor invasion originating from a separate urethral carcinoma (pT2). Sections of possible deep penetration to prostate from bladder by the tumor should also be taken to document higher stage (pT4) bladder cancer. Likewise, tumor mass along the distal ureter/ureteral orifice should be closely examined whether or not tumor is arising from the distal ureter, for appropriate staging. Lymph nodes must be dissected from the lymphadenectomy specimens and all grossly and tentatively identified lymph nodes in the specimen should be submitted. (Table 20)
VII. REPORTING OF HISTOLOGIC GRADE

Use of the WHO (2004) / ISUP classification system is recommended (Grade B) [113,275]. Based on institutional / clinician preference, other systems may be used along side. Grading should also take cancer heterogeneity into consideration; approximately one-third of patients with pTa tumor had cancer containing a different histologic grade. Currently, grading of papillary urothelial tumors is typically based on the worst grade present (Grade C).

VIII. REPORTING VARIANT UROTHELIAL HISTOLOGY

Urothelial cancer is known to show variant histologic features otherwise known as divergent differentiation, with estimates ranging from 7% to 81% in series specifically reporting differentiation patterns of urothelial carcinomas [117,702]. Current evidence suggests that urothelial cancer with divergent differentiation has a worse prognosis when compared with pure urothelial cancer, although stage matched cohorts show limited differences (Level 3). Billis and colleagues [703] in a study of 165 TURBT noted that 7% of tumors showed squamous and/or glandular differentiation. Those patients with divergent differentiation had higher clinical stage at presentation compared to conventional urothelial carcinoma [703]. Wasco et al [704] in a study of 448 consecutive TURBTs and 295 subsequent cystectomy, noted that urothelial cancers with divergent differentiation were more likely to be muscularis propria invasive at TURBT and extravesical fat invasive at cystectomy compared to pure urothelial cancers. Jozwicki et al [705] performed mapping in 38 cystectomy specimens, and then correlated the mapping studies with survival time, the presence of greater than 80% pure urothelial cancer within a specimen was a favorable prognostic factor, and increasing numbers of histologic subtypes (increasingly divergent differentiation) led to a less favorable prognosis.

Divergent morphology must be documented because of its prognostic implications (Grade B). Further, reporting facilitate correlation with subsequent metastasis, were it to occur at remote sites. When multiple divergent (aberrant) morphologies are present, one should provide relative percentages for each of the patterns e.g. invasive urothelial carcinoma (75%) with squamous (20%) and glandular (5%) differentiation.

IX. LYMPHOVASCULAR INVASION (LVI)

Tumour stage reflected by the AJCC/UICC TNM system represents the gold standard for prediction of recurrence after radical cystectomy in patients with invasive bladder cancer. Thus, accurate staging provides broadly applicable prognostic information and is the basis of all authoritative patient management decisions [706].

In addition to advanced tumour stage, however, other pathological factors have been evaluated as possible risk factors for recurrence and poor survival. Among them, lymphovascular invasion (LVI) marks the initial step of the metastatic process. Its significance in predicting outcome of affected patients, however, remains controversial.

According to literature data, LVI can be observed in about 30-50% of cystectomy specimens (Table 21) [60,707-717]. Prevalence of LVI correlates significantly with increasing T classification [708,710,712-714,717-721], high tumour grade [712-714,717,718], and presence of lymph node metastasis [710,712-714,717,721,722]. However, in a considerable number of patients with histologically proven nodal disease LVI is not detected within the bladder wall. In the comprehensive study by Lotan et al. LVI was observed in 9.0% of T1, 23.0% of T2, 50% of T3, and 78% of T4 tumours, respectively [712]. Likewise, the authors detected LVI in 151 out of 581 (26%) node-negative and 122 out of 169 (72%) node-positive cancers. In a recent international validation study collecting 4,257 patients from 12 centres, Shariat et al. rendered similar data: LVI was present in 11.0% of T1, 31.3% of T2, 52.3% of T3, and 60.9% of T4 tumours, respectively, and its presence was significantly associated with high tumour grade (5.1% G1, 38.2% G2, 33.5% G3) and presence of lymph node metastasis (22.5% N0, 64.7% N1-2) [717].

LVI has repeatedly been associated with poor outcome of patients undergoing radical cystectomy for invasive bladder cancer. This effect is primarily observed in patients with node-negative cases disease [708,712-714,717,718,723]. In detail, LVI proved to be a predictor of local, distant, and overall tumour recurrence as well as a predictor of adverse overall and disease-specific survival, independent of tumour stage and grade [711,712,715-718,724,725]. In some studies, however, discordant results were obtained. Thus, in the study by Canter et al., LVI independently predicted overall and disease-specific survival, whereas no independent influence on recurrence-free survival was noted [708]. In other studies, some of them involving rather low numbers of patients, LVI was identified as an adverse prognostic variable only in univariate analysis, yet lost prognostic significance in multivariate analysis [709,710,713,726-728]. Finally, in two studies, both involving less than 100 patients, the presence of LVI was not found to be significantly related to outcome [729,730].
### Table 19. URINARY BLADDER: Biopsy and Transurethral Resection of Bladder Tumor (TURBT)

Note: Use of checklist for biopsy specimens is optional. Select a single response unless otherwise indicated.

**Relevant Clinical History**
- Cystoscopic impression of the mucosa
- Indication of procedure
- Previous history of cancer in bladder or elsewhere in the genitourinary tract
- Prior therapy

**Procedure**
- Biopsy
- TURBT
- Other (specify):

**Histologic Type**
- Urothelial (transitional cell) carcinoma
- Urothelial (transitional cell) carcinoma with % of squamous differentiation
- Urothelial (transitional cell) carcinoma with % of glandular differentiation
- Urothelial (transitional cell) carcinoma with % of micropapillary component
- Urothelial (transitional cell) carcinoma with variant histology (specify):
  - Squamous cell carcinoma, typical
  - Squamous cell carcinoma, variant histology (specify):
  - Adenocarcinoma, typical
  - Adenocarcinoma, variant histology (specify):
  - Small cell carcinoma
  - Undifferentiated carcinoma (specify):
  - Mixed cell type (specify):
  - Other (specify):
  - Carcinoma, type cannot be determined

**Associated Epithelial Lesions (select all that apply)**
- None identified
- Urothelial (transitional cell) papilloma (World Health Organization [WHO] 2004/ International Society of Urologic Pathology [ISUP])
- Urothelial (transitional cell) papilloma, inverted type
- Papillary urothelial (transitional cell) neoplasm, low malignant potential (WHO 2004/ISUP)
- Hyperplasia
- Dysplasia
- Carcinoma in situ
- Cannot be determined

**Histologic Grade**
- Not applicable
- Cannot be determined

**Urothelial Carcinoma (WHO 2004/ISUP)**
- Papilloma
- PUNLMP
- Low-grade
- High-grade
- Primary Grade
- Secondary grade
- Other (specify):

**Urothelial Carcinoma (WHO 1973)**
- Papilloma
- Grade 1
- Grade 2
- Grade 3
- Primary Grade
- Secondary Grade

**Adenocarcinoma and Squamous Cell Carcinoma**
- GX: Cannot be assessed
- G1: Well differentiated
- G2: Moderately differentiated
- G3: Poorly differentiated
- Other (specify):

**Tumor Configuration (select all that apply)**
- Papillary
- Solid/nodule
- Flat
- Ulcerated
- Indeterminate
- Other (specify):

**pT1 Tumors**
- Muscularis Mucosae Present
- Thin-Walled blood vessels present
- Depth of Lamina propria invasion (micrometer)

**Type of tumor invasion**
- Single cells
- Nodular
- Trabeculae
- Infiltrative

**Stromal Reaction**
- Stromal retraction
- Stromal edema
- Inflammation
- Fibroblastic proliferation
- Fibrosis

**Adequacy of Material for Determining Muscularis Propria Invasion**
- Muscularis propria (detrusor muscle) not identified
- Muscularis propria (detrusor muscle) present
- Presence of muscularis propria indeterminate

**Lymph-Vascular Invasion**
- Not identified
- Present
- Indeterminate
Adding LVI, together with other morphological (presence of carcinoma in situ in the cystectomy specimen) and clinical (neoadjuvant chemotherapy, adjuvant chemotherapy, adjuvant radiotherapy) parameters to multivariate nomograms assessing risk for disease recurrence or survival significantly improved accuracy of prediction compared with the AJCC/UICC staging system [711,716]. Likewise, adding LVI alone to a base model including tumour stage and grade, surgical margin status, number of lymph nodes removed, and adjuvant chemotherapy significantly improved predictive accuracy for disease recurrence and cancer-specific survival in node-negative cases, yet only marginally in node-positive cases [717].

The significance of LVI has additionally been addressed in patients undergoing partial cystectomy or transurethral tumour resection for bladder cancer (TURB). Thus, Zhang et al. recently presented 100 patients with muscle-invasive bladder cancer who underwent bladder-conserving therapy, i.e. partial cystectomy. LVI was present in 16% of cases and was independently associated with cancer-specific survival, yet not with recurrence-free survival [731].

In all, six studies have so far evaluated the significance of LVI in TURB material [721,732-735]. The reported prevalence of LVI is 6-28%, which not unexpectedly is lower than in radical cystectomy specimens [721,732-735]. According to a recent investigation involving matched TURB and radical cystectomy material from 75 patients, concordance between LVI diagnoses of TURB and cystectomy material is good in muscle-invasive cancers, while it is only low in superficial tumours [721]. Overall sensitivity and specificity of LVI detection in TURB samples were 37% and 87%, and positive predictive values were 65% and 67%, respectively. Similar to the situation in cystectomy specimens, presence of LVI in TURB material proved to be an independent predictor of tumour recurrence [733] and progression [732,733] as well as patients’ overall [734] and disease-specific [732] survival, particularly in clinical stage I or II [723].

Whether or not lymphatic invasion and venous invasion should be considered separately has not been adequately addressed because most studies have not attempted to differentiate between venous and lymphatic invasion [60,709,712-715,717,718,724,730,731,734,735]. Lotan et al refer to difficulty and lack of reproducibility when using routine light microscopic examination of haematoxylin and eosin stained slides [712]. Some studies have, however, differentiated between lymphatic and venous invasion and defined venous invasion as tumour present in vessels with a thick vascular wall and blood cells within the lumen [720,726,728,736,737]. Using this definition, the prevalence of venous invasion was generally lower than that of lymphatic invasion [710,719,726-728,736,737]. With respect to prediction of outcome, venous invasion proved to be superior to lymphatic invasion in two of these studies [720,737], whereas a stronger prognostic effect for lymphatic invasion was noted in one study [736].

Despite unanimity regarding the relationship between presence of LVI and bladder cancer aggressiveness, there are major issues of concern that have hindered its integration in treatment guidelines for bladder cancer and clinical decision making. In fact, the major factor is poor diagnostic reproducibility: reported prevalence and levels of prognostic significance vary considerably, differing from one study to another. The lack of reproducibility when using routine light microscopic examination of haematoxylin and eosin stained slides is well-known [712,738]. These differences have mainly been attributed to lack of standardized assessment of LVI, as demonstrated by divergent, often poorly described histological criteria used by pathologists to identify...
**Table 20. URINARY BLADDER: Cystectomy, Partial, Total, or Radical; Anterior Exenteration**

Select a single response unless otherwise indicated.

### Relevant Clinical History
- Diagnosis of previous material
- Chemotherapy
- Radiotherapy
- Preoperative Examination

### Specimen
- Bladder
- Other (specify):
- Not specified

### Procedure
- Partial cystectomy
- Total cystectomy
- Radical cystectomy
- Radical cystoprostatectomy
- Anterior exenteration
- Other (specify):
- Not specified

### Tumor Site (select all that apply)
- Trigone
- Right lateral wall
- Left lateral wall
- Anterior wall
- Posterior wall
- Dome
- Other (specify):
- Not specified

### Tumor Size
- Greatest dimension: _____ cm
- Additional dimensions: _____ x _____ cm
- Cannot be determined (see Comment)

### Histologic Type
- Urothelial (transitional cell) carcinoma
- Urothelial (transitional cell) carcinoma with % of squamous differentiation
- Urothelial (transitional cell) carcinoma with % of glandular differentiation
- Urothelial carcinoma with % of Micropapillary component
- Urothelial (transitional cell) carcinoma with variant histology (specify):
- Squamous cell carcinoma, typical
- Squamous cell carcinoma, variant histology (specify):
- Adenocarcinoma, typical
- Adenocarcinoma, variant histology (specify):
- Small cell carcinoma
- Undifferentiated carcinoma (specify):
- Mixed cell type (specify):
- Other (specify):
- Carcinoma, type cannot be determined

### Associated Epithelial Lesions (select all that apply)
- None identified
- Urothelial (transitional cell) papilloma (World Health Organization [WHO] 2004/ International Society of Urologic Pathology [ISUP])
- Urothelial (transitional cell) papilloma, inverted type
- Papillary urothelial (transitional cell) neoplasm, low malignant potential (WHO 2004/ISUP)
- Hyperplasia
- Dysplasia
- Carcinoma in situ
- Cannot be determined

### Histologic Grade
- Not applicable
- Cannot be determined

### Urothelial Carcinoma (WHO 2004/ISUP)
- PUNLMP
- Low-grade
- High-grade
- Primary Grade
- Secondary Grade
- Other (specify):

### Urothelial Carcinoma (WHO 1973)
- Papilloma
- Grade 1
- Grade 2
- Grade 3
- Primary pattern
- Secondary pattern

### Adenocarcinoma and Squamous Cell Carcinoma
- GX: Cannot be assessed
- G1: Well differentiated
- G2: Moderately differentiated
- G3: Poorly differentiated
- Other (specify):

### Tumor Configuration (select all that apply)
- Papillary
- Solid/nodule
- Flat
- Ulcerated
- Indeterminate
- Other (specify):
Microscopic Tumor Extension (select all that apply)
- None identified
- Perivesical fat
- Rectum
- Prostate
  - Prostatic stroma
  - Prostatic urethra
  - Focal involvement
  - Extensive involvement
  - Seminal vesicle (specify laterality):
    - Vagina
    - Uterus and adnexae
    - Pelvic sidewall (specify laterality):
    - Ureter (specify laterality):
    - Other (specify):

Margins (select all that apply)
- Cannot be assessed
- Margins uninvolved by invasive carcinoma
Distance of invasive carcinoma from closest margin: ___ mm
Specify margin: ____________________________
- Margin(s) involved by invasive carcinoma
Specify margin(s):
- Margin(s) uninvolved by carcinoma in situ
- Margin(s) involved by carcinoma in situ
Specify margin(s):

Lymph-Vascular Invasion
- Not identified
- Present
- Indeterminate

Pathologic Staging (pTNM)

TNM Descriptors (required only if applicable) (select all that apply)
- m (multiple primary tumors)
- r (recurrent)
- y (post-treatment)

Primary Tumor (pT)
- pT0: No evidence of primary tumor
- pTa: Noninvasive papillary carcinoma
- pTis: Carcinoma in situ: “flat tumor”
- pT1: Tumor invades subepithelial connective tissue (lamina propria)
- pT2: Tumor invades muscularis propria (detrusor muscle)
  - pT2a: Tumor invades superficial muscularis propria (inner half)
  - pT2b: Tumor invades deep muscularis propria (outer half)
- pT3: Tumor invades perivesical tissue
  - pT3a: Microscopically
  - pT3b: Macroscopically (extravesicular mass)
- pT4: Tumor invades any of the following: prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
  - pT4a: Tumor invades prostatic stroma or uterus or vagina
  - pT4b: Tumor invades pelvic wall or abdominal wall

Regional Lymph Nodes (pN)
- pNX: Lymph nodes cannot be assessed
- pN0: No lymph node metastasis
- pN1: Single regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac or presacral lymph node)
- pN2: Multiple regional lymph node metastases in the true pelvis (hypogastric, obturator, external iliac or presacral lymph node metastasis)
- pN3: Lymph node metastasis to the common iliac lymph nodes
- Number of nodes examined
- Number with metastases
- Size of largest metastases
- Number of nodes with micrometastasis or isolated tumor cells
- Extracapsular extension of metastasis

Distant Metastasis (pM)
- Not applicable
- pM1: Distant metastasis
Specify site(s), if known:

Additional Pathologic Findings (select all that apply)
- Adenocarcinoma of prostate (use protocol for carcinoma of prostate)
- Urothelial (transitional cell) carcinoma involving urethra, prostatic ducts and acini with or without stromal invasion (use protocol for carcinoma of urethra)
- Urothelial dysplasia (low-grade intraurothelial neoplasia)
- Inflammation/regenerative changes
- Therapy-related changes
- Cystitis cystica glandularis
- Keratinizing squamous metaplasia
- Intestinal metaplasia
- Other (specify):

Tumor Bank

Comment(s)
<table>
<thead>
<tr>
<th>Author</th>
<th>Surgery Year</th>
<th>Type of Surgery</th>
<th>No. Pts</th>
<th>pT stage</th>
<th>+LN (%)</th>
<th>+ LVI (%)</th>
<th>BI (%)</th>
<th>LI (%)</th>
<th>Followup (months)</th>
<th>Evolution (survival /progression)</th>
<th>Statistical Significance (MVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdel-Latif et al, 2004</td>
<td>'97-'99</td>
<td>RC, LA</td>
<td>418</td>
<td>T1-T4</td>
<td>26</td>
<td>32</td>
<td>n/a</td>
<td>n/a</td>
<td>36.6 (mean)</td>
<td>+LVI: 27* -LVI:56* (3-ys survival +LN)</td>
<td>Independent (+LN)</td>
</tr>
<tr>
<td>Bassi et al, 1999</td>
<td>'82-'94</td>
<td>RC, LA</td>
<td>369</td>
<td>T1-T4</td>
<td>21</td>
<td>n/a</td>
<td>6</td>
<td>30</td>
<td>48.5 (median)</td>
<td>+BI: 29% -BI: 56% +LI: 39% -LI: 61% (5-ys survival)</td>
<td>Not independent</td>
</tr>
<tr>
<td>Bolenz et al, 2010</td>
<td>'85-'08</td>
<td>RC, LA</td>
<td>1099</td>
<td>T1-T4</td>
<td>None</td>
<td>27</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>+LVI: 69% -LVI:74%</td>
<td>Independent</td>
</tr>
<tr>
<td>Carter et al, 2008</td>
<td>'88-'06</td>
<td>RC, LA</td>
<td>356</td>
<td>T1-T4</td>
<td>28</td>
<td>32</td>
<td>n/a</td>
<td>n/a</td>
<td>45.4 (mean)</td>
<td>+LVI: 52 mo OS -LVI: 97 mo OS</td>
<td>Independent (CSS, OS)</td>
</tr>
<tr>
<td>Cho et al, 2009</td>
<td>'01-'07</td>
<td>TURBT</td>
<td>118</td>
<td>T1</td>
<td>n/a</td>
<td>28</td>
<td>n/a</td>
<td>n/a</td>
<td>35 (mean)</td>
<td>+LVI: 30% -LVI:11%</td>
<td>Independent (progression, metastasis)</td>
</tr>
<tr>
<td>Hara et al, 2001</td>
<td>'85-'00</td>
<td>RC, LA</td>
<td>154</td>
<td>T1-T4</td>
<td>20</td>
<td>50</td>
<td>n/a</td>
<td>n/a</td>
<td>23 (mean)</td>
<td>+LVI: 42% -LVI:83%</td>
<td>Not independent</td>
</tr>
<tr>
<td>Harada et al, 2005</td>
<td>'89-'03</td>
<td>RC, LA</td>
<td>114</td>
<td>T1-T4</td>
<td>18</td>
<td>n/a</td>
<td>33</td>
<td>48</td>
<td>n/a</td>
<td>+BI: 49% -BI: 67% +LI: 53% -LI: 68%</td>
<td>Not independent</td>
</tr>
<tr>
<td>Harada et al, 2006</td>
<td>'89-'04</td>
<td>RC, LA</td>
<td>124</td>
<td>T1-T4</td>
<td>18</td>
<td>n/a</td>
<td>28</td>
<td>47</td>
<td>n/a</td>
<td>+BI: 37%R -BI: 12%R +LI: 34%R -LI: 6%R</td>
<td>Not independent</td>
</tr>
<tr>
<td>Herrmann et al, 2008</td>
<td>'86-'05</td>
<td>RC, LA</td>
<td>614</td>
<td>T1-T4</td>
<td>28</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>44 (mean)</td>
<td>+LVI vs –LVI: 1.7 RR</td>
<td>Independent (CSS, OS)</td>
</tr>
<tr>
<td>Hong et al, 2005</td>
<td>'91-'02</td>
<td>RC, LA</td>
<td>125</td>
<td>T1-T4</td>
<td>None</td>
<td>9</td>
<td>21</td>
<td>41</td>
<td>41 (median)</td>
<td>+BI: HR 4.88 - BI: HR 1 +LI: HR 1.2 -LI: HR 1</td>
<td>Independent, BI only (CSS)</td>
</tr>
<tr>
<td>Leissner et al, 2003</td>
<td>'87-'97</td>
<td>RC, LA</td>
<td>283</td>
<td>T1-T4</td>
<td>31</td>
<td>n/a</td>
<td>13</td>
<td>54</td>
<td>32.8 (mean)</td>
<td>+BI vs –BI: RR 1.82</td>
<td>Independent, BI only (RFS)</td>
</tr>
<tr>
<td>Lotan et al, 2005</td>
<td>'84-'03</td>
<td>RC, LA</td>
<td>750</td>
<td>T1-T4</td>
<td>22</td>
<td>36</td>
<td>n/a</td>
<td>n/a</td>
<td>15 (mean)</td>
<td>-LN, +LVI: 86.9% -LN, -LVI: 72.1%</td>
<td>Independent in -LN, (RFS, CSS, OS)</td>
</tr>
<tr>
<td>Manoharan et al, 2010</td>
<td>'92-'08</td>
<td>RC, LA</td>
<td>357</td>
<td>T1-T4</td>
<td>20</td>
<td>29</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>+LVI: 42% -LVI:67% (10-ys CSS)</td>
<td>Not independent</td>
</tr>
<tr>
<td>Palmieri et al, 2010</td>
<td>'95-'07</td>
<td>RC, LA</td>
<td>265</td>
<td>T1-T4</td>
<td>23</td>
<td>29</td>
<td>n/a</td>
<td>n/a</td>
<td>108 (median)</td>
<td>+LVI: 29% -LVI:53% (10-ys CSS)</td>
<td>Independent (CSS)</td>
</tr>
<tr>
<td>Quek et al, 2005</td>
<td>'71-'04</td>
<td>RC, LA</td>
<td>702</td>
<td>T1-T4</td>
<td>22</td>
<td>35</td>
<td>n/a</td>
<td>132</td>
<td>132 (median)</td>
<td>-LVI: 74% +LVI: 42% (10-ys RFS)</td>
<td>Independent (RFS, OS)</td>
</tr>
<tr>
<td>Shariat et al, 2010</td>
<td>'79-'08</td>
<td>RC, LA</td>
<td>4257</td>
<td>T0-T4</td>
<td>25</td>
<td>33</td>
<td>n/a</td>
<td>43</td>
<td>43 (median)</td>
<td>+LVI: 39% -LVI:72% (10-ys CSS)</td>
<td>Independent (RFS, CSS)</td>
</tr>
</tbody>
</table>
LVI [707,738]. If histological criteria are mentioned, most studies refer to presence of tumour cells within endothelium-lined spaces without underlying muscular wall [60,712-714,717,721,725]. In fact, identification of a clear-cut endothelial lining is considered crucial in differentiating LVI from stromal retraction, which a frequent finding around tumour cell nests, particularly at the leading edge of invasion (fig 58). Stromal retraction is commonly over-diagnosed as vascular invasion; however, at least in the breast cancer literature, there is strong evidence that stromal retraction is not a processing artifact, has independent prognostic significance in node negative disease on its own merit, and may possibly be early phase of vascular invasion [740]. Finally, varying levels of experience of pathologists evaluating LVI, and knowledge of the potential problems and mimics, may influence accuracy of diagnosis, illustrating the need for strict morphological criteria to diminish the problem of interobserver variability [707,738].

Another related problem that is not commonly discussed is that the general approach to assessing LVI in diagnostic surgical pathology does not recognize the varied biologic mechanisms involved tumor vascularization, some of which are not readily visible at the light microscopic level [741].

In 2006, Algaba suggested the following morphological criteria for the diagnosis of LVI on haematoxylin and eosin stained slides: morphological features in favour of LVI are tumour cell thrombi within isolated spaces with an unequivocal endothelial lining, preferably located next to arterioles and with a normal surrounding stromal tissue (Figure 58 A,B) [707]. The tumour thrombus is usually floating, completely free, within the vessel lumen and may show some fibrin precipitate and/or blood cells around it. The tumour cells are usually tightly cohesive and display a smooth border, the cells in the periphery of the thrombus having a shell-like morphology. In contrast, morphological features arguing against LVI are tumour cell clusters, particularly with invasion of multiple spaces, surrounded by an ectatic capillary network inherent to an abnormal stroma. Moreover, in pseudoinvasion due to tissue retraction, the pseudothrombus usually displays a surface with a blurred outline and shreds of cytoplasm may be present between the pseudothrombus and the supposed vessel wall.

Figure 58. A) Unequivocal presence of urothelial carcinoma cells within endothelial-lined vessels. B) Invasive urothelial carcinoma with retraction artifact.”

Table 21. Literature review of significance of LVI in bladder cancer (studies with >100 patients) (continued)

<table>
<thead>
<tr>
<th>Author</th>
<th>Surgery Year</th>
<th>Type of Surgery</th>
<th>No. Pts</th>
<th>pT stage</th>
<th>+LN (%)</th>
<th>+LVI (%)</th>
<th>BI (%)</th>
<th>LI (%)</th>
<th>Followup (months)</th>
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<tr>
<td>Sonpavde et al, 2010</td>
<td>71-’08</td>
<td>RC, LA</td>
<td>707</td>
<td>T2</td>
<td>None</td>
<td>15</td>
<td>n/a</td>
<td>n/a</td>
<td>60.9 (median)</td>
<td>+LVI vs –LVI: HR 2.2</td>
<td>Independent (RFS)</td>
</tr>
<tr>
<td>Zhang et al, 2010</td>
<td>’02-’07</td>
<td>PC</td>
<td>100</td>
<td>T2-T4</td>
<td>n/a</td>
<td>16</td>
<td>n/a</td>
<td>n/a</td>
<td>31.5 (median)</td>
<td>+LVI: 32% -LVI:72% (5-ys CSS)</td>
<td>Independent (CSS)</td>
</tr>
</tbody>
</table>

pTN stage = pathological tumor stage
LVI = lymphovascular invasion; BI = blood vessel invasion; LI = lymphatic invasion
+LN = lymph node metastasis; +LM = loco-regional metastasis
RC = radical cystectomy, LA = bilateral pelvic lymphadenectomy, PC = partial cystectomy; TURBT = transurethral resection of bladder tumor
RFS = recurrence free survival, CSS = cancer-specific survival; OS = overall survival;
HR = hazard ratio, RR = relative risk

LVI [707,738]. If histological criteria are mentioned, most studies refer to presence of tumour cells within endothelium-lined spaces without underlying muscular wall [60,712-714,717,721,725]. In fact, identification of a clear-cut endothelial lining is considered crucial in differentiating LVI from stromal retraction, which a frequent finding around tumour cell nests, particularly at the leading edge of invasion (Fig 58). Stromal retraction is commonly over-diagnosed as vascular invasion; however, at least in the breast cancer literature, there is strong evidence that stromal retraction is not a processing artifact, has independent prognostic significance in node negative disease on its own merit, and may possibly be early phase of vascular invasion [740]. Finally, varying levels of experience of pathologists evaluating LVI, and knowledge of the potential problems and mimics, may influence accuracy of diagnosis, illustrating the need for strict morphological criteria to diminish the problem of interobserver variability [707,738]. Another related problem that is not commonly discussed is that the general approach to assessing LVI in diagnostic surgical pathology does not recognize the varied biologic mechanisms involved tumor vascularization, some of which are not readily visible at the light microscopic level [741].

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<th>pT stage</th>
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<th>BI (%)</th>
<th>LI (%)</th>
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<tr>
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<td>71-’08</td>
<td>RC, LA</td>
<td>707</td>
<td>T2</td>
<td>None</td>
<td>15</td>
<td>n/a</td>
<td>n/a</td>
<td>60.9 (median)</td>
<td>+LVI vs –LVI: HR 2.2</td>
<td>Independent (RFS)</td>
</tr>
<tr>
<td>Zhang et al, 2010</td>
<td>’02-’07</td>
<td>PC</td>
<td>100</td>
<td>T2-T4</td>
<td>n/a</td>
<td>16</td>
<td>n/a</td>
<td>n/a</td>
<td>31.5 (median)</td>
<td>+LVI: 32% -LVI:72% (5-ys CSS)</td>
<td>Independent (CSS)</td>
</tr>
</tbody>
</table>
The role of ancillary techniques, such as immunohistochemistry, in the differentiation of LVI from pseudoinvasion still remains to be defined. Almost all published reports on bladder cancer rely solely on haematoxylin and eosin stained slides, and immunohistochemistry; if used at all, immunohistochemistry seems to be reserved for equivocal cases. However, data obtained from other types of cancer clearly demonstrate that additional histochemical and/or immunohistochemical staining may be help to identify LVI and increase the accuracy of identification with LVI by proving true vascular invasion and/or avoiding false-positive reporting due to overinterpretation of stromal retraction artefacts. Thus, immunostaining using monoclonal antibodies directed against endothelial markers, such as CD31 and podoplanin (D2-40), the latter specific for lymphatic endothelial cells, have been shown to increase the detection rate of LVI compared to conventional haematoxylin and eosin staining and to render clinically significant information in breast [742,743], colorectal [744], endometrial [745], gastric [746], and oral squamous cell carcinoma [747,748].

In bladder cancer, two studies, published already in the early nineties, indicated the potential value of these ancillary techniques: Angioinvasion diagnosed on haematoxylin and eosin stained slides was confirmed by immunohistochemistry in only 5 out of 36 [749] or 2 out of 5 [750] cases, respectively. Both studies are fairly old and did use antibodies directed against Ulex euopeaus agglutinin I (UEA I), von Willebrand factor, and QBEND/10, which are antibodies that have generally been replaced with more specific markers in current practice. Therefore, we cannot exclude that some technical aspects inherent to the immunohistochemical staining evaluation may have caused the high rate of putative false-positive reporting of LVI on haematoxylin and eosin stained slides. In 2009, Afonso et al. published the first systematic study investigating the potential value of CD31 and D2-40 immunostaining in bladder cancer including 83 patients with radical cystectomy. [751] Using haematoxylin and eosin stained slides, blood and lymphatic vessel invasion were diagnosed in 19 (23%) and 18 (22%) cases, respectively. Immunohistochemistry significantly improved the recognition of vascular invasion for both lymphatic and blood vessels, regarding particularly for identifying single intravascular single tumour cells (40% for CD31, 37% for D2-40), yet not compared regarding malignant to tumor emboli (13% for CD31, 19% for D2-40). Overall agreement between the three different methods used to identify LVI was 42.2%. Univariate analysis rendered vascular invasion diagnosed on haematoxylin and eosin stained slides as well as blood and lymphatic vessel invasion diagnosed by immunohistochemistry as significant prognostic variables regarding for overall survival. On multivariate analysis, blood vessel invasion detected by CD31 immunostaining proved to be the only independent prognostic factor. Finally, another recent study demonstrated a significant association between lymphatic invasion, assessed by D2-40 immunohistochemistry, and presence of lymph node metastasis [752].

LVI is an important prognostic marker in the assessment of bladder cancer, including both cystectomy and TURB specimens, and should routinely be reported upon in the pathological report (Grade B). LVI can predict tumor behavior and guide treatment decisions when detected in TURBT specimens (Level 2) [721,723,733,734]. LVI was shown as predictor of poorer outcome including progression and metastasis in patients with T1 bladder cancer in TUR specimens [723,733,734]. When LVI is identified in TURBT it will be present in 65% of matched cystectomies and associated with nodal metastases in 41% of cases [721]. LVI was also shown to be an independent prognostic variable in bladder cancer patients treated with radical cystectomy (Level 2) [712,714,715]. In a retrospective study of 750 patients with bladder cancer, LVI was shown to be an independent predictor of recurrence and decreased cause-specific and overall survival in node-negative invasive bladder cancer treated with cystectomy [712]. Recent multicenter studies clearly proved LVI to be an independent prognostic variable, significantly improving predictive accuracy of standard prognostic models. This effect was, however, mainly observed in node-negative cases. Standardization of assessment is urgently needed, and we would recommend that the evaluation of LVI on haematoxylin and eosin stained slides should be performed following the criteria presented by Algaba to ensure reproducibility and reliability of pathological diagnoses [707]. The use of endothelial cell markers, such as CD31 or D2-40, is an interesting tool which may facilitate detection of LVI and improve diagnostic accuracy in equivocal cases. The general use of immunohistochemistry in the routine setting, however, cannot be recommended, since performing two immunostains on even selected paraffin blocks with bladder cancer would be extremely time consuming and cost intensive. In addition, the clinical consequences of an LVI diagnosis, either in transurethral or cystectomy specimens, currently remains controversial due to inconsistency of studies on adjuvant chemotherapy specimens. The over-diagnosis of stromal retraction as LVI, however, does remains to be a major diagnostic problem. Adherence to strict morphological criteria embedded in a setting of continuous medical education and quality control is essential.

Level of evidence: 4
Recommendation: C
X. REPORTING ON LYMPH NODES

The minimum number of lymph nodes required in cystectomy specimen is not established. Recent studies have emphasized the importance of lymph node density (LND) for nodal staging. LND is defined by the ratio of positive lymph nodes to the total number of lymph nodes sampled, but again, the minimum number of lymph nodes in the specimen for optimal LND estimation yet to be established [753]. Prior studies suggested that the number of lymph node, size of tumor metastasis and presence of extranodal extension have prognostic significance (Level 3) [707,712,754]. Single-institutions cystectomy series have shown for both node-negative and node-positive patients with invasive bladder cancer that overall survival improves with an increasing number of lymph nodes examined [754]. In a study by Fang et al [755], minimum number of lymph nodes submission for radical cystectomy and pelvic lymphadenectomy was required, having to submit more tissue, including fat, if minimum number of 16 lymph nodes was not reached. In a span of 4 years, the median number of lymph node increased from to 20 from 15, and this policy was found to decrease mortality risk by 48% and significant in multivariate analysis [712]. Stephenson et al [756], showed the prognostic importance in measuring aggregate lymph node metastasis diameter. Fleischmann et al [757] have recently shown that extracapsular extension of lymph node metastases defines a subgroup with a very poor prognosis.

XI. REPORTING OF PROSTATE INVOLVEMENT

In surveillance biopsies of prostate/ prostatic urethra it is important to report the status of urethral mucosa (CIS or not), if prostatic glands are represented in the biopsy specimen and if so, are they involved by urothelial neoplasia or not. Involvement of the prostatic ducts and acini without stromal invasion is staged as pTis using the staging system for “Urothelial carcinoma of the Prostate”. Involvement of prostate may be through direct invasion from a bladder primary (pT4, staging system for “Urothelial carcinoma of the Bladder”) or urothelial carcinoma arising from the prostatic urethra with secondary prostatic stromal involvement or prostatic stromal invasion secondary to urothelial carcinoma involving prostatic ducts and acini. In the two latter situations, the staging system for “Urothelial carcinoma of the Prostate” is used. Patients with urothelial carcinoma involving prostatic stroma have a significantly worse 5 year disease specific survival than patients with urothelial carcinoma of the prostatic urethra (Level 3). Cheville et al [758] demonstrated that patients with prostatic urothelial carcinoma involving prostatic stroma have a significantly poorer 5 year disease specific survival than patients with urothelial carcinoma of the prostatic urethra. Shen et al [759] showed that patients with prostatic CIS or urethral lamina propria invasion had a similar, but higher incidence of lymph node metastasis and lower long-term and 5-year survival than those patients without prostatic involvement. Similarly, prostatic stromal invasion and periprostatic/seminal vesical invasion had a similar, but much higher nodal metastasis and worse survival than patients with only prostatic CIS or urethral lamina propria invasion [759]. It is apparent that an important etiology of the wide range of detection of prostatic stromal invasion in various series is likely the manner of examination of the prostate [760].

XII. FROZEN SECTIONS

Frozen section is not an optimal method for a primary diagnosis of invasive urothelial carcinoma or to perform pathologic staging prior to a cystectomy [761]. The criteria for indicating open partial cystectomy are quite strict. In these cases the urologist may send the pathologist samples of the margins in order to determine their status. The cystectomy specimen should be oriented or marked in such a way that the pathologist is able to recognize the margins. These should be suitably inked and the selection of the margins to be frozen should be made by means of a perpendicular section of the full thickness of the wall. In radical cystectomy, the ureteral margins are very rarely affected by the tumor. If the urologist suspects this may be the case, frozen section is indicated. Segment of ureter submitted separately should have proper labelling of the true margin. The situation is completely different if the macroscopic appearance is normal, as the intraepithelial lesions are uncommon and only the unequivocal cases of CIS should be diagnosed. Assessment for CIS at the margin in frozen section may be difficult. In most cases the status of the urethral mucosa is known through preoperative biopsies. Some institutions determine the status of the urethral margin intraoperatively. Lymph node frozen section evaluation is indicated when the possibility of not performing cystectomy is considered.

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Committee 3 A

Molecular Markers for Bladder Cancer Screening, Early Diagnosis, and Surveillance

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Abstract:

Due to the lack of disease-specific symptoms diagnosis and follow-up of bladder cancer has remained a challenge to the urologic community. Cystoscopy, commonly accepted as a gold standard for the detection of bladder cancer, is invasive and relatively expensive while urine cytology is of limited value specifically in low grade disease. Through the last decades numerous molecular assays for the diagnosis of urothelial cancer have been developed and were investigated with regard to their clinical use. However, although all of these assays have been shown to have superior sensitivity as compared to urine cytology, none of them has been included in clinical guidelines. The key reason for this situation is that none of the assays has been included into clinical decision making so far. We reviewed the current status and performance of modern molecular urine tests following systematic analysis of the value and limitations of commercially available assays. Despite considerable advances through recent years the authors feel that at this stage the added value of molecular markers for the diagnosis of urothelial tumors has not yet been identified. Current data suggest that some of these markers may have the potential to play a role in screening and surveillance of bladder cancer. Well designed protocols and prospective, controlled trials will be needed to provide the basis to determine whether integration of molecular markers into clinical decision-making will be of value in the future.
Molecular Markers for Bladder Cancer Screening, Early Diagnosis, and Surveillance

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I. INTRODUCTION

Bladder cancer represents an important cause of cancer morbidity and mortality. In 2010, once again, it was the second most common genitourinary cancer in the United States, with a projected 70,530 new cases and 14,680 deaths.[1] Currently, it is estimated that there are more than 1,000,000 men and women alive in the United States and Europe who have a history of bladder cancer. At the time of initial diagnosis, approximately 70% of patients have cancers confined to the epithelium or the subepithelial connective tissue. These cancers usually are managed with endoscopic resection and the selective use of intravesical therapy. The recurrence rate for these tumors ranges from 50% to 70%, and between 10% and 15% progress to muscle-invasive disease over 5 years.[2,3] Disease recurrence may occur in the bladder or in the upper urinary tract even after several years, necessitating life-long surveillance. Management of this population is costly because of the extended surveillance and need for repeated use of endoscopic and intravesical therapies. Patients with muscle-invasive and metastatic disease have a much more precarious survival outcome and also contribute greatly to the cost of bladder cancer care because of the expense of radical cystectomy and systemic chemotherapy. As a result, bladder cancer is the most expensive cancer to treat on a per patient basis in the United States.[4]

Due to the lack of disease-specific symptoms diagnosis and follow-up of bladder cancer has remained a challenge to the urologic community. Cystoscopy, commonly accepted as a gold standard for the detection of bladder cancer, is invasive and relatively expensive thus limiting the frequency of its use. Although new cystoscopic technologies such as fluorescence or narrow-band imaging are emerging, the invasiveness and added costs of these procedures underscores the need for better, simpler and cheaper diagnostic tests in the management of bladder cancer patients.[5-7]

Voided urine cytology is a highly specific, noninvasive adjunct to cystoscopy. It has good sensitivity for detecting high-grade urothelial cancer, but sensitivity for detection of low-grade tumors ranges from only 4% to 31%.[8] Furthermore the accuracy of cytology is dependent upon the level of expertise of the pathologist and, in consequence, not readily available in all places. Thus, specifically in the surveillance of papillary low grade tumors a noninvasive, highly sensitive and specific bladder cancer marker could decrease the frequency of cystoscopies, thereby improving patient quality of life, and potentially decrease costs by substituting a less expensive, noninvasive test for the more expensive endoscopic procedure. In high grade disease increased sensitivity of markers might lead to earlier detection of tumor recurrence and, in consequence improve patient survival.

The potential to decrease costs associated with cystoscopy would depend upon the cost of the noninvasive biomarker and its specificity such that a false positive result and the unnecessary need for further evaluation and associated patient anxiety would not be a frequent occurrence. Correspondingly, the use of urinary cytology in monitoring for persistence or recurrence of high grade disease would also allow for a decrease in the frequency of cystoscopies if its specificity were sufficiently high and pathologists were adequately trained so that they could deliver a reliable negative reading. Use of other urinary markers would depend upon their having a similarly high specificity for high risk disease in this context.

The requirements for an ideal marker have been
defined using the terms “easier, better, faster, cheaper”[9] “Easier” in this definition refers to the assay’s analytical performance and robustness. For an assay to be clinically applicable, it should be able to be performed easily and promptly in a clinical environment. “Better” is by far the most important challenge that has to be addressed. Demonstrating information equal to current clinically available variables is not enough. Any newly discovered marker should provide additional information that is helpful to the clinician for the management of the disease thus providing an added value to the current situation. “Faster” means that a new marker should be able to make the information available in an efficient and timely manner. Even if the marker has been proven to offer valuable information regarding the disease, an unreasonable period of time for its delivery could considerably decrease its practical utility. “Cheaper” is essential for a marker to be cost-effective. With health care expenditures reaching record levels, medical decision making is increasingly affected by economic concerns. Nevertheless, many parameters must be considered when assessing economic impact of a marker: in addition to the mere costs of the assay, potential clinical benefits (avoidance of further diagnostic interventions or ineffective therapy, or benefit from targeted therapy) need to be considered.

A significant amount of laboratory and clinical investigations have developed numerous new urine markers for the diagnosis of bladder cancer. Many of them exhibit sensitivity considerably superior to that of standard urine cytology, particularly in low to moderate grade diatheses, and are frequently used. However, despite FDA approval of some of these assays, none of them has achieved acceptance as a standard diagnostic procedure in clinical guidelines.[10,11]

In this report we try to delineate the reasons for this situation. Furthermore, we will focus in this manuscript on characterizing any “added value” and corresponding clinical utility of modern diagnostic markers. To this end, we define “added value” as either improvement of diagnostic accuracy, reduction (not necessarily replacement) of other diagnostic (occasionally invasive) measures, improvement in quality of life, and/or reduction of costs. Each of these will be assessed in the context of “requirement for an ideal marker” as described above.

1. WHY DID WE FAIL IN THE PAST?

Although non-invasive tests are labelled to diagnose bladder cancer, it remains unclear how they can effectively be integrated into clinical decision making, particularly when making an initial diagnosis because the presenting signs and symptoms may be caused by a number of different diseases and conditions. This situation is different from that in prostate cancer screening where the diagnosis is usually being sought in asymptomatic individuals who may themselves request a screening test.

It seems obvious that new tests for the initial diagnosis of bladder cancer should be investigated in patients with symptoms and/or signs associated with this disease. This will pertain largely to patients who have gross hematuria, those who may have irritative voiding symptoms without urinary tract infection, and those found on routine urinalysis to have microscopic hematuria. However, an investigation of the literature shows that this approach is often neglected. In contrast, the vast majority of studies are case-control trials comparing artificially composed study cohorts, in which the prevalence of the disease frequently exceeds 50%. High disease prevalence is usually not seen in urological practice and such an evaluation is likely to result in an optimistic assessment of the positive predictive value. Therefore, this study design may be misleading when the findings are translated into routine clinical use.

In conclusion, an insufficient evaluation process is one of the reasons for the lack of incorporation of modern bladder cancer tests into clinical decision making. We still lack “good clinical practice” guidelines for the evaluation of diagnostic markers. The different phases for development and validation of diagnostic markers in clinical practice have been defined.[12] However, these four phases, defined in analogy to the classification used for therapeutic trials, still provide only a framework for the detailed assessment of a new diagnostic marker.[7,13]

2. POTENTIAL INDICATIONS FOR MARKER USE

The following putative indications for the use of diagnostic bladder cancer markers can be delineated:

- Screening
  - Voiding symptoms, hematuria, risk populations (occupational exposure/lifestyle)
- Reflex testing
- Follow-up of patients with bladder cancer

a) Screening

Bladder cancer screening could be an indication for the use of a non-invasive diagnostic test. Although the mortality/incidence ratio is higher for bladder than prostate cancer, the low prevalence of bladder cancer in the general population along with the low mortality from bladder cancer due to a large number of cases with non-fatal tumors has been an obstacle to develop effective screening strategies for bladder cancer. Nevertheless, data from a few screening trials and theoretical considerations on cost-effectiveness issues recently have revitalized this
discussion.[14] Screening of well-defined high risk populations with a disease prevalence comparable to other tumor entities that have been accepted for screening (e.g. breast cancer or colorectal cancer) may offer a solution to this problem.[15]

1. Voiding symptoms

Irritative voiding symptoms may occur in patients with bladder cancer. This may occur in association with gross hematuria in which the bleeding itself may produce irritation, or the involvement of the trigone, bladder neck, or prostatic urethra by carcinoma in situ. However, the prevalence of bladder cancer in patients with irritative voiding symptoms barely exceeds that of age-matched controls because of so many other conditions that cause these symptoms. For example the close association of voiding symptoms due to prostate enlargement – common in the male population with bladder cancer – is a significant confounding factor and might prevent adequate patient selection. An effective selection of patients at risk of having bladder cancer based upon any degree of voiding symptoms appears impossible. In consequence, despite a good correlation between irritative voiding symptoms and bladder cancer, this condition alone is currently not suited for the identification of a patient cohort that should undergo further assessment for bladder cancer.

2. Hematuria

We do have increased bladder cancer prevalence rates in gross hematuria justifying a complete clinical work-up of these patients.[15-19] This is in contrast to microhematuria, a frequent condition in the general population. Although the prevalence of bladder cancer [20,21] is lower in patients with microscopic hematuria, complete urological work-up remains a matter of discussion.[22] This dilemma has resulted in the discrimination between high risk and low risk populations with a focus of diagnostic efforts on those patients at higher risk. However, apart from bladder cancer, there may be other conditions correlated with hematuria that may require urological intervention. However, information on these additional conditions is rare. Finally, there is concern that primary care physicians do not always refer patients with hematuria for evaluation thus introducing a further selection bias.[23,24]

The current pathways for the assessment of patients with hematuria have disadvantages. While endoscopy remains invasive and costly, it is still required because of the low sensitivity of urine cytology. In addition, the sensitivity of imaging for the detection of upper urinary tract tumors is insufficient; further confounding the problem of reaching an accurate diagnosis of urothelial cancer. As a result, assessment of patients with hematuria could be an area where new diagnostic markers could be clinical helpful. Since hematuria assessment is not a screening approach in its original sense the respective studies were grouped below among the diagnostic studies.

3. Risk populations

Exposure to specific chemical carcinogens is a well-established risk factor for urothelial cancer. Exposure to aromatic amines, in chemical industry workplaces involving use of these chemical substances and in the rubber industry, is associated with bladder cancer. An excess risk was also reported for dyers in textile industries, painters, varnishers and hairdressers. Other agents having been associated with UBC are polycyclic aromatic hydrocarbons (PAHs), used in aluminum production, coal gasification, coal tars, roofing and carbon black manufacture [25]

While these professions are rarer today and safety measures reducing exposure were introduced at least in Western plants an excess risk of bladder cancer still exists among workers exposed to diesel engine exhaust, such as drivers. In a meta-analysis, the relative risk among truck-drivers was 1.17 (95%CI 1.06-1.29) and among bus drivers, it was 1.33 (95%CI 1.22-1.45) [26]

Today, cigarette smoking is the most important risk factor for UBC, accounting for 50% of cases in men and 35% in women. A meta-analysis reported that current cigarette smokers have a risk of 2.57 (95%CI 2.20-3.00) compared with non-smokers.[27] A positive dose-response relationship is found with both number of cigarettes smoked daily and number of years of smoking.

Screening for bladder cancer requires definition of cohorts with adequate disease prevalence. The prevalence data provided above suggest that professional exposure alone may not justify screening; however, professional exposure in combination with other risk factors may yield populations with disease prevalence suitable for a screening approach. However, this will be further modulated by performance characteristics of the marker used and cost/benefit considerations.

b) Reflex testing

Use of molecular markers for so-called “Reflex testing” has gained some interest. The idea behind this strategy is to improve the accuracy of a previous test (mostly cytology) but also to minimize expenses for molecular assays. In most cases bladder cancer patients with a negative cytology test subsequently undergo reflex testing with a more sensitive assay. This procedure makes use of the high specificity of urine cytology on the one hand and aims at improving sensitivity of non-invasive diagnosis. Several studies on reflex testing have been published using the UroVysion assay.[28,29] As with most findings, it is important to validate the clinical utility of markers. One study prospectively validated the role of UroVysion in
patients with atypical cytology and noted cystoscopic findings had an important effect on the performance of the marker.[30] Nevertheless, any “added value” of this approach in the context of what we have described above requires validation.

c) Follow-up

Surveillance of patients with a history of bladder cancer is a key area for the use of new diagnostic markers, because the prevalence of the disease is high in this group and new urinary tests will therefore have a better positive predictive value than urine cytology. These tests can detect bladder cancer before they are visually evident. [28,31] However, this causes a significant problem in defining negative tests. Currently, there is no easy way of separating false positive tests from true positive tests when patients do not have clinically evident tumor.

In general, two different directions for a use of urine tests are conceivable:

- Surveillance of patients with low risk tumors aimed at a reduction of the frequency of diagnostic cystoscopies.
- Follow-up of patients with high risk tumors with the intention to recognize tumor recurrence and progression as early as possible.

Some studies suggest that a use of non-invasive diagnostic markers in follow-up of bladder cancer may be helpful; [8,32-34] however, prospective analyses to define the consequences from a negative or positive test result are still lacking.

II. MATERIALS AND METHODS

1. DATA COLLECTION

This review was restricted to commercially available assays (Tab. 1). The assessment was based upon a systematic literature search in medical databases (PubMed). All studies on the diagnostic use of the respective markers were screened and reviews as well as repeated publications of the same data were identified and excluded. Studies investigating prognosis were not considered for this analysis but are part of a second paper. [35] For some markers, well-executed meta-analyses were used as a basis for assessment [33,34] while for other markers detailed analysis of studies that had been published in English through January 2011 was performed. Sensitivity was assessed based upon histopathologic results only. Studies on non-urothelial tumors or trials not comprising information required for a basic assessment (e.g. stage, grade) were excluded. If deemed necessary additional publications in other languages were considered.

2. CRITERIA FOR ASSESSMENT OF REPORTING, MARKER STATUS AND LOE

It was a specific challenge of this assessment to classify the different markers and trials according to

- The Level of Evidence (LoE) for diagnostic procedures (Oxford classification) [36].
- The accuracy of data reporting according to the STARD criteria [37,38].
- The status of the marker with regard to clinical implementation (IBCN classification) [12].

By this procedure we intended that readers should be informed on the quality of marker studies and the status of a given marker with regard to clinical implementation in a structured and reproducible way. Furthermore, use of the respective tools were to be made in order to

- encourage readers, reviewers and publishers to use a structured and transparent process for manuscript assessment, but also
- to identify deficiencies of the tools available and produce proposals for their improvement.

All statements and recommendations were discussed within the group. Recommendations were provided and categorized according to the criteria of the Agency for Health Care Policy and Research (AHCPR) [39] and required consensus of the group.

III. MARKER PERFORMANCE

In this part of the assessment, information on the performance of commercially available molecular diagnostic markers is provided. This information is based upon a critical evaluation of the currently available literature.

As of March 2010, six urinary tumor marker tests have been cleared by the U.S. Food and Drug Administration (FDA) and are in clinical use. These tests are:

- The quantitative BTA TRAK® and the qualitative point-of-care BTA (bladder tumor antigen) stat® test (both by Polymedco Inc., Cortlandt Manor, NY, USA).
- The quantitative immunoassay NMP22® and the qualitative, point-of-care test NMP22® BladderChek® (Matritech Inc., Newton, MA, USA).
- The UroVysion® Bladder Cancer Kit (Vysis Inc., Downers Grove, IL, USA), a multiple marker fluorescence in situ hybridization (FISH) test.
- The uCyt™ test, an immunocytochemical assay (Scimedx Inc., Denville, NJ, USA).

With the exception of the uCyt test, which is only
<table>
<thead>
<tr>
<th>Test/Marker</th>
<th>Marker detected/Marker type</th>
<th>Specimen</th>
<th>Assay type</th>
<th>F D A approval</th>
<th>Manufacturer</th>
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<td>Voided urine</td>
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<td>Exfoliated cells</td>
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<td>B: Red blood cells</td>
<td>B: Voided urine</td>
<td>B: Interference-contrast microscopy or Red blood cell analyzer</td>
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<td>Dipstick immunoassay</td>
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<td>Follow-up</td>
<td>Scimedx, Inc.</td>
</tr>
<tr>
<td>UroVysion</td>
<td>Alterations in chromosomes 3, 7, 17 and 9p21</td>
<td>Voided urine, Exfoliated cells</td>
<td>Multi-colored, multi-probe FISH</td>
<td>Diagnosis, follow-up</td>
<td>Abbott, Vysis</td>
</tr>
</tbody>
</table>
cleared for monitoring bladder cancer recurrence, all tests are FDA-approved as adjunctive tests for use in the initial diagnosis of bladder cancer and surveillance of bladder cancer patients, in conjunction with standard procedures.

The performance of biomarkers depends upon their sensitivity (positivity of a marker in the presence of disease), specificity (negativity of a marker in the absence of disease), positive predictive value (probability of disease if a marker is positive), and negative predictive value (probability of no disease if a marker is negative). A threshold can be set for interpreting a test result as positive or negative, this in turn influencing a marker’s sensitivity or specificity (Fig. 1). A marker’s predictive value will be influenced by the prevalence of a condition in a test population, thereby affecting calculations of the probability of detecting true versus false positives and true versus false negatives, this may be misleading in interpreting test results and their use. This can be important in both low risk and high risk disease in influencing how a marker may be applied in screening, surveillance, or determining efficacy of treatment.

1. DIAGNOSIS AND SURVEILLANCE

Performance characteristics may be obtained by assessment of trials claiming to investigate a diagnostic use of non-invasive molecular markers. These trials are inhomogeneous since they are composed from case control studies with a high prevalence of cases and from trials targeting frequently poorly characterized cohorts (usually designed as “cases suspicious for bladder cancer”, hematuria in some cases) with a lower prevalence of bladder cancer. Therefore, the reported range of sensitivity is usually wider as compared to that in follow up studies.

Few trials may be classified as true screening trials investigating predefined cohorts of asymptomatic individuals (e.g. smokers, professionally exposed individuals, cohorts randomly invited for screening) rendering marker positive individuals for urological evaluation. These studies are addressed separately.

a) Urine-based Markers

1. NMP22

Nuclear matrix proteins (NMPs) are part of the structural framework of the nucleus and provide support for the nuclear shape. These proteins have also been attributed roles in DNA replication, in ribonucleic acid transcription and in the regulation of gene expression. One member of this family, nuclear mitotic apparatus protein (NMP22), is much more prevalent in malignant urothelial cells than in their normal counterparts. Apoptosis is accompanied
Contingency Analysis of Sensitivity and Specificity

Disease Status
Present (+) Absent (-)

<table>
<thead>
<tr>
<th>Test Result</th>
<th>Present (+)</th>
<th>Absent (-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pos (+)</td>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td>Neg (-)</td>
<td>c</td>
<td>d</td>
</tr>
</tbody>
</table>

Sensitivity = true positives \(a\) / (true positives \(a\) + false negatives)
Sensitivity = true negatives \(d\) / (true negatives \(d\) + false positives)

Contingency Analysis of Predictive Values

Disease Status
Present (+) Absent (-)

<table>
<thead>
<tr>
<th>Test Result</th>
<th>Present (+)</th>
<th>Absent (-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pos (+)</td>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td>Neg (-)</td>
<td>c</td>
<td>d</td>
</tr>
</tbody>
</table>

Positive Predictive Value = true positives \(a\) / (true pos \(a\) + false positive)
Negative Predictive Value = true negatives \(d\) / (true neg \(d\) + false negative)

Figure 1. Contingency analysis of sensitivity and specificity

Figure 2. Contingency analysis of predictive values
with a release of NMP22 into the urine, and patients with bladder cancer have a significantly elevated concentration of NMP22. Both a laboratory-based quantitative microplate enzyme immunoassay and a qualitative point-of-care test (BladderChek\textsuperscript{TM} Test; Matritech Inc., Massachusetts, USA) are available and are FDA-approved for use in bladder cancer surveillance. The latter is also approved for detection of bladder cancer in high-risk patients.

### Sensitivity

There have been several meta-analyses that have evaluated the sensitivity of commonly used markers (Table 2). When compared with cytology, NMP22 as well as other markers generally have a significantly higher sensitivity for detecting bladder cancer. This improvement in sensitivity is primarily in detection of low grade and low stage bladder cancers with significant overlap in studies comparing markers and cytology for high grade cancer, high stage cancers and patients with CIS (Table 2 and 3). Nevertheless, in general urinary bladder markers also perform better in patients with higher stage disease (Table 4) and higher biologic aggressiveness (Table 5).

Boman and colleagues evaluated NMP22 (cut-off > 4 U/ml) sensitivities in 250 patients and found sensitivities of 46% (41/90), 58% (21/36), 76% (22/29) in detecting tumors ≤ 10 mm, 11–20 mm and > 21 mm, respectively.\cite{40} Sanchez-Carbajo and colleagues evaluated 187 patients with NMP22 (cut-off > 14.6 U/ml) and reported sensitivities of 83% (19/23), 81% (34/42) and 93% (38/41) in detecting tumors < 5 mm, 5–30 mm and > 30 mm, respectively.\cite{41}

The data on the impact of tumor number on sensitivity

---

**Table 2. Marker Sensitivity and Specificity of Cytology and Commercially Available Markers (data from Meta-analyses)**

<table>
<thead>
<tr>
<th>Marker</th>
<th>Median Sensitivity (range)</th>
<th>Median Specificity (range)</th>
<th>Total Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cytology</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glas (51)</td>
<td>55 (48-62)*</td>
<td>94 (90-96)*</td>
<td>3,444</td>
</tr>
<tr>
<td>Lotan (8)</td>
<td>34 (20-53)</td>
<td>99 (83-99)</td>
<td>2,767</td>
</tr>
<tr>
<td>Van Rhijn (32)</td>
<td>35 (13-75)</td>
<td>94 (85-100)</td>
<td>5,545</td>
</tr>
<tr>
<td>Mowatt (52)</td>
<td>44 (38-51)*</td>
<td>96 (94-98)*</td>
<td>14,260</td>
</tr>
<tr>
<td><strong>BTA stat</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glas (51)</td>
<td>70 (66-74)*</td>
<td>75 (64-84)*</td>
<td>1,160</td>
</tr>
<tr>
<td>Lotan (8)</td>
<td>71 (57-82)</td>
<td>73 (61-82)</td>
<td>2,534</td>
</tr>
<tr>
<td>Van Rhijn (32)</td>
<td>58 (29-74)</td>
<td>73 (56-86)</td>
<td>3,461</td>
</tr>
<tr>
<td><strong>NMP22 (assay/bladder check)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glas (51)</td>
<td>67 (60-73)*</td>
<td>78 (72-83)*</td>
<td>2,290</td>
</tr>
<tr>
<td>Lotan (8)</td>
<td>73 (47-87)</td>
<td>80 (58-91)</td>
<td>2,413</td>
</tr>
<tr>
<td>Van Rhijn (32)</td>
<td>71 (47-100)</td>
<td>73 (55-98)</td>
<td>2,041</td>
</tr>
<tr>
<td>Mowatt (52) pooled</td>
<td>68 (62-74)*</td>
<td>79 (74-84)*</td>
<td>10,119</td>
</tr>
<tr>
<td>Mowatt (52) BladderChek</td>
<td>65 (50-85)</td>
<td>81 (40-87)</td>
<td>2,426</td>
</tr>
<tr>
<td>uCyt+/Immunocyt</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Van Rhijn (32)</td>
<td>67 (52-100)</td>
<td>75 (62-82)</td>
<td>959</td>
</tr>
<tr>
<td>Mowatt (52)</td>
<td>84 (77-91)*</td>
<td>75 (68-83)*</td>
<td>3,041</td>
</tr>
<tr>
<td>This assessment</td>
<td>81 (42-100)</td>
<td>75 (62-95)</td>
<td>4,899</td>
</tr>
<tr>
<td><strong>FISH (Urovysion)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hajdinjak (31)</td>
<td>72 (69-75)*</td>
<td>83 (82-85)*</td>
<td>2,477</td>
</tr>
<tr>
<td>Mowatt (52)</td>
<td>76 (65-84)*</td>
<td>85 (78-92)*</td>
<td>3,101</td>
</tr>
<tr>
<td>This assessment</td>
<td>72 (23-100)</td>
<td>80 (40-100)</td>
<td>2,852</td>
</tr>
</tbody>
</table>

*95% CI
is still controversial. Poulakis et al. evaluated 739 patients using NMP22 (cut-off ≥ 8.25 U/ml) and found sensitivities of 79% (165/208), 90% (83/92) and 97% (96/99) in patients with one, two to three, and more than three tumors, respectively.[42] On the other hand, Sanchez-Carbayo and colleagues evaluated 187 patients using NMP22 (cut-off ≥14.6 U/ml) and found sensitivities of 72% (18/25) and 75% (61/81) in patients with single and multiple tumors, respectively.[41] This discrepancy may relate to the level of NMP22 reaching threshold based upon the amount of apoptotic cell debris (the basis of a positive test) shed into the urine. Tumor volume may reflect either size or number of lesions in contributing to a positive test result.

There is also a possible impact of marker sensitivity based on whether the marker is used for detection or surveillance. However, this may be related to the fact that tumors are larger at diagnosis or have a more advanced stage than during surveillance. Boman found that NMP22 has higher sensitivity for new as compared to recurrent tumors; this appeared due to

<table>
<thead>
<tr>
<th>Marker</th>
<th># studies</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytology</td>
<td></td>
<td>.12 (.04-.31)</td>
<td>.26 (.17-.37)</td>
<td>.64 (.38-.84)</td>
</tr>
<tr>
<td>Lotan (8)</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Van Rhijn (32)</td>
<td>9</td>
<td>0.17</td>
<td>0.34</td>
<td>0.58</td>
</tr>
<tr>
<td>BTA stat</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lotan (8)</td>
<td>8</td>
<td>.47 (.38-.56)</td>
<td>.73 (.59-.83)</td>
<td>.94 (.55-.99)</td>
</tr>
<tr>
<td>Van Rhijn (32)</td>
<td>7</td>
<td>0.45</td>
<td>0.6</td>
<td>0.75</td>
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<tr>
<td>NMP22</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Van Rhijn (32)</td>
<td>3</td>
<td>0.41</td>
<td>0.53</td>
<td>0.8</td>
</tr>
<tr>
<td>Lotan (8)</td>
<td>7</td>
<td>.61 (.35-.81)</td>
<td>.71 (.41-.90)</td>
<td>.79 (.63-.89)</td>
</tr>
<tr>
<td>Immunocyt</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Van Rhijn (32)</td>
<td>1</td>
<td>0.78</td>
<td>0.9</td>
<td>1</td>
</tr>
<tr>
<td>This assessment</td>
<td>19</td>
<td>0.75</td>
<td>0.84</td>
<td>0.84</td>
</tr>
<tr>
<td>FISH (Urovysion)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Van Rhijn (32)</td>
<td>2</td>
<td>0.56</td>
<td>0.78</td>
<td>0.95</td>
</tr>
<tr>
<td>This assessment</td>
<td>21</td>
<td>0.53</td>
<td>0.81</td>
<td>0.79</td>
</tr>
</tbody>
</table>

Table 3. Sensitivity of Cytology and Commercially Available Markers (data from Meta-analyses) Based on Tumor Grade

Table 4. Association of Cytology and Commercially Available Markers (data from Meta-analyses) with Tumor Stage (Lotan (8))

Table 5. Sensitivity of Cytology and Commercially Available Markers (data from Meta-analyses) and Association with Tumor Aggressiveness (Mowatt (52))
higher stage and grade at presentation and larger tumor size.[40]

In two large prospective multicenter studies using the NMP22 BladderChek test, the NMP22 assay was positive in 44 of 79 patients with cancer (sensitivity 55.7%; 95% confidence interval [CI], 44.1%-66.7%) in the detection setting and sensitivity was 49.5% (51/103; 95% CI, 39.5%-59.5%) in the surveillance setting.[32,43] While the sensitivity for surveillance was lower, the overlapping confidence intervals suggest no significant difference in performance of NMP22 in detection and surveillance setting.

- **Specificity**
  
  The main disadvantage of current markers is their lower specificity compared with cytology (Table 1). NMP22 is a protein that localizes with the spindle poles during mitosis and thus regulates chromatid and daughter cell separation.[44] There is a substantially higher level of NMP22 in the urine of patients with bladder cancer. However, because this protein is released from dead and dying urothelial cells, many benign conditions of the urinary tract, such as stones, infection, inflammation, and hematuria may carry these proteins as well and cystoscopy can cause a false-positive reading. In a study of NMP22 and BTA stat in 278 symptomatic patients who presented to a urology clinic, Sharma et al found that greater than 80% of the false-positive results were clinically categorized as benign inflammatory or infectious conditions, renal or bladder calculi, recent history of a foreign body in the urinary tract, bowel interposition segment, another genitourinary cancer or an instrumented urinary sample.[45] History of ureteral stents or any bowel interposition segment had a 100% false-positive rate. Exclusion of all 6 clinical categories improved the specificity and positive predictive value of NMP22 (95.6%, 87.5%) and BTA stat (91.5%, 69.7%), and was similar to urinary cytology.

  One consideration that is often raised is the possibility that a urine based marker may become positive prior to visualization of a tumor. This has been termed an “anticipatory positive” result. There are several studies that found a greater likelihood of recurrence in patients with a positive FISH assay compared to those with negative assays in the absence of a visualized tumor.[46-48] This has also been reported for NMP22 and ImmunoCyt/uCyt, albeit in a small number of patients.[16,49,50] Thus the lack of specificity is the major limitation of these urine markers. Strategies to manage patients with a positive marker,[12,51] without cystoscopically visible tumor is crucial to the future applicability of markers.

- **Data quality**
  
  As for other markers discussed in this assessment, quality of reporting according to the STARD criteria is moderate to poor, in part due to the fact that the majority of trials were conducted earlier.[37,38] We conclude that the level of evidence of studies on NMP22 is LoE III and in some studies LoE IIb according to the Oxford classification.[36] Phase III IBCN trials are lacking.[12,51] This translates into a maximal LoE Grade IIa for meta-analyses.[8,33,34,52,53]

2. **BTA stat, BTA TRAK**

Among the non-invasive tests developed to detect urothelial carcinoma, those derived from basement membrane fragments found in urine from bladder cancer patients included a series called BTA assays. The original BTA test was a colorimetric three-step, latex-agglutination process that qualitatively detected bladder tumor-associated analytes (BTA) using human immunoglobulin G.[54-56] The BTA analytes were polypeptides ranging from 16 to 65 kDa thought to be released into the urine by proteases released from tumor cells during stromal invasion.[54-56] This test was supplanted by 2 newer versions, the BTA stat and the BTA TRAK which detect different protein(s) than the original.[54-57] Extrapolation of sensitivity or specificity results from studies of the original BTA test to BTA stat or BTA TRAK are, therefore, not valid. The original BTA test is no longer commercially available.

Both BTA stat and TRAK detect human complement factor H related protein (hCFHrp) and complement factor H.[57] hCFHrp is thought to interrupt the complement cascade and confer a selective growth advantage to cancer cells by allowing them to evade the host immune system. The dissociation of C3 activating convertase and degradation of C3b are thought to be enhanced by complement factor H.[55-58] Both tests are non-invasive and approved by the Food and Drug Administration (FDA) as adjuncts to cystoscopy in the detection of urothelial cancer, not as primary diagnostic tools.[59,60] BTA stat is a qualitative test, while BTA TRAK is quantitative.[1,6] Both have been performed on fresh, refrigerated, or frozen urine obtained as voided or catheterized specimens.[40,42,45,49,55,59,61-74]

The BTA stat is an inexpensive, office-based, single-step, immunochromatographic assay usually performed on voided fresh or refrigerated urine samples producing results in 5 minutes with minimal training of personnel.[57] Five drops of urine are placed into a well containing a colloidal gold conjugate antibody and allowed to react. Only if tumor antigen is present does a visible colored line form when the antigen conjugate complexes are captured by a second antibody. BTA stat has been used in the detection of initial, recurrent, and upper tract urothelial carcinoma (Tab. 6).[40,42,45,49,62-74]

The BTA TRAK is a sandwich immunoassay method
requiring trained laboratory technologists several hours to complete.[75] In this assay, antihuman complement factor H related protein monoclonal antibody coated onto 96-well microtiter plate captures its target in urine. A second alkaline phosphatase labeled reporter antibody and a substrate solution are used to detect hCFHrp. Human complement factor H is also detected. Comparison to a calibration curve created from kit standards is used to determine the amount of hCFHrp present. The cut-off limit recommended by the manufacturer is 14 units/ml, where 1 unit is 4.7 ng of hCFHrp (Tab. 6).[58,59,61]

Using a PubMed search for “BTA”, we identified 7 review articles in English on bladder tumor markers in use that included BTA stat or TRAK testing. [34,52,54,56,58-60] Sample source documents from these were selected based on frequency of citation and to include global urologic participants. With the exception of those studies performed on archived urine specimens from prior studies,[55,61] the majority of studies discussed are International Bladder Cancer Network (IBCN) Phase II studies.

Table 6. BARD stat and TRAK assay: Patient demographics

<table>
<thead>
<tr>
<th>Author</th>
<th>Gender</th>
<th>Race</th>
<th># of Sites</th>
<th>Urine sample type</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarosdy 1997</td>
<td>M 443</td>
<td>F 332</td>
<td>14+</td>
<td>Voided Archived frozen</td>
<td>Yes</td>
</tr>
<tr>
<td>Babjuk 2002</td>
<td>M 141</td>
<td>F 77</td>
<td>2</td>
<td>Voided, NS</td>
<td>Yes</td>
</tr>
<tr>
<td>Ellis 1997</td>
<td>Partial record</td>
<td>NS</td>
<td>14</td>
<td>Voided, frozen</td>
<td>NS</td>
</tr>
<tr>
<td>Tsui 2007</td>
<td>Partial record</td>
<td>NS</td>
<td>NS</td>
<td>Voided fresh</td>
<td>NS</td>
</tr>
<tr>
<td>Serretta 2000</td>
<td>M 151</td>
<td>F 28</td>
<td>1</td>
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</tr>
<tr>
<td>Giannopoulos 2000</td>
<td>M 145</td>
<td>F 23</td>
<td>NS</td>
<td>Voided fresh</td>
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<tr>
<td>Poukalis 2001</td>
<td>M 485</td>
<td>F 254</td>
<td>2</td>
<td>Voided fresh</td>
<td>Yes</td>
</tr>
<tr>
<td>Nasuti 1998</td>
<td>NS</td>
<td>NS 1</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Wiener 1998</td>
<td>M 199</td>
<td>F 92</td>
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<td>Voided Fresh &amp; frozen</td>
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</tr>
<tr>
<td>Sharma 1999</td>
<td>NS</td>
<td>NS 1</td>
<td>NS</td>
<td>Voided NS</td>
<td>NS</td>
</tr>
<tr>
<td>Sozen 1999</td>
<td>M 127</td>
<td>F 13</td>
<td>NS</td>
<td>Voided or cath</td>
<td>Yes</td>
</tr>
<tr>
<td>Leyh 1999</td>
<td>M 172</td>
<td>F 68</td>
<td>98% white 6</td>
<td>Voided or cath</td>
<td>Yes</td>
</tr>
<tr>
<td>Pode 1999</td>
<td>M 207</td>
<td>F 43</td>
<td>NS</td>
<td>Voided fresh</td>
<td>NS</td>
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<tr>
<td>Ramakumar 1999</td>
<td>M 152</td>
<td>F 44</td>
<td>NS</td>
<td>1</td>
<td>Voided fresh</td>
</tr>
<tr>
<td>Raitanen 2001</td>
<td>NS</td>
<td>NS 18</td>
<td>Voided fresh</td>
<td>NS</td>
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<tr>
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<td>M 208</td>
<td>F 96</td>
<td>NS</td>
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</tr>
<tr>
<td>Schroeder 2004</td>
<td>M 80</td>
<td>F 35</td>
<td>NS</td>
<td>1</td>
<td>Unknown Collection frozen</td>
</tr>
</tbody>
</table>

NS = Not stated

Level 2a evidence as identified by a meta-analysis of data on BTA Stat and TRAK testing was provided in these review articles, with the highest number of subjects reported in the Glas and van Rhijn articles. [34,52] Each included many of the same source documents, and thus each was dependent on the quality of these sources. As described by Glas[52], the quality of the literature is weak and we concur, based on our evaluation using the STARD checklist. [38] No study met all 25 STARD items.

There are several clinical scenarios in which either of the BTA tests could prove useful. The first is as a diagnostic tool for the detection of primary urothelial carcinoma in subjects with signs and symptoms of bladder cancer or at screening of risk populations. The FDA has not approved either BTA stat or TRAK for this indication.[6] “Tumor markers in the diagnosis of primary bladder cancer. A systematic review” by Glas would appear to address this situation.[52] In this meta-analysis, of 1160 subjects providing urine samples for BTA stat testing, the sensitivity was 70% (95% CI: 66-74%) and specificity 75% (95% CI: 64-
The sensitivity and specificity of the BTA TRAK test was 66% (95% CI: 62-71), and 65% (95% CI: 45-81) on data collected from 829 subjects who provided urine samples for this same meta-analysis. Thus, level 2a evidence does not support the use of either BTA test alone for the detection of urothelial carcinoma (Tab 7 and 8).

Glas[52] further contributes to our understanding of the literature by noting how study design influenced results. With regard to the BTA stat test, sensitivity was estimated to be significantly lower in case control studies (66%, 95% CI: 60-71) when compared to cohort studies (77%; 95%CI: 71-82). Specificity of the BTA stat test was overestimated when interpretation of results occurred in a manner which was not blinded. Glas[52] described the studies available for this meta-analysis as ‘weak’ as most were not a consecutive series of subjects suspected of having a bladder tumor with independent assessment of the marker test and reference standard.

The second clinical situation, monitoring of subjects with a prior history of bladder cancer for recurrence, is the indication for which the FDA has approved the BTA tests as an adjunct to cystoscopy.[60] “Urine markers for bladder cancer surveillance: A systematic review” by van Rhijn[34] appears to address this scenario. These authors reported a total of 1377 subjects on whom the BTA stat was performed and 306 subjects on whom the BTA TRAK was performed in the setting of surveillance for recurrent disease. The median sensitivity was higher for BTA TRAK than stat (71% vs. 58%, respectively). The median specificity was higher (73%) for 2084 BTA stat-tested subjects than for 195 BTA TRAK-tested subjects (66%). Subset analysis of recurrent tumor stratified by grade showed lower sensitivities for grade 1 and 2 tumors for both BTA stat and TRAK (grade 1 = 45% and 55%, respectively; grade 2 = 60% and 59%, respectively) as compared to grade 3 tumors (75% and 74%, respectively). A trend of increasing sensitivity and specificity for overall tumor detection has also been noted with increasing tumor stages. [58] Furthermore, the BTA stat test has been shown to have a lower sensitivity for detecting recurrent as opposed to primary tumors, possibly related to the smaller size of recurrent tumors BTA TRAK showed increasing sensitivity and specificity with higher tumor grades and stages (Tab. 7 and 8).[56]

Unfortunately, both current forms of the BTA test are limited by conditions producing false positive results. Because complement factor H is present at high concentrations in blood, a positive BTA stat or TRAK test will occur when hematuria is present, regardless of the presence or absence of urothelial tumor.[59,60] Greater than 80% of false positives to either form of BTA test occur in subjects with hematuria, dysuria, incontinence, a history of intravesical therapy, ureteral stents or nephrostomy tubes, renal or bladder calculi, benign inflammatory disease (urinary tract infections or prostatitis), bowel interpositions or other genitourinary cancers (renal or prostate).[45,59,60,63,67] While use of exclusionary

Table 7. BARD stat assay: Individual Analyses for Overall Sensitivity and Specificity

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>% Sensitivity</th>
<th>% Specificity</th>
<th>N True Positives</th>
<th>N True Negatives</th>
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NS = Not stated  
* = 289 samples from 250 patients  
6 = 280 samples from 250 patients  
182
criteria improve the performance of both BTA tests, the signs and symptoms of benign inflammatory conditions overlap those seen in subjects with urothelial carcinoma. This limits the usefulness of these tests for discriminating between malignant and non-malignant states.[45,67] In particular, false positives for up to 2 years after intravesical bacillus Calmette-Guerin (BCG) therapy limits the BTA tests' usefulness in monitoring for recurrent tumor.[64] False positives are more commonly seen with the BTA stat as opposed to the BTA TRAK test.[60] False positives are seen in < 5% of subjects with no known urinary pathology.[45]

Although the value of this and other biomarkers in detecting high risk (high grade) disease has been suggested in numerous studies, their high rate of false positive results and consequent low specificity (through the influence of inflammatory conditions and prior intravesical therapies either with chemotherapy of BCG) somewhat limits their practical usefulness in monitoring for disease persistence or recurrence. In this regard, urinary cytology may be of value because of its high specificity in the setting of high grade disease.

Relatively few recent studies have been published on the BTA tests, and most date from 1999 to 2001. This may in part be explained by the decreasing levels of specificity reported for the BTA stat test between 1997 and 2001, and thus, lower enthusiasm for their use. Additionally, the increase in regulatory controls for office-based laboratory procedures such as the BTA stat test and declining re-imbursement for such point-of-contact testing by Medicare and private healthcare insurance companies have likely reduced use of these tests by many urologists. The cost to perform BTA TRAK testing and its limited use in only bladder cancer subjects may also have discouraged clinical laboratories from performing this test, particularly in comparison to cytology, which is routinely performed on multiple fluids from multiple organ sites.

**Suggested future trials for use of the BTA stat and TRAK tests.**

At this time, we have not found evidence to endorse use of either BTA test in screening for bladder cancer. Use of BTA stat in subjects with a history of urothelial cancer and a normal urinalysis could be prospectively studied to determine if this combination of tests (which might fail to detect small, low grade recurrences) could safely reduce the frequency of surveillance cystoscopies without compromising cancer control. The suggestion by Blumenstein[76] that serial measurements of BTA TRAK tests could be useful in predicting recurrence in the individual patient requires confirmation in a large, prospective, multi-center trial. As multiple candidate antibodies were obtained during the development of the BTA tests, it is possible that an additional antibody that does not cross-react with substances in the urine of those with benign inflammatory conditions and/

### Table 8. BARD stat and TRAK assay: Tumor Characteristics

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NA = Not applicable
NS = Not stated
* included more than one group together
^ grade and stage unknown in 32, 33 subjects, respectively
or hematuria could be isolated and used to further refine BTA testing.

3. UBC tests

UBC-Rapid and UBC-ELISA tests are immunological assays available from IDL, IDL Biotech, (Borlange, Sweden). Both assays detect cytokeratin 8 and 18 fragments in urine. Cytokeratins are intermediate filament type cytoskeletal proteins specific for epithelial cell origin. In human cells, a total of 20 cytokeratins have been identified and the expression of cytokeratins 8, 18, 19, and 20 at the protein or mRNA level has been evaluated as bladder cancer markers.[77] Since cytokeratins are intracellular proteins, the detection of these proteins in urine is possible only when they are released in urine following cell death. The UBC-Rapid assay is a qualitative point-of-care assay wherein cytokeratin 8 and 18 fragments present in urine react with gold-labeled antibodies forming a complex. This complex migrates to the reaction zone where it reacts with a specific antibody to produce a dark line (positive result). Any excess of gold-labeled antibodies continues to migrate into the second capture zone to form a second dark line (test control).[78]

UBC-ELISA is a solid-phase 2-step sandwich assay. Specimens, standards, and controls are incubated with microliter wells coated with a mouse monoclonal anti-UBC antibody. Following incubation, unbound samples are washed off and the wells are incubated with a horseradish peroxidase second antibody. Following washing, the wells are developed using tetramethylbenzidine substrate and the color intensity is measured at 450 nm. Levels of UBC in urine specimens are calculated from a standard curve. The manufacturer-suggested cutoff limit for UBC-ELISA is 12 μg/L. UBC-ELISA requires sending samples to specialized laboratories, where trained personnel can conduct the ELISA.

Pubmed search of the term “UBC and bladder cancer” resulted in 73 hits. After examining the title and the abstract of each article, nineteen articles were found to be on UBC tests. In these nineteen studies, 623 subjects have been assayed by the UBC-Rapid test and 3,102 individuals have been assayed by UBC-ELISA.

According to the STARD criteria the quality of many articles was moderate to good with a few articles displaying excellent quality of reporting. The majority of studies provided LoE Grade III and IV evidence. Three cohort studies were classified as LoE IIb and one study by Hedelin et al was a prospective screening study.[79]

Meta-analysis of UBC-Rapid in three studies reporting 623 patients (but UBC-Rapid assay was performed on 515 patients) showed an overall sensitivity of 59.3% with 86.1% specificity. However, it is noteworthy that barring the initial study[78], in two other studies, the overall sensitivity was less than 50%. [71,72] For UBC-ELISA, different studies have used different cut-off limits with a range between 0.16 μg/L and 15 μg/L. In one study, the cut-off limit was called an “Index value”, which was calculated by dividing the value during follow-up divided by the value before the first transurethral resection.[74] In some studies, the UBC values were normalized to creatinine, whereas in other studies they were not normalized; the manufacturer does not recommend such normalization. For these reasons, a meta-analysis of UBC-ELISA results from different studies cannot be and should not be performed.

4. Survivin

Survivin is an anti-apoptotic protein that is a member of the inhibition of apoptosis protein (IAP) gene family. Survivin levels are elevated in bladder cancer, and therefore, survivin has been suggested as a promising biomarker for bladder cancer.[80-82] The commercially available bio-dot assay (Fujirebio Diagnostics, Inc.) for Survivin is a technique that is routinely performed in any research laboratory to detect a variety of proteins. In Survivin bio-dot assay (a dot-blot assay) urine samples are blotted onto a nitrocellulose or Immobilon® membrane, along with recombinant survivin protein blotted at various concentrations. Following sequential incubations with a rabbit polyclonal anti-survivin antibody and a horseradish peroxidase-conjugated secondary antibody, the dots are visualized by chemiluminescence. The intensity of the specimens and the standard-dots is measured by densitometry and the amount of survivin in specimens is determined from a standard curve. This assay however has not been used recently and the current assays reported in various articles are either quantitative reverse transcription polymerase chain reaction (Q-PCR) or qualitative reverse transcription PCR (RT-PCR) assays. In the latter survivin mRNA expression is detected by agarose gel electrophoresis, followed by ethidium bromide staining.

Pubmed search of the term “Survivin and bladder cancer” resulted in 126 hits, which included 12 reviews. After examining the title and the abstract of each article, ten articles were found to have evaluated the efficacy of survivin as a urine marker using the bio-dot, Q-PCR or RT-PCR assays. One of these studies was a prospective cohort screening study but it did not include any bladder cancer cases.

According to the STARD criteria the quality of many articles was moderate to good, with a few articles displaying excellent quality of reporting. The majority of studies provided LoE Grade III and IV evidence. Three cohort studies were classified as LoE IIb and one study by Davies et al had both a retrospective blinded cohort and a prospective cohort.[83]
According to the STARD criteria, the quality of the bladder cancer.\[90\]

Previously, urine specimen who used that LCA-esion (SSH) and cDNA microarray, conducted on voided urine without detectable bladder abnormalities \[89\].

Recently, in suppressive subtractive hybridization and have developed bladder abnormalities as evaluated by ultrasound when compared to those without detectable bladder abnormalities \[89\].

LCA- levels to urinary protein concentration is carried out when using the sandwich ELISA for BLCA-4 measurement.

Pubmed search for the term “BLCA-4 and bladder cancer” resulted in 14 hits, which included six reviews on bladder tumor markers. After examining the title and the abstract of each article, three articles were found to evaluate the efficacy of the BLCA-4 marker for the detection of bladder cancer. All of these studies were case-control and from a single institution \[86-88\]. Another study also found that LCA-4 is differentially up-regulated in bladder cancer cells and tissues and was identified by two dimensional gel electrophoresis of the nuclear matrix components from normal and tumor tissues. \[85\]

The initial assay for BLCA-4 measurement in urine was an indirect ELISA. \[86,87\]

In those studies, the cut-off limit to detect bladder cancer was set at 13 μg/mg protein. Later a sandwich ELISA that utilizes 2 monoclonal antibodies was developed and a cut of limit of absorbance was 0.04 units at 630 nm was used for calculating the sensitivity and specificity \[88\].

Therefore unlike the previous indirect ELISA, neither urine precipitation nor normalization of the BLCA-4 levels to urinary protein concentration is carried out when using the sandwich ELISA for BLCA-4 measurement.

Since the dot-blot assay detects survivin protein and the PCR assays detect mRNA expression, the results reported in studies using the dot blot assays and PCR assays cannot be and should not be used to perform a meta-analysis of the Survivin marker. Furthermore, in each study the PCR primers used for Q-PCR or RT-PCR were different, and therefore, no two PCR studies are alike. In addition, Q-PCR is quantitative and RT-PCR is qualitative, and therefore, the results of these PCR studies also should not be used to perform a meta-analysis. Davies et al reported that urinary survivin levels decrease after radical prostatectomy; this study also reported an unusually high false positive rate, at 50%. Given that each study has used different techniques to assay survivin expression, this marker is not ready for diagnosis and/or surveillance of bladder cancer patients.

5. BLCA-4

BLCA-4 assay is a sandwich ELISA commercially available from Eichrom Technologies. BLCA-4 is a nuclear matrix protein and has homology to ELK3 gene, a member of the ETS family of transcription factors. \[84\] BLCA-4 is differentially up-regulated in bladder cancer cells and tissues and was identified by two dimensional gel electrophoresis of the nuclear matrix components from normal and tumor tissues. \[85\]

The initial assay for BLCA-4 measurement in urine was an indirect ELISA. \[86,87\]

In those studies, the cut-off limit to detect bladder cancer was set at 13 μg/mg protein. Later a sandwich ELISA that utilizes 2 monoclonal antibodies was developed and a cut of limit of absorbance was 0.04 units at 630 nm was used for calculating the sensitivity and specificity. \[88\]

Therefore unlike the previous indirect ELISA, neither urine precipitation nor normalization of the BLCA-4 levels to urinary protein concentration is carried out when using the sandwich ELISA for BLCA-4 measurement.

b) Cell-based assays

1. DD23

DD23 is a murine monoclonal antibody that was evaluated in 1996 with quantitative fluorescence image analysis in exfoliated urothelial cells. \[93\]

When used as a quantitative marker to detect bladder cancer, sensitivity was 85% (41 cases) and specificity in asymptomatic age-matched controls was 95% (41 subjects). \[93\]

The DD23 assay test was subsequently developed using an avidin-biotin alkaline phosphatase immunocytochemical procedure. \[94,95\]

A single positive cell was considered a positive urine test. In 308 cases under surveillance for non-muscle invasive bladder cancer, sensitivity was 81% and specificity 60%. \[94\]

In another study from the same authors in 81 patients analysing 151 samples sensitivity was 70% and specificity 60%. \[95\]

The authors concluded...
that DD23 was able to enhance the sensitivity of cytology, in particular for low grade tumors.[94,95] The first results in patients under surveillance are characterized by a low specificity which implies that DD23 is not an ideal marker to lower the cystoscopy frequency in these patients.

The body of evidence for DD23 is limited. Only few reports on marker performance have been published. Reporting quality is moderate to poor, the level of evidence provided ranges from 4 to 2B, marker status according to the IBCN criteria is considered to be level I. In summary, current data do not permit definite conclusions on a clinical use of DD23.

2. uCyt+™ / Immunocyt™

The uCyt+™ assay, formerly Immunocyt™, is a commercially available immunocytological assay based upon microscopical detection of tumor-associated cellular antigens in urine-derived urothelial cells by immunofluorescence (Scimedx Inc., Denville, NJ, USA). For tumor cell detection an antibody cocktail containing fluorescein-labeled monoclonal antibodies M344 and LDQ10 directed against sulfated mucin glycoproteins and Texas-red linked antibody 19A211 against glycosylated forms of high molecular carcinoembryonic antigens (hmCEA) is used. After staining the samples are studied for immunofluorescence examining more than 500 nuclei. In most studies specimens with ≥1 green or red urothelial cell are considered immunocytologically positive.

The uCyt™ test is a cell based assay. Assay costs and requirements concerning lab equipment, time for specimen processing and reading as well as experience necessary for adequate interpretation of the staining must be considered high. These properties restrict the use of this test to more specialized laboratories. Reproducibility, i.e. inter-observer variability, is reasonable provided that reading is performed by trained staff with high experience.[96]

A literature search on the terms “immunocytology”, “immunocyt”, “uCyt”, and “bladder cancer” yielded 49 hits. After removal of reviews, meta-analyses and redundant trials, 20 studies assessable for criteria concerning assay performance and comprising more than 5,000 individuals were identified forming the basis for this assessment of assay performance. [17,97-129]

Accuracy of reporting according to the STARD criteria [37,38] was mostly moderate or poor, only few papers displaying good reporting quality. Specifically, information on the training and experience of investigators – a parameter highly affecting uCyt™ results – was not provided and information on the blinding of investigators towards clinical observations was rare. The majority of trials provided LoE Grade 3 and 4 evidence; however, information from 8 cohort studies was classified as LoE 2b.

One remarkable feature of the uCyt™ assay is a reproducibly high sensitivity specifically in low grade lesions. On average, detection rate for low grade tumors was 75%, sensitivity for G2 and high grade tumors was approximately 85% (Tab. 9). Overall specificity was 75%. Discriminating between diagnostic and follow-up trials, sensitivity appears to be lower specifically in low and intermediate grade lesions in diagnostic studies as compared to follow-up trials. However, this conclusion is based upon a small number of cases.

The uCyt™ assay has been reported to be confounded by a variety of different urological conditions (BPE, hematuria, urolithiasis or inflammatory conditions). However, studies in hematuria populations suggest that the impact of these conditions on test specificity is limited.[17,97]

In general, the uCyt™ assay appears more sensitive but less specific as compared with urine cytology. Side-by-side comparisons with other assays have been reported. However, interpretation is difficult since adequate experience of the investigators is a prerequisite to obtain meaningful results for the uCyt™ assay but is not disclosed in these publications.

There was one prospective trial on marker-guided follow-up providing information that may be classified as LoE grade 1b [130,131] according to the Oxford classification for diagnostic procedures. [36] The very same trial was classified as a phase III trial concerning the IBCN classification on marker development,[12] while all remaining studies were considered phase II.

Mian and coworkers [130] reported on a prospective marker-based follow-up trial in 942 patients: after an initial 3 month follow-up including cystoscopy, cytology and uCyt™ test patients were divided into 3 categories according to their risk profile. Low risk patients were followed using uCyt™ and cytology; cystoscopy was performed if one of the tests was positive or after 1 year. Intermediate risk tumors were followed by cytology, uCyt™ and Urovysion™. Negative patients or patients with a positive p16/CEP3 FISH test were further followed as low risk patients, while patients with positive cytology, uCyt™ and CEP7/17 positive Urovysion™ test underwent cystoscopy. High risk patients were followed by cystoscopy every 3 months. The authors reported that in low risk patients the number of cystoscopies could be safely reduced and significant costs were saved. [131] However, precise data required for understanding of the author’s conclusions are lacking. In addition, analysis of the benefit or “added value” in comparing fewer cystoscopies in low risk disease patients, reliability of cytology in high risk patients, and costs of uCyt and Urovysion are required in considering the results in the context of the type of cancer diathesis being monitored.
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<td>37</td>
<td>1/3</td>
<td>6/6</td>
<td>4/5</td>
<td>20/21</td>
<td>15/25</td>
<td></td>
</tr>
</tbody>
</table>

Table 9. Performance characteristics for uCyt+TM

Low grade tumors acc. to the 2004 classification were included in the G1 category acc. to the 1973/1998 classification, high grade tumors acc. to the 2004 classification and CIS were included in the G3 category;

inf. = informative; UUT = upper urinary tract tumors; # = no. of test (not of patients; therefore not considered for specificity calculation)

cohort study: consecutive patients, no healthy controls included; marker guided prospective trial: clinical decision making based upon marker result;

LoE: case control studies were considered LoE grade IV, studies including diagnostic and follow up patients were considered LoE grade IIb, studies including clearly defined patient cohorts, consecutive cases were considered LoE grade IIb, results from a marker guided prospective trial were considered LoE grade Ib;

* Marker status according to IBCN classification 2008; ** no. of requirements met acc. to STARD recommendations

Note: Li data for specificity but not considered for sensitivity analysis.
<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Cohort</th>
<th>Type</th>
<th>Case/Control</th>
<th>Total</th>
<th>6/7</th>
<th>17/23</th>
<th>10/12</th>
<th>60/82</th>
<th>870/904 inf. PPV</th>
<th>327/341 inf. PPV</th>
<th>1881/1991 inf. PPV</th>
<th>Data Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toma (2004)</td>
<td>Cohort</td>
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<td>126</td>
<td>6/7</td>
<td>85.7</td>
<td>17/23</td>
<td>73.9</td>
<td>10/12</td>
<td>83.3</td>
<td>60/82</td>
<td>72.5</td>
<td>3b</td>
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<tr>
<td>Tetu (2005)</td>
<td>Cohort</td>
<td>Follow-up</td>
<td>904</td>
<td>48/64</td>
<td>75 (LMP+LG)</td>
<td>34/40</td>
<td>85</td>
<td>453/734</td>
<td>62</td>
<td>870/904 inf. PPV</td>
<td>26 PPV</td>
<td>93 NPV</td>
</tr>
<tr>
<td>Messing (2005)</td>
<td>Cohort</td>
<td>Follow up</td>
<td>341</td>
<td>22/28</td>
<td>79</td>
<td>9/10</td>
<td>90</td>
<td>4/6</td>
<td>67</td>
<td>206/274</td>
<td>75</td>
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<td>mixed</td>
<td>35</td>
<td>35/35</td>
<td>100</td>
<td>12/17</td>
<td>70.6</td>
<td>3b</td>
<td>II</td>
<td>15/25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mian (2006)</td>
<td>Marker-guided</td>
<td>Follow up</td>
<td>942</td>
<td>96/121</td>
<td>79.3</td>
<td>74/88</td>
<td>84.1</td>
<td>82/89</td>
<td>92.1</td>
<td>1152/1588 #72.5</td>
<td>1881/1991 inf. PPV</td>
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<tr>
<td>Soyuer (2009)</td>
<td>Case/Control</td>
<td>mixed</td>
<td>90</td>
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<td>77.4</td>
<td>21/23</td>
<td>91.3</td>
<td>31/36</td>
<td>86.1</td>
<td>PPV 90</td>
<td>NPV 79.5</td>
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<td>Horstmann (2009)</td>
<td>Cohort</td>
<td>Follow up</td>
<td>221</td>
<td>20/32</td>
<td>62</td>
<td>44/53</td>
<td>82</td>
<td>20/28</td>
<td>72</td>
<td>78/108</td>
<td>72</td>
<td>PPV 72</td>
</tr>
<tr>
<td>Schmitz-Dräger (2008/2010)</td>
<td>Cohort (gross hematuria)</td>
<td>diagnostic</td>
<td>103</td>
<td>7/8</td>
<td>87</td>
<td>11/13</td>
<td>85</td>
<td>64/78</td>
<td>82</td>
<td>100/103 inf. PPV</td>
<td>57.6</td>
<td>NPV 94.4</td>
</tr>
<tr>
<td>Li (2010)</td>
<td>Case/Control</td>
<td>mixed</td>
<td>191</td>
<td>76/93</td>
<td>81.6</td>
<td>85/98</td>
<td>86.7</td>
<td>4</td>
<td>II</td>
<td>15/25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>4899</td>
<td>334/446</td>
<td>74.9</td>
<td>290/344</td>
<td>84.3</td>
<td>387/462</td>
<td>83.8</td>
<td>2.068/2.745</td>
<td>75.3</td>
<td>4.992/5.242</td>
</tr>
</tbody>
</table>
3. **UroVysion**

The UroVysion multicolor fluorescence in situ hybridization (FISH) test (Vysis, Abbott Laboratories, Des Plaines, IL, USA) is a cell based assay containing probes to the centromeres of chromosomes 3, 7, and 17 and to the 9p21 locus. The assay was approved by the U.S. Food and Drug Administration (FDA) for surveillance of patients with previous bladder cancer but also for diagnosis in hematuria. A minimum of 25 morphologically abnormal cells is viewed. Detection of 4 or more cells that have gains in 2 or more of chromosomes 3, 7, and 17 in the same cell or at least 12 cells without a signal for P16 tumor suppressor gene locus 9p21 are mostly classified as a pathologic result. However, a variety of different definitions and cut-off levels are being used.[33]

Assay costs and requirements concerning lab equipment, time for specimen processing and reading as well as experience necessary for adequate interpretation of the staining must be considered high. These properties restrict the use of this test to more specialized laboratories but may also explain the great ranges in sensitivity and specificity reported for this assay. Reproducibility has been reported to be good provided that the reading is performed by experienced laboratory staff. The UroVysion assay has been reported to be confounded by a variety of different urological conditions (other tumors, urolithiasis or inflammatory conditions). Another limitation is that the rate of non-informative cases of appr. 10% must be anticipated (Tab. 10).

A literature search on the terms “FISH”, “UroVysion”, and “bladder cancer” yielded 331 hits. After removal of reviews, metaanalyses and redundant trials, 21 studies assessable for criteria concerning assay performance and comprising 2852 individuals were identified forming the basis for this assessment of assay performance.[28,46-48,99,101-106,110,132-141]

Accuracy of reporting according to the STARD criteria [37,38] was mostly moderate or poor, few – mostly more recent - papers displaying good reporting quality. Specifically, information on the training and experience of investigators – a parameter highly affecting UroVysion results – is not provided and information on the blinding of investigators towards clinical observations is rare. Ten trials provided LoE Grade 3 and 4 evidence; however, information from 11 cohort studies was classified as LoE 2b.

The broad range for sensitivity and specificity of UroVysion FISH reported in different papers is notable and may not only reflect patient selection, study design or tumor prevalence but also technical aspects such as cut-off definitions and experience of laboratory staff. However, in systematic reviews and meta-analyses sensitivity has been found to exceed 70% and even approach 80% when omitting small

and low grade lesions. [33] This is paralleled by a high specificity of appr. 80%, however, again with a broad range from 43 – 100% (Tab. 10).

In general, the UroVysion assay appears more sensitive (even in high grade disease) but less specific as compared with urine cytology. A recent meta-analysis of FISH showed that overall performance of FISH was better than that of cytology (area under the curve: 87% vs 63%).[33] This difference, however, was almost entirely attributable to the difference in overall performance in diagnosing pTa patients; the higher performance disappeared when pTa patients were excluded from the analysis (area under the curve: 94% vs 91%). Side-by-side comparisons with other assays have been reported; however, interpretation is difficult since adequate experience of the investigators is prerequisite to obtain meaningful results for the UroVysion assay but not disclosed in these publications.

Mian and coworkers [130] reported on a prospective marker-based follow-up trial in 942 patients: after an initial 3 month follow-up including cystoscopy, cytology and uCyt™ test patients were divided into 3 categories according to their risk profile. Intermediate risk tumors were followed by cytology, uCyt™ and UroVysion™. Negative patients or patients with a positive p16/CEP3 FISH test were further followed as low risk patients, while patients with positive cytology, uCyt™ and CEP7/17 positive UroVysion™ test underwent cystoscopy. Information on the results of the UroVysion data, however, has not been published yet.

Although there is a relatively high rate of false-positive results translating into a relatively low PPV of the test, findings from several studies suggest that the low specificity in follow-up trials may be explained in part as an anticipatory positive result, in which a premalignant change precedes the discovery of a recurrent malignancy.[28,132,142] One study [132] found that 89% of the patients that had a false-positive test had a positive bladder biopsy within 12 months of the test, while another found that FISH preceded tumor recurrence in 85% of patients. [142] Nonetheless, the real role of an anticipatory positive result is still unclear as many patients with non-muscle-invasive bladder cancer eventually experience disease recurrence.

In considering the observations and conclusions reported in these studies, it also becomes important to consider the cost of these tests, especially if sufficient information is otherwise available through less costly standard examinations (cystoscopy, cytology) or other approved biomarkers. Because of the importance of determining any “added value” in the use of a particular test, costs, difficulty in performance, confusion of interpretation in a particular clinical setting, and the “emotional stress” encountered by both patient and physician in
Table 10. Performance characteristics for UroVysionTM

low grade tumors acc. to the 2004 classification were included in the G1 category acc. to the 1973/1998 classification, high grade tumors acc. to the 2004 classification and CIS were included in the G3 category;
inf. = informative; UUT = upper urinary tract tumors; # = no. of test (not of patients; therefore not considered for specificity calculation)
cohort study: consecutive patients, no healthy controls included;
LoE: case control studies were considered LoE grade IV, studies including diagnostic and follow up patients were considered LoE grade IIIb, studies including clearly defined patient cohorts, consecutive cases were considered LoE grade IIb, results from marker guided prospective trials were considered LoE grade Ib;

* Marker status according to IBCN classification 2008; ** no. of requirements met acc. to STARD recommendations

<table>
<thead>
<tr>
<th>Author (year) Reference</th>
<th>Study design</th>
<th>Study type</th>
<th>Diagnosis/ Follow-up</th>
<th>No. of patients</th>
<th>Grade I/ LG</th>
<th>Grade II</th>
<th>Grade III/ HG/CIS</th>
<th>Remarks</th>
<th>% Sensitivity</th>
<th>% Specificity</th>
<th>LoE</th>
<th>IBCN*/STARD** Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bubendorf (2001)</td>
<td>Case control</td>
<td>mixed</td>
<td>91</td>
<td>15/21 (71)</td>
<td>25/29 (86)</td>
<td>16/17 (94)</td>
<td>26/27 (96.3)</td>
<td>Concordance voided/ barbotage 85%</td>
<td>4</td>
<td>II 15/25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placer (2002)</td>
<td>Case control</td>
<td>mixed</td>
<td>86</td>
<td>8/15 (53.3)</td>
<td>10/12 (83.3)</td>
<td>19/19 (100)</td>
<td>29/34 (85.3)</td>
<td></td>
<td>4</td>
<td>II 18/25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sarosdy (2002)</td>
<td>Cohort</td>
<td>mixed</td>
<td>Follow-up</td>
<td>438</td>
<td>12/22 (55)</td>
<td>7/9 (78)</td>
<td>17/18 (94)</td>
<td>75/114 (65.8) 260/275 (94.5) controls</td>
<td>2b</td>
<td>II 19/25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mian (2003)</td>
<td>Cohort</td>
<td>Mixed</td>
<td>57</td>
<td>7/8 (87)</td>
<td>19/19 (100)</td>
<td>1/1 (100)</td>
<td>11/24 (46.4)</td>
<td>5/57 n. inf.</td>
<td>3b</td>
<td>II 16/25</td>
<td></td>
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</tr>
<tr>
<td>Skacel (2003)</td>
<td>Cohort</td>
<td>diagnostic</td>
<td>Follow-up</td>
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<td>19/23 (83)</td>
<td>28/35 (80)</td>
<td>23/24 (96)</td>
<td>28/29 (97)</td>
<td>2b</td>
<td>II 19/25</td>
<td></td>
<td></td>
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<tr>
<td>Veeramachaneni (2003)</td>
<td>n.r.</td>
<td>mixed</td>
<td>121</td>
<td>1/3 (33)</td>
<td>12/14 (84)</td>
<td>0/1 (0)</td>
<td>n.r.</td>
<td>36/121</td>
<td>4</td>
<td>II 15/25</td>
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</tr>
<tr>
<td>Krause (2004)</td>
<td>Case control</td>
<td>mixed</td>
<td>84</td>
<td>10/14 (71)</td>
<td>10/11 (91)</td>
<td>44/44 (100)</td>
<td>25/35 (71)</td>
<td>4/106</td>
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<td>II 17/25</td>
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<td>Varella-Garcia (2004)</td>
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<td>Follow-up</td>
<td>19</td>
<td>2/2 (100)</td>
<td>3/3 (100)</td>
<td>1/2 (50)</td>
<td>12/12 (100)</td>
<td>12/14 (85.7)</td>
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<td>II 17/25</td>
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<tr>
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<td>Follow-up</td>
<td>49</td>
<td>1 2 / 3 5 (34.3)</td>
<td>12/14 (85.7)</td>
<td></td>
<td>1 2 / 3 5 (34.3)</td>
<td>12/14 (85.7)</td>
<td>2b</td>
<td>II 17/25</td>
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<tr>
<td>Kipp (2005) 139</td>
<td>Cohort Prospective</td>
<td>Follow-up</td>
<td>37</td>
<td>12/25 (48)</td>
<td>12/12 (100)</td>
<td>After intravesical prophylaxis</td>
<td>2b</td>
<td>II 17/25</td>
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<tr>
<td>Laudadio (2005) 140</td>
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<td>300</td>
<td>14/25 (56)</td>
<td>18/19 (95)</td>
<td>167/256 (65)</td>
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<td>3b</td>
<td>II 16/25</td>
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<tr>
<td>Junker (2006) 141</td>
<td>Cohort diagnostic</td>
<td>121</td>
<td>n.r. (37)</td>
<td>n.r. (65.4)</td>
<td>n.r. (91.7)</td>
<td>23/28 (82.6)</td>
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<td>2b</td>
<td>II 16/25</td>
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<tr>
<td>Bergmann (2007) 142</td>
<td>Cohort mixed Follow-up</td>
<td>41</td>
<td>30/39# (77)</td>
<td>80/86# (93)</td>
<td>16/162 n. inf.</td>
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<td>II 17/25</td>
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<td>Moonen (2007) 143</td>
<td>Cohort Follow-up</td>
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<td>6/27 (21.4)</td>
<td>7/19 (36.8)</td>
<td>12/18 (66.7)</td>
<td>37/41 (89.7)</td>
<td>10/113 n. inf.</td>
<td>2b</td>
<td>II 18/25</td>
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<tr>
<td>Yoder (2007) 27</td>
<td>Cohort Follow-up</td>
<td>249</td>
<td>6 / 1 9 (31.6)</td>
<td>15/20 (75)</td>
<td>3 8 / 4 2 (90.5)</td>
<td>1 4 7 / 1 6 8 (87.5)</td>
<td>35/56 pat. UC neg., FISH pos. develop tumor</td>
<td>2b</td>
<td>II 20/25</td>
<td></td>
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<tr>
<td>Riesz (2007) 144</td>
<td>Case control diagnostic</td>
<td>50</td>
<td>4/9 (44.4)</td>
<td>16/16 (100)</td>
<td>1 4 / 1 4 (100)</td>
<td>11/11 (100)</td>
<td>5/55 n. inf.</td>
<td>4</td>
<td>I 14/25</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Frigerio (2007) 145</td>
<td>Case control mixed</td>
<td>56</td>
<td>10/18 (55)</td>
<td>21/24 (87.5)</td>
<td>n.r.</td>
<td>4</td>
<td>I (14/25)</td>
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<tr>
<td>Ferra (2009) 133</td>
<td>Cohort Reflex Susp./pos. Cytol. Follow-up</td>
<td>140</td>
<td>9/19 (47.4)</td>
<td>45/60 (75)</td>
<td>27/68 (39.7)</td>
<td>10/161 n. inf.</td>
<td>3b</td>
<td>II 17/25</td>
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<tr>
<td>Caraway (2010) 146</td>
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<td>600</td>
<td>170/263 (64.6)</td>
<td>540/632# (85.4)</td>
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<td>3b</td>
<td>II 16/25</td>
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</tr>
<tr>
<td>Youssef (2010) 147</td>
<td>Cohort Follow-up</td>
<td>142</td>
<td>1/7 (14.3)</td>
<td>3/10 (30)</td>
<td>100/106 (94.3)</td>
<td>19/142 n. inf.</td>
<td>2b</td>
<td>II 18/25</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Mian (2010) 148</td>
<td>Cohort Diagnostic (UUT)</td>
<td>55</td>
<td>24/24 (100)</td>
<td>34/38 (89.5)</td>
<td>1/68 n. inf.</td>
<td>2b</td>
<td>II 17/25</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>2852</td>
<td>124/232 (53.4)</td>
<td>152/187 (81.3)</td>
<td>2 9 6 / 3 7 3 (79.3)</td>
<td>1 0 3 6 / 1 2 9 3 (80.1)</td>
<td>206/2263 (9.1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
assessing the reliability of a test result should all be considered in the application of any marker for “routine” clinical use.

2. SCREENING

Screening for bladder cancer, i.e. investigation of an asymptomatic population, represents a specific diagnostic challenge. While screening for breast cancer and colorectal cancer has gained social acceptance, bladder cancer screening has not been considered a reasonable approach mainly due to the low prevalence of the disease in an unselected population. Nevertheless, few studies have been published reporting on screening for bladder cancer in populations with an increased risk of developing bladder cancer.

a) Hematuria:

Messing et al. invited 1575 men aged 50 years and older to test their urine repetitively with a chemical reagent strip for hemoglobin.[21,143-145] Participants with positive test results underwent standard urologic evaluation. Bladder cancer stages and grades as well as the outcomes of men with screen-detected tumors were compared with the grades, stages, and outcomes of an age-matched cohort of men with newly diagnosed BC who were reported to the Wisconsin Tumor Registry in 1988 (n=509). Two hundred fifty-eight screening participants (16.4%) were evaluated for hematuria, and 21 participants (8.1%) were diagnosed with bladder cancer. Proportions of low-grade (Grade 1 and 2) superficial (Stage Ta and T1) versus high-grade (Grade 3) superficial or invasive (Stage ≤ T2) cancers in screened men (52.4% vs. 47.7%) and in men from the tumor registry (60.3% vs. 39.7%) were similar (p=0.50). The proportion of high-grade superficial or invasive bladder tumors were lower in screened men (10%) than in unscreened men (60%; p=0.002). At 14 years of follow-up, cancer specific survival in screen-detected patients was 100%, whereas 20.4% of unscreened men had died of bladder cancer (p=0.02).

Hedelin et al. investigated 2000 randomly selected men, age 60-70 years, invited to participate in a screening program based upon dipstick for hematuria and the UBC assay.[146] Men with 5-10 red blood cells (RBC)/μl and an International Prostate Symptom Score (IPSS) of >10 and all men with ≥25 RBC/μl and/or elevated UBC levels underwent both white-light and fluorescence cystoscopy. In 14% of the responding 1096 men microhematuria with 5-10 RBC/μl was observed. One tumor was detected in the 62 men with 5-10 RBC/μl and an IPSS of >10. Among the 10% of men (n=112) with ≥25 RBC/μl, four bladder tumors were detected. Another two tumors were detected in men without hematuria but with a positive UBC test. The authors concluded that hematuria-based screening among older men smokers with ≥25 RBC/μl on dipstick testing might be a scenario to be considered.

A key problem of this concept is the high prevalence of hematuria in the general population, along with its low specificity, raising unnecessary anxiety in screened subjects and requiring urologic work-up in a high number of individuals without bladder cancer. Hedelin and coworkers tried to correct for this parameter by increasing the cut-off level for hematuria but the efficacy of this measure need to be confirmed. On the other hand, detection of additional diseases requiring intervention is frequent in hematuria patients and needs also to be taken into account when considering this approach.[19,147]

b) Smoking:

Steiner et al. invited 183 subjects identified as smoking 40+ pack-years to join a bladder cancer screening program including urinary dipstick test, urine cytology, NMP 22 BladderChek and UroVysion. [14] 75 subjects with at least one positive test result were offered urologic work-up. 5 urothelial cancers (3 bladder tumors 1x pTa LG, 2x carcinoma in situ and two upper urinary tract tumors (pTaG1 and pT2N2G3)) were detected. While this study found a higher incidence of cancer, another study of 1502 subjects with greater than 10 years of smoking screened for bladder cancer using BladderChek found only 2 cancers and one patient with atypia.[15]

c) Professional exposure:

In a prospective study, Hemstreet et al. assessed the risk for the development of bladder cancer in a group of 1788 Chinese workers who were exposed to benzidine using a biomarker profile over a period of 6 years.[100] This biomarker profile included the analysis of DNA ploidy, G-actin, and tumor-associated antigen P-300. Although the biomarker profile placed only 21% of the exposed workers in a high or moderate risk group, 87% of the 28 bladder cancer cases found in the entire cohort were found in this group, and all of the tumors were clinically organ-confined. Interestingly, a positive biomarker profile occurred 15 to 33 months before the clinical detection of bladder cancer.

Giberti et al. investigated 171 workers at an Italian Coke plant with long-term exposure to PAHs using dipstick testing for hematuria, cytology and the uCyt+ assay.[148] Although uCyt+ was positive in 12% of the screened subjects subsequent urological work-up yielded no urothelial cancers in this cohort. While the relatively young age of the screened subjects (mean 53 years) may have affected disease prevalence, a low cut-off value for the uCyt+ assay could be responsible for the low specificity observed.

Several other studies investigating professionally exposed risk populations (Fire fighters, chemical
workers, workers in alloy smelters [147,149,150] using NMP22, uCyte+ or a mix of different molecular markers, demonstrated good sensitivity and specificity for the markers. However, due to the low prevalence of disease (≤ 1%) in the cohorts studied, the positive predictive value of the assays remains unsatisfactory.

Davies et al. targeted another risk group screening 457 patients with spinal cord injury for 5 years using urine cytology, the BTA stat test and the survivin assay.[83] A total of 1075 urine specimens from 457 patients were analyzed. Of the 1073 BTA stat tests, 119 showed positive reactions (specificity 88.9%) and 954 were negative. In the survivin assays, 47 samples had a score of one, 38 a score of two, and 9 a score of three (specificity 91.2%). No cytology specimens were noted to have malignant cells (specificity 100%). None of the three patients diagnosed with bladder cancer had a positive test result.

In summary, despite a limited number of studies there is evidence that screening for bladder cancer in general is feasible and screened subjects may benefit from early cancer detection. However, cost calculations based upon the results from published trials suggest costs between $ 25,000 – 50,000/cancer detected.[6] This finding clearly points at a careful selection of high risk populations and demonstrates the necessity of an effective design of future protocols.

3. PROBLEMS OF MARKER COMPARISON

There is a variety of reasons for why a comparison of markers, aiming at the identification of "the best" marker, is of limited value:

• Different performance profile
• Threshold definitions
• Technical aspects
• Cost-benefit considerations

This assessment has demonstrated that markers have different performance profiles. While some of these markers may have a similar sensitivity through all tumor grades, others may have a higher sensitivity in high grade tumors. Similarly, specificity particularly in urine-based markers and, to a lesser extent of cell-based assays, is highly dependent upon the composition of the tumor-negative cohort. While these markers in general may have good specificity in a healthy control population, they uniformly have a lower specificity in cohorts comprising patients suffering from non cancer-related urological diseases (e.g. inflammatory conditions, stone disease, hematuria, or BPE). As a consequence, a different composition of a study population will directly affect the results of a given study.

Several investigators have demonstrated a correlation between sensitivity and specificity for a variety of biomarkers. As for PSA in prostate cancer for example, an increased cut-off level will both, increase specificity and decrease sensitivity (and vice versa for a decreased cut-off). Since different threshold definitions are in use for several assays (e.g. UBC, NMP22, UroVysion), the choice of a cut-off level will automatically have significant impact on the performance of a given assay (see above).

While investigator bias may not play a role in point-of-care assays, this is of particular relevance for cell-based tests (e.g. UroVysion or uCyte+). The precision of these tests is clearly correlated with training status and experience of the laboratory staff.[96] Since the experience of investigators is not reported in the literature despite specific recommendations to do this (STARD), it is impossible to estimate the impact of investigator bias in the comparison of different assays.

Furthermore, it is the scientific norm to report innovations, “promising” results, and initially “positive” observations, all of which contribute to an enthusiasm for an early clinical application. However, such initial reports may be limited in their study design, length of follow-up, and numbers needed to provide statistical power in order to validate results. These together with misapplication of observations to different clinical scenarios may account for the commonly observed failure to validate initially promising albeit preliminary reports.

With decreasing financial resources of health care systems worldwide cost-benefit considerations have gained considerable importance. This aspect, however, has rarely been addressed and included in a side-by-side comparison of different assays.

Although these problems and limitations discussed above currently prevent a sufficient comparison between different markers and urine cytology, it is evident that there is an urgent need to identify the optimal diagnostic armamentarium for the different clinical scenarios. Therefore, well designed prospective studies are needed to confirm the significance of urine cytology and identify an potential added value of the markers.

4. RECOMMENDATIONS

As with other previous reviews and meta-analyses, this assessment confirms the overall superiority of molecular markers over conventional urine cytology concerning test sensitivity. This improved sensitivity is more pronounced in low grade tumors but is also seen in high grade bladder cancer. In contrast, urine cytology is clearly superior to that of the molecular markers with regard to specificity, and its role in bladder cancer diagnosis needs to be considered in this context.
5. MARKER PERFORMANCE

There is no marker that meets all of the postulates of a so-called “ideal” marker,[9] but markers have been described with a high overall sensitivity, a high specificity for low or high grade disease, high specificity, reasonable expense and point-of-care capabilities. However, it is obvious that urologists will have to select markers that meet specific clinical needs. In a screening scenario high specificity of a marker is mandatory since otherwise the number of patients undergoing a marker-initiated evaluation will be inappropriately high. This contrasts to the requirements in a follow-up setting, when sensitivity of an assay is of key importance in order not to miss bladder cancer persistence or recurrence. In addition, the diagnostic strategy might also affect selection of a marker: several investigators may favor markers with good performance in low grade disease since approx. 70% of all bladder tumors are low grade. Other urologists may prefer markers with a high sensitivity in high grade disease, arguing that it may be appropriate to delay detection of a low grade tumor that does not pose life-threatening risk but that high grade tumors should be reliably detected.

Importantly, there are additional obstacles that make it difficult to identify the most accurate test system in any clinical situation. This finding impedes a simple comparison of tests based upon performance data reported in case-control studies. Several parameters have been shown to affect the performance of a given test.

- Patient selection
- Prevalence of the disease
- Study design
- Study endpoints
- Sample size
- Technique/standardization/Cut-off
- Experience

Furthermore, reimbursement policy in different countries will have additional influence on the use of molecular markers.

In order to obtain a better idea on the performance of a given assay, marker assessment needs to follow a standardized and transparent evaluation process. It remains one of the great challenges in marker development to define a standard procedure and, finally, introduce this standard into the scientific community.

6. PROBLEMS IN THE ASSESSMENT OF MARKER TRIALS

The question of marker performance has been addressed within a number of meta-analyses.[6,33,53,151]. However, the problems of these analyses are significant for several reasons and, in consequence, conclusions derived from these analyses are highly biased. One of the key problems is the highly differing quality of the trials, which hardly permits common analysis. Furthermore, different study design, patient selection, tumor prevalence, distribution of tumor grade and stage, study endpoints and several other parameters will further confound the results of any combined analysis.

In order to standardize the evaluation of molecular markers several tools for assessment of diagnostic markers were used in this analysis. These tools included for the analysis a questionnaire for the quality of reporting (STARD), the definition of the level of evidence according to the Oxford criteria, and the classification of the marker status.[12,36-38]

Concerning the reporting quality, no single study included all 25 STARD items.[37,38] Certain items, such as use of Mesh headings to identify sensitivity, specificity or diagnostic accuracy, or reporting of adverse events associated with testing were uniformly missing, although these items may have less importance to data quality than others. While the majority of studies included some population demographics, race, for example, was recorded in only one of the sampled sources. All authors provided information on test performance techniques, and most described collection and handling of specimens; however, information on the reproducibility of test results, the training and qualifications of those performing the assays, whether testers were blinded from other results, and handling of indeterminate, out-lying, or missing results were often lacking or ambiguous.[70] Many studies stratified subjects according to grade [WHO 1998 and 2004] and stage of tumors [TMN 1997] and provided subset analyses of sensitivity and specificity of the tests for these subsets. Due to mostly low numbers of subjects in some groups, the validity of drawing conclusions from this data is uncertain. Authors are generally to be commended for a reasonable
description of statistical methods used, including confidence intervals on reported data. Clearly, implementation of standardized reporting of studies that adhere to consistent guidelines such as STARD recommendations would improve our understanding of tumor markers.

It can be argued, that STARD guidelines are yet imperfect. According to experiences made throughout this assessment, some items are differently interpreted by observers and opinions on the necessity of including all items, and the relative importance of certain items, was not universally agreed upon. However, currently STARD provides us with a starting point for collecting comparable data among studies.

Recently, a new definition for diagnostic trials was developed for the Oxford Classification on the Levels of Evidence.[36] This classification has been used in this assessment but appears more difficult to apply if compared to the recommendations for therapeutic trials. This was partly due to deficits in reporting. But for some studies, application of certain criteria was not possible. Nevertheless, the new Oxford classification on diagnostic trials is promising but may need minor modification.

For definition of the stage of implementing new markers into clinical decision making the IBCN classification has been developed and was used in this assessment.[12] However, using this classification it became evident that more precise definitions on the requirements for allocating a given study to a certain stage are mandatory and that this classification requires revision.

7. KEY QUESTIONS:

a) (How) can molecular markers support screening of patients at risk of having or developing bladder cancer?

Considering bladder cancer screening the key question to be answered is if early detection of bladder cancer may have any impact on cure rates and, subsequently, on patient survival. Through the last decades a growing body of evidence has been accumulated suggesting that early detection and treatment of bladder cancer may indeed reduce cancer specific mortality [127-129] thus providing arguments for this procedure.

However, due to the low prevalence of bladder cancer in the general population (0.001%) and in people above the age of 50 (0.67% - 1.13%), mass screening for bladder cancer, with the possibility of detecting a significant number of false positives requiring an unnecessary work-up, would certainly not be cost-effective. [6] As a consequence of these considerations those few trials addressing screening for bladder cancer targeted high risk populations.

Data obtained in high-risk groups undergoing urinary dipstick screening for bladder cancer suggest that the bladder tumors discovered when evaluating all patients with asymptomatic microscopic hematuria may be more amenable to curative treatment than those normally encountered, thereby reducing morbidity and mortality associated with bladder cancer in these patients. [20,21,143-145] Since improved survival of screened patients was not demonstrated in a randomized fashion but only in comparison with a cancer register, this study presents interesting information; however, it cannot serve to provide a final decision on the benefit of hematuria screening.

Meanwhile, further studies targeting risk populations such as smokers and professionally exposed individuals could demonstrate that screening for bladder cancer using molecular markers is feasible. However, despite selecting risk populations in most of these trials tumor prevalence was still too low to make bladder cancer screening a cost-effective procedure.

Since identification of high risk populations suited for a screening scenario remains the key problem for bladder cancer screening the development and validation of respective risk calculators (risk-adapted screening) might be an option for the future.

| Question: (How) can molecular markers support screening of patients at risk of having or developing bladder cancer? |
| Statement: Feasibility of bladder cancer screening has been demonstrated in several prospective trials. The results from one study using dip-stick testing for hematuria suggests a survival benefit of individuals undergoing hematuria screening. Because of weak controls in this report validation of the results and improved definition of risk populations suited for screening is required. |
| References: [14,21,143,144] |
| Recommendation: Bladder cancer screening using urine for testing is promising but cannot be recommended at present. |
| LoE: 1b  Grade: B  Agreement: 92% |

b) (How) can molecular markers be used in reflex testing for bladder cancer?

Reflex testing e.g. in the follow-up of patients with bladder cancer with atypical cytology finding is a logical approach. However, experience with this procedure at present is very limited and does not permit a definite statement. In consequence, this strategy should be exploited in more detail within prospective controlled studies.
c) (How) can molecular markers support follow-up of patients with superficial low risk bladder cancer?

There is clear evidence that modern molecular markers outperform urine cytology concerning sensitivity in the diagnosis of patients with non-invasive low grade tumors. In addition, due to the low risk of tumor progression a marker-guided surveillance could significantly reduce the number of control cystoscopies without placing patients at significant risk. However, until today only one prospective trial using a marker-guided surveillance protocol has been performed. Information from this study, however, is still preliminary and does not yet permit recommendation of this procedure for clinical routine use.

| Question: (How) can molecular markers support follow-up of patients with superficial low risk bladder cancer? |
| Statement: Marker-guided follow-up of patients with non-muscle-invasive low risk tumors appears feasible. However, studies proving the efficacy of this concept and demonstrating an added value for patients or the health system are lacking. |
| Recommendation: Marker-guided follow-up of patients with superficial low grade bladder cancer appears attractive; however, based upon current levels of evidence this procedure cannot be recommended at present. |

LoE: 1b Grade: B Agreement: 92%

8. OUTLOOK

Although molecular bladder cancer assays have been shown to have superior sensitivity as compared to urine cytology, none of them has been included in clinical guidelines. The key reason for this situation is that none of the assays have been incorporated into clinical decision making so far. In consequence, an added value of molecular markers for the diagnosis of urothelial tumors has not yet been identified.

However, the current data suggest that some of these markers do have the potential to play a role in screening and surveillance of bladder cancer in the future. Current screening protocols however are hampered by a low disease prevalence thus inhibiting an acceptable cost/benefit ratio. The introduction of risk calculators into screening protocols could make up for the deficits of a mass screening approach.

Furthermore, the introduction of molecular markers in the follow-up of patients with low risk bladder cancer might also represent a scenario that should
be further investigated. Preliminary reports suggest that this procedure is feasible. However, detailed information for a definite judgment is lacking.

The scientific community is urged to develop protocols and conduct prospective trials to provide the basis for an integration of molecular markers into clinical decision making in the future.[7,84,153]

IV. APPENDIX

Questions

**Question:** (How) can molecular markers support screening of patients at risk of having or developing bladder cancer?

**Statement:**
Feasibility of bladder cancer screening has been demonstrated in several prospective trials. The results from one study using dip-stick testing for hematuria suggest a survival benefit of individuals undergoing hematuria screening. Because of weak controls in this report validation of the results and improved definition of risk populations suited for screening is required.

**Recommendation:**
Bladder cancer screening using urine for testing is promising but cannot be recommended at present.

LoE: 1b  Grade: B  Agreement: 92%

**References:** [14,15,21,143,144]

**Question:** (How) can molecular markers be used in reflex testing for bladder cancer?

**Statement:**
At present experience with reflex testing is very limited (mostly restricted to FISH technique) and therefore does not permit a definite statement. Reflex testing should be explored in more detail within prospective controlled studies.

**Recommendation:**
Reflex testing is considered experimental at present and should not be used within a clinical setting.

LoE: 2b  Grade: B  Agreement: 92%

**References:** [28,132,142,152]

**Question:** (How) can molecular markers support follow-up of patients with superficial low risk bladder cancer?

**Statement:**
Marker-guided follow-up of patients with non-muscle-invasive low risk tumors appears feasible. However, studies proving the efficacy of this concept and demonstrating an added value for patients or the health system are lacking.

**Recommendation:**
Marker-guided follow-up of patients with superficial low grade bladder cancer appears attractive; however, based upon current levels of evidence this procedure cannot be recommended at present.

LoE: 1b  Grade: B  Agreement: 92%

**References:** [14,15,21,143,144]

**Question:** (How) can molecular markers support follow-up of patients with superficial high risk bladder cancer?

**Statement:**
Molecular markers detect high grade bladder cancer with high sensitivity. At this stage it remains unclear how molecular markers can support surveillance of patients with high grade bladder cancer.

**Recommendation:**
A use of molecular markers in surveillance of patients with high grade bladder cancer cannot be recommended.

LoE: 2b  Grade: B  Agreement: 92%
<table>
<thead>
<tr>
<th>Level</th>
<th>Prognosis</th>
<th>Diagnosis</th>
<th>Economic and decision analyses</th>
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<tbody>
<tr>
<td>1a</td>
<td>Systematic review (SR) (with homogeneity*) of inception cohort studies; CDR validated in different populations</td>
<td>SR (with homogeneity*) of Level 1 diagnostic studies; CDR with 1b studies from different clinical centres</td>
<td>SR (with homogeneity*) of Level 1 economic studies</td>
</tr>
<tr>
<td>1b</td>
<td>Individual inception cohort study with &gt; 80% follow-up; CDR validated in a single population</td>
<td>Validating** cohort study with good « « reference standards; or CDR» tested within one clinical centre</td>
<td>Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multi-way sensitivity analyses</td>
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<tr>
<td>1c</td>
<td>All or none case-series</td>
<td>Absolute SpPins and SnNouts» «</td>
<td>Absolute better-value or worse-value analyses « « «</td>
</tr>
<tr>
<td>2a</td>
<td>SR (with homogeneity*) of either retrospective cohort studies or untreated control groups in RCTs</td>
<td>SR (with homogeneity*) of Level 2 diagnostic studies</td>
<td>SR (with homogeneity*) of Level 2 economic studies</td>
</tr>
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<td>2b</td>
<td>Retrospective cohort study or follow-up of untreated control patients in an RCT; Derivation of CDR» or validated on split-sample$$ only</td>
<td>Exploratory** cohort study with good» « « reference standards; CDR» after derivation, or validated only on split-sample$$ or databases</td>
<td>Analysis based on clinically sensible costs or alternatives; limited review(s) of the evidence, or single studies; and including multi-way sensitivity analyses</td>
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<td>2c</td>
<td>«Outcomes» Research</td>
<td>-</td>
<td>Audit or outcomes research</td>
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<td>3a</td>
<td>-</td>
<td>SR (with homogeneity*) of 3b and better studies</td>
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<tr>
<td>3b</td>
<td>-</td>
<td>Non-consecutive study; or without consistently applied reference standards</td>
<td>Analysis based on limited alternatives or costs, poor quality estimates of data, but including sensitivity analyses incorporating clinically sensible variations.</td>
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<td>4</td>
<td>Case-series (and poor quality prognostic cohort studies***)</td>
<td>Case-control study, poor or non-independent reference standard</td>
<td>Expert opinion without explicit critical appraisal, or based on economic theory or « first principles»</td>
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<td>Expert opinion without explicit critical appraisal, or based on physiology, bench research or « first principles»</td>
<td>Expert opinion without explicit critical appraisal, or based on physiology, bench research or « first principles»</td>
<td>Expert opinion without explicit critical appraisal, or based on economic theory or « first principles»</td>
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</tbody>
</table>

NOTES

Users can add a minus-sign "-" to denote the level of that fails to provide a conclusive answer because:

* EITHER a single result with a wide Confidence Interval
* OR a Systematic Review with troublesome heterogeneity.

Such evidence is inconclusive, and therefore can only generate Grade D recommendations.

* By homogeneity we mean a systematic review that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies. Not all systematic reviews with statistically significant heterogeneity need be worrisome, and not all worrisome heterogeneity need be statistically significant. As noted above, studies displaying worrisome heterogeneity should be tagged with a "-" at the end of their designated level.

" Clinical Decision Rule. (These are algorithms or scoring systems that lead to a prognostic estimation or a diagnostic category.)

" See note above for advice on how to understand, rate and use trials or other studies with wide confidence intervals.

§ Met when all patients died before the Rx became available, but some now survive on it; or when some patients died before the Rx became available, but none now die on it.
§§ By poor quality cohort study we mean one that
failed to clearly define comparison groups and/
or failed to measure exposures and outcomes in
the same (preferably blinded), objective way in
both exposed and non-exposed individuals and/
or failed to identify or appropriately control known
confounders and/or failed to carry out a sufficiently
long and complete follow-up of patients. By poor
quality case-control study we mean one that
failed to clearly define comparison groups and/
or failed to measure exposures and outcomes in
the same (preferably blinded), objective way in
both cases and controls and/or failed to identify
or appropriately control known confounders.

§§§ Split-sample validation is achieved by collecting
all the information in a single tranche, then
artificially dividing this into “derivation” and
“validation” samples.

“ An “Absolute SpPin” is a diagnostic finding
whose Specificity is so high that a Positive result
rules-in the diagnosis. An “Absolute SnNout” is
a diagnostic finding whose Sensitivity is so high
that a Negative result rules-out the diagnosis.

“ Good, better, bad and worse refer to the
comparisons between treatments in terms of
their clinical risks and benefits.

“ Good reference standards are independent of
the test, and applied blindly or objectively to
applied to all patients. Poor reference standards
are haphazardly applied, but still independent
of the test. Use of a non-independent reference
standard (where the ‘test’ is included in the
‘reference’, or where the ‘testing’ affects the
‘reference’) implies a level 4 study.

“ Better-value treatments are clearly as good
but cheaper, or better at the same or reduced
cost. Worse-value treatments are as good and
more expensive, or worse and the equally or
more expensive.

** Validating studies test the quality of a specific
diagnostic test, based on prior evidence. An
exploratory study collects information and trawls
the data (e.g. using a regression analysis) to find
which factors are ‘significant’.

*** By poor quality prognostic cohort study we mean
one in which sampling was biased in favour of
patients who already had the target outcome, or
the measurement of outcomes was accomplished
in <80% of study patients, or outcomes were
determined in an unblinded, non-objective way, or
there was no correction for confounding factors.

**** Good follow-up in a differential diagnosis study
is >80%, with adequate time for alternative
diagnoses to emerge (for example 1-6 months
acute, 1 - 5 years chronic)
### STARD checklist for reporting of studies of diagnostic accuracy

**version January 2003**

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<th>Item #</th>
<th>Item Description</th>
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<td><strong>TITLE/ABSTRACT/KEYWORDS</strong></td>
<td>1</td>
<td>Identify the article as a study of diagnostic accuracy (recommend MeSH heading &lt;sensitivity and specificity&gt;).</td>
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<tr>
<td><strong>INTRODUCTION</strong></td>
<td>2</td>
<td>State the research questions or study aims, such as estimating diagnostic accuracy or comparing accuracy between tests or across participant groups.</td>
</tr>
<tr>
<td><strong>METHODS</strong></td>
<td>3</td>
<td>The study population: The inclusion and exclusion criteria, setting and locations where data were collected.</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>4</td>
<td>Participant recruitment: Was recruitment based on presenting symptoms, results from previous tests, or the fact that the participants had received the index tests or the reference standard?</td>
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<td><strong>Test methods</strong></td>
<td>7</td>
<td>The reference standard and its rationale.</td>
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<tr>
<td><strong>Statistical methods</strong></td>
<td>12</td>
<td>Methods for calculating or comparing measures of diagnostic accuracy, and the statistical methods used to quantify uncertainty (e.g. 95% confidence intervals).</td>
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<tr>
<td><strong>RESULTS</strong></td>
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<td>When study was performed, including beginning and end dates of recruitment.</td>
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<td><strong>Participants</strong></td>
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<td>Clinical and demographic characteristics of the study population (at least information on age, gender, spectrum of presenting symptoms).</td>
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<tr>
<td><strong>Test results</strong></td>
<td>17</td>
<td>Time-interval between the index tests and the reference standard, and any treatment administered in between.</td>
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<tr>
<td><strong>Estimates</strong></td>
<td>21</td>
<td>Estimates of diagnostic accuracy and measures of statistical uncertainty (e.g. 95% confidence intervals).</td>
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<tr>
<td><strong>DISCUSSION</strong></td>
<td>25</td>
<td>Discuss the clinical applicability of the study findings.</td>
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REFERENCES


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Committee 3 B

Molecular Markers for Bladder Cancer Staging and Prognosis

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## V. HIGH-THROUGHPUT TUMOR PROFILING
Molecular Markers for Bladder Cancer Staging and Prognosis

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I. INTRODUCTION

Intensive molecular research over the last decade has provided great insight to the biology of bladder cancer and is beginning to shape clinical practice. Technologies such as high-throughput transcript profiling, microarrays, and proteomics have facilitated the identification and understanding of molecular pathways and molecules that are active in bladder cancer. Molecular profiling of bladder cancer is beginning to offer additional means to predict tumor behavior and thereby potentially improve treatment outcomes. In addition, new markers can conceivably serve as targets for novel therapeutic approaches and allow improved selection of therapeutic options.

It is now clear that different forms of bladder cancer develop along independent but possibly interrelated molecular pathways. Each of the steps associated with the development of malignancy, including tumor initiation, progression, and metastasis involve multiple genetic and epigenetic events indicating that few tumors are genetically and/or phenotypically identical. This is reflected by the heterogeneity in clinical and histologic presentation, intrinsic biologic potential of the various diatheses, and treatment outcomes. Current methods of risk stratification do not fully predict these distinctions. In this review, we will discuss the challenges and statistical considerations of molecular marker research and then explore recent advances regarding the biology and potential clinical utility and consequent integration of molecular markers for bladder cancer staging, prognostication, and therapeutic development.

II. EVIDENCE ACQUISITION

The literature was reviewed using the National Library of Medicine database (http://www.pubmed.gov). A MEDLINE search was performed with emphasis on urothelial malignancies and prognostic markers using combinations of the following terms: urinary tract cancer, bladder carcinomas, urothelial carcinomas, detection, bladder, recurrence, and prognostic markers. Basically, articles were considered between 2000 and 2011. No evidence level 1 information from prospective randomized trials was available. Articles were selected for this review with regards to the following criteria: evolution of concepts, development and refinement of techniques, quality of the study, and relevance. Older studies were included selectively if historically relevant or in case of scanty data in more recent publications.

III. EVIDENCE SYNTHESIS

1. CHALLENGES AND STATISTICAL CONSIDERATIONS FOR BLADDER CANCER PROGNOSTIC MOLECULAR MARKER RESEARCH

Despite a plethora of molecular markers reported to be clinically “promising,” there is currently no single prognostic molecular marker in routine clinical use. Challenges for the application of molecular markers in cancer care include analytical and regulatory barriers.[3-8] In addition, the absent use of bladder cancer molecular markers in clinical practice is a result of poor application of statistics and study design by which such markers might have been validated. Molecular marker research is usually done in the context of standard clinical care, rather than clinical trials. This has been largely guided by intuition and anecdotal experience rather than well-structured analyses. As a result, most molecular marker findings are not reproducible. Furthermore, most molecular markers that appear biomedically
and statistically significant at one center are not confirmed by studies at other centers.[9-14] This prompted the development of guidelines intended to ensure that molecular marker studies conform to some basic standards in design and reporting.[4-8]

In 2002, the National Cancer Institute’s Early Detection Research Network developed a 5 phase approach to systematic discovery and evaluation of molecular markers.[15-17] These phases of research are generally ordered in a sequence from discovery to validation and ultimately to assessment of benefit according to the strength of evidence that each provides. This approach is not only an intellectual process but also provides a clear scale by which researchers, patients, reviewers, and investors can evaluate the status of a molecular marker in its development process. The phases of research are generally ordered according to the strength of evidence that each provides in favor of the biomarker. The results from earlier phases are generally necessary to design later phases. This classification of studies into a sequence of phases, from discovery to validation and assessment of benefit has been adapted by several bladder cancer groups (Figure 1).

In an effort to address the pervasive problem of inadequacies in the design, analysis, and reporting of molecular marker prognostic studies, a set of reporting recommendations such as the REMARK has been developed and adopted by many prominent journals (Figure 2).[19-21] The goal of these guidelines is to encourage transparent and complete reporting and to help readers judge the data and understand the context in which the conclusions apply. Indeed, it provides a detailed description as to the minimum amount of information that should be given in the reporting of results from molecular marker studies. The REMARK lists 20 items that investigators should attempt to report in any molecular marker study. Another tool aimed at standardizing the quality of molecular marker research is the Tumor Marker Utility Grading System (Figure 3).[22] This is a scale of levels of evidence, designed to help place molecular marker studies into a context of validity.

An issue that has received less attention is the degree to which research on molecular markers has made sufficient use of clinically relevant statistics, such as the assessment of predictive accuracy, decision analysis, and/or experimental methodology. The fundamental idea behind the concept of personalized medicine is that it is possible to identify patterns of demographic, clinical, genomic/proteomic, and other types of biological data that can be used together to benefit individual patients. Most molecular markers do not provide sufficient information to be used independent of other information. However, the optimal use of molecular markers would be in the incorporation in a model that includes standard clinical data together with relevant additional data.

<table>
<thead>
<tr>
<th>Phase</th>
<th>Goals/aims</th>
<th>Experimentation</th>
<th>Sample details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preclinical Testing</td>
<td>Exploratory; nominate and rank candidate biomarker profiles</td>
<td>Preclinical study for hypothesis generation</td>
<td>Possible bias: small size and convenience sampling</td>
</tr>
<tr>
<td>0</td>
<td>Develop an assay with clinically reproducible results</td>
<td>Reproducibility and robustness of assay; No assessment of benefit</td>
<td>Sample population assay developed from candidate biomarker profile</td>
</tr>
<tr>
<td>I</td>
<td>Test on small sample to determine benefit</td>
<td>Marker optimization, establish prediction rules, determine cut-offs</td>
<td>Sample population assay developed from candidate biomarker profile</td>
</tr>
<tr>
<td>II</td>
<td>Determine operating characteristics &amp; internal validation</td>
<td>Retrospective design</td>
<td>Sample population should be the target population</td>
</tr>
<tr>
<td>III</td>
<td>External validation</td>
<td>Retrospective or prospective, Generalizability, Impact on clinical decision-making</td>
<td>Multi-institutional, large study</td>
</tr>
<tr>
<td>IV</td>
<td>Assess whether biomarker reduces the burden of disease</td>
<td>Post-approval reporting and testing for other disease processes or disease stages</td>
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</tr>
</tbody>
</table>

Figure 1. Modification of the structured phase-approach to the systematic discovery, evaluation, and validation of biomarkers
**INTRODUCTION**

1. State the marker examined, the study objectives, and any pre-specified hypotheses.

**MATERIALS AND METHODS Patients**

2. Describe the characteristics (e.g., disease stage or co-morbidities) of the study patients, including their source and inclusion and exclusion criteria.

3. Describe treatments received and how chosen (e.g., randomized or rule-based).

**Specimen characteristics**

4. Describe type of biological material used (including control samples) and methods of preservation and storage.

**Assay methods**

5. Specify the assay method used and provide (or reference) a detailed protocol, including specific reagents or kits used, quality control procedures, reproducibility assessments, quantitation methods, and scoring and reporting protocols. Specify whether and how assays were performed blinded to the study endpoint.

**Study design**

6a. State the method of case selection, including whether prospective or retrospective and whether stratification or matching (e.g., by stage of disease or age) was used.

6b. Specify the time period from which cases were taken, the end of the follow-up period, and the median follow-up time.

7. Precisely define all clinical endpoints examined.

8. List all candidate variables initially examined or considered for inclusion in models.

9. Give rationale for sample size; if the study was designed to detect a specified effect size, give the target power and effect size.

**Statistical analysis methods**

10. Specify all statistical methods, including details of any variable selection procedures and other model-building issues, how model assumptions were verified, and how missing data were handled.

11. Clarify how marker values were handled in the analyses; if relevant, describe methods used for cutpoint determination.

**RESULTS**

**Data**

12. Describe the flow of patients through the study, including the number of patients included in each stage of the analysis (a diagram may be helpful) and reasons for dropout. Specifically, both overall and for each subgroup extensively examined report the numbers of patients and the number of events.

13. Report distributions of basic demographic characteristics (at least age and sex), standard (disease-specific) prognostic variables, and tumor marker, including numbers of missing values.

**Analysis and presentation**

14. Show the relation of the marker to standard prognostic variables.

15. Present univariate analyses showing the relation between the marker and outcome, with the estimated effect (e.g., hazard ratio and survival probability). Preferably provide similar analyses for all other variables being analyzed. For the effect of a tumor marker on a time-to-event outcome, a Kaplan-Meier plot is recommended.

16. For key multivariable analyses, report estimated effects (e.g., hazard ratio) with confidence intervals for the marker and, at least for the final model, all other variables in the model.

17. Among reported results, provide estimated effects with confidence intervals from an analysis in which the marker and standard prognostic variables are included, regardless of their statistical significance.

18. If done, report results of further investigations, such as checking assumptions, sensitivity analyses, and internal validation.

**DISCUSSION**

19. Interpret the results in the context of the pre-specified hypotheses and other relevant studies; include a discussion of limitations of the study.

20. Discuss implications for future research and clinical value.

*Figure 2. Reporting recommendations for tumor marker prognostic studies (REMARK) NCI-EORTC (with permission from McShane et al.[21])*
Levels of evidence for grading clinical utility of tumour markers

<table>
<thead>
<tr>
<th>Level</th>
<th>Type of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Evidence from a single high-powered prospective study that is specifically designed to test marker or evidence from meta-analysis and/or overview of Level II or III studies. In the former case, the study must be designed so that therapy and follow-up are dictated by protocol. Ideally, the study is a prospective randomised trial in which diagnostic and/or therapeutic clinical decisions in one arm are determined based at least in part on marker results, and diagnostic and/or therapeutic clinical decisions in control arm are made independently of marker results. However, may also include prospective but not randomised trials with marker data and clinical outcome as primary objective.</td>
</tr>
<tr>
<td>II</td>
<td>Evidence from study in which marker data are determined in relationship to prospective therapeutic trial that is performed to test therapeutic hypothesis but not specifically designed to test marker utility (i.e. marker study is secondary objective of protocol). However, specimen collection for marker study and statistical analysis are prospectively determined in protocol as secondary objectives.</td>
</tr>
<tr>
<td>III</td>
<td>Evidence from large but retrospective studies from which variable numbers of samples are available or selected. Therapeutic aspects and follow-up of patient population may or may not have been prospectively dictated. Statistical analysis for tumor marker was not dictated prospectively at time of therapeutic trial design.</td>
</tr>
<tr>
<td>IV</td>
<td>Evidence from small retrospective studies which do not have prospectively dictated therapy, follow-up, specimen selection, or statistical analysis. May be matched case controls, etc.</td>
</tr>
<tr>
<td>V</td>
<td>Evidence from small pilot studies designed to determine or estimate distribution of marker levels in sample population. May include ‘correlation’ with other known or investigational markers of outcome, but not designed to determine clinical accuracy.</td>
</tr>
</tbody>
</table>

Figure 3. Levels of evidence for grading clinical utility of biomarkers: Tumor Marker Utility Grading System (TMUGS) (reproduced with permission of Hayes et al. [22])

with regards to assay performance (i.e., medications or nutrition that may interfere with an assay), so that the model could then be used to provide individual patient care.

To determine the value of a new molecular marker, it is not sufficient to show that it is significantly related to prognosis or outcome, statistically significant in a multivariable model that includes the standard clinical and pathologic factors, or more significant than standard clinical and pathologic factors. Rather, for a molecular marker to be clinically useful, it is necessary to show that adding the molecular marker to an existing model based on the most important clinical and pathologic factors substantively improves the predictive accuracy (discrimination and calibration) of the model. The next step is to assess whether the increase in accuracy and risk assessment translates into improved individualized, evidence-based treatment recommendations with eventual superior patient outcomes. Indeed, an improvement only in predictive accuracy, although necessary, is not in itself sufficient to assess whether using the marker in practice would actually benefit patients.

Establishing clinical relevance of a molecular marker test to guide therapeutic decisions requires demonstrating that it can classify patients into distinct subgroups with different recommended managements. While this would be ideally assessed in a randomized clinical trial, the substantial human and financial resources necessary for such randomized trials would make such an evaluation impractical for most molecular markers. However, decision analytic techniques can often be used instead of trials. The key point of decision analysis is that the consequences of clinical decisions would be incorporated in these analyses. This decision analytic evaluation should be performed during later stages of research and before clinical implementation of a tool. Furthermore, external validation needs to be performed prior to utilization of the model. Wider adoption of decision analytic methods will provide better insights as to whether any of the plethora of new molecular markers improves assessment, treatment outcomes, and ultimate health.

2. PROMISING TISSUE-BASED PROGNOSTIC MOLECULAR MARKERS

a) Cell Cycle Markers

The cell cycle is a series of carefully coordinated and regulated steps that govern cellular proliferation. Progression through the cell cycle is mediated in part by the buildup of cyclins, proteins that activate cyclin-dependent kinases (cdks). Cdk then phosphorylate the retinoblastoma (Rb) protein, a classic tumor suppressor and key component of the G1/S checkpoint. This allows DNA replication to proceed. Cdk inhibitors of both the inosin phosphokinase (INK) family, such as p16INK4A and the KIP family, such as p21 and p27, act as brakes on cell cycle progression (Figure 4). The p53 protein serves as the ‘guardian of the genome’ by inducing multiple mechanisms of cell cycle arrest after cell stress.[29]
most common genetic alterations found in human cancer, including bladder cancer. Alterations in the p53 and reilinistoma (Rb) tumor suppressor genes are predominant components in the development of bladder cancer, but the downstream effectors and other pathways that contribute to urothelial transformation remain to be more fully defined. p21WAF1/CIP1 and p27Kip1 are cyclin-dependent kinase inhibitors that can arrest the cell cycle by blocking G1/S progression. p21 is a well-characterized p53-inducible gene. As we will discuss, alterations of p53, pRB, p21, and p27 expression are markers that have prognostic significance in bladder cancer patients.

1. p53

The tumor suppressor p53 is the most commonly found mutated gene in human cancer. Activated by various types of cellular stress, including DNA damage and oncogene activation, p53 acts as a sequence specific transcription factor and appears to initiate a cascade of molecular events that result in cell cycle arrest, DNA repair, and apoptosis, thereby preventing the generation of genetically altered cells. Mutation or loss of chromosome 17p and consequent functional inactivation of p53 leads to the loss of ability to affect the important cell process and consequent uncontrolled proliferation and growth of a malignancy.

Many studies have demonstrated that the majority of invasive bladder cancers display allelic loss of the p53 gene. While most of these support that p53 nuclear accumulation is predictive of outcome, particularly for patients treated with radical cystectomy, there is evidence for and against almost every aspect of the role of p53 in cancer biology and clinical outcomes or application. These discrepancies may be related to the choice of antibody used in p53 assays, variability in interpretation and stratification criteria, and inconsistencies in specimen handling and other technical procedures. A meta-analysis of the role of p53 in bladder cancer, found 117 studies including 10,026 patients, with sample sizes ranging from 12 to 270 patients (mean 86, SD 53).[9] Immunohistochemistry was the most commonly (96% of the 117 studies) used approach for assessment of p53 status, with molecular analysis being used in the other 5 studies.

In a tissue microarray study containing specimens from over 400 bladder cancer patients, the proportion of altered p53 progressively increased in specimens from normal urothelium to non-muscle-invasive bladder cancer to carcinoma in situ and then to muscle-invasive bladder cancer, being highest in metastatic lymph node specimens. In accordance with all large previous studies, the degree of p53 expression (reflecting chromosome 17p abnormalities) was significantly associated with pathologic tumor stage, lymphovascular invasion, lymph node metastases, pathologic tumor grade, disease recurrence, and bladder cancer-specific death. Interestingly, the p53 phenotype was a stronger predictor of bladder cancer outcomes (disease recurrence and survival) in patients treated with radical cystectomy than chromosomal alterations and degree of expression of p21, pRB, p27, p16, cyclin E1, and cyclin D1. In a multi-institutional tissue microarray study comprising over 1200 patients treated with radical cystectomy for bladder cancer, p53 improved the accuracy of predictive models that included standard clinical and pathologic features for prediction of disease recurrence and bladder cancer-specific survival. Interestingly, in patients with advanced bladder cancer, p53 was a stronger predictor of bladder cancer outcomes than standard clinical and pathologic features.

Figure 4. Two-pathway model of the disease pathogenesis of Bladder cancer (BC). This figure shows the combination of molecular and pathological data. Arrow thickness is indicative for the percentage of tumors. The FGFR3 mutation is largely responsible for the favorable molecular pathway. Among many others, P53 and Ki-67 over-expression are examples of unfavorable NMI-BC. Molecular alterations, not included in the figure in the interest of clarity, are represented by the bottom arrow. Abbreviations: FGFR3, fibroblast growth factor receptor 3 gene; mt, mutation; ↑, elevated expression (Ki-67, p53); CIS, carcinoma in situ.
cancer (pT3-4 N0 or pT, any N+), adding p53 to a base model of clinical and pathologic characteristics did not improve overall predictive accuracy.[56] However, p53 improved prediction of recurrence-free and cancer-specific survival in patients with pT1-2N0 disease by a statistically and prognostically significant margin.[47] Taken together, these studies suggest that p53 can improve bladder cancer prognostication in high risk disease; however, the prognostic value of p53 decreases significantly in advanced disease.

Although p53 nuclear accumulation is associated with mutations in the p53 gene of chromosome 17, significant discordance exists. Lamy et al showed inactive p53 variants in up to 44% of bladder cancers, with the highest proportion in high grade tumors.[58] Stern et al investigated the frequency of p53 mutations in bladder cancer, taking into account DNA repair genotypes.[59] They found that tumor progression pathways may differ among subjects with different DNA repair polymorphisms, possibly explaining the inter-individual variation observed for the type and frequency of p53 gene mutations.

In addition to genetic factors, environmental exposures are likely to play an important role in bladder carcinogenesis. Based on this concept, Ryk et al suggested that the occurrence of p53 mutations may be due to genetic polymorphisms resulting in altered metabolism and repair.[60] This may result from individual modulation of mutagenic DNA adduct levels, and may then be of importance for an individual’s risk of developing bladder cancer.

Accurately sub-stratifying patients with high grade urothelial carcinoma involving the lamina propria (stage T1) regarding risk and potential treatment outcomes represents a particular challenge for urologists. There is conflicting data on whether p53 immunohistochemistry can reliably categorize patients with T1 tumors into different risk strata with regards to clinical outcomes.[33,48] A preliminary report from the EPICURO showed that p53 overexpression correlated with higher grade and stage of the disease in 995 patients with non-muscle-invasive bladder cancer.[61] However, the prognostic significance of p53 dropped out in multivariate analyses. In a follow-up study, using both immunohistochemistry and gene sequencing of 119 tumors, these authors found that the p53 pathway is inactivated in most T1 grade 3 tumors, but failed to identify any prognostic value for p53 in these patients.[61] Moonen et al also reported no additional value for p53 mutation analysis over known prognostic factors using specimens from 105 patients with high-risk non-muscle-invasive bladder cancer.[62] Another group reported that p53 nuclear accumulation was not predictive of response to intravesical BCG, cancer recurrence, progression, or cancer-specific survival.[63] A recent prospective trial found no clinical utility for p53 expression in predicting survival in high-risk patients with T1 tumors, but this may have been affected by the low event rate related to treatment efficacy.

Finally, in a recent study of 80 consecutive patients with pT1N0 bladder cancer, expression of p53 was altered in 25% of patients and p53 was independently associated with bladder cancer recurrence (HR 3.66; p=0.033) and cancer-specific mortality (HR 5.25; p=0.016).[57] The concordance index of a base model that included tumor grade, lymph node status, lymphovascular invasion, and concomitant carcinoma in situ for bladder cancer recurrence and bladder cancer-specific mortality was 54.7% and 64.3%, respectively. Addition of p53 increased the concordance indices of the base model for bladder cancer recurrence and cancer-specific mortality to 60% and 67.9%, respectively. The authors concluded that p53 can help stratify the heterogeneous population of pT1 patients into risk groups that can be used to guide clinical decision-making regarding observation versus adjuvant therapy. These findings are in line with data from the ISBC analysis combining immunohistochemical p53 staining results from 23 different studies.[50] This combined analysis of 929 patients with T1 bladder cancer demonstrated an independent prognostic value of p53 immunohistochemistry in multivariable analysis regarding tumor progression but not overall survival. However, these observations need to be reproduced by other groups.

At this time, the use of p53 is still not established despite more than 100 studies evaluating utility in bladder cancer patients. In the meta-analysis mentioned above, p53 independently predicted recurrence, progression, and mortality in only 27% (9 of 34), 50% (12 of 24), and 29% (10 of 35), respectively.9 In the studies that used Cox regression modeling, the overall risk of recurrence was 1.6 (95% CI 1.2-2.1), progression was 3.1 (1.9-4.9), and mortality was 1.4 (1.2-1.7). Nevertheless, given that most larger, well-done studies have shown a prognostic value to p53 in patients with advanced urothelial carcinoma of the bladder, a large multicenter adjuvant chemotherapy study was initiated with the goal of randomizing patients with a nuclear p53 accumulation (p53+) to adjuvant chemotherapy or observation within 10 weeks following radical cystectomy (for details see: https://www.uscnorris.com/p53/). This clinical trial might shed more light on the role of p53 in identifying patients at high risk for disease recurrence as well as response to adjuvant chemotherapy using MVAC.

2. pRB

The retinoblastoma protein (pRb) is a pivotal cell cycle regulator that plays a role in stem cell maintenance, tissue regeneration, differentiation, and developmental programs. Interference with
In patients who undergo cystectomy, p21 may play an independent role in predicting outcome but this varies by disease stage. In patients with muscle-invasive bladder cancer, p21 was an independent predictor of both disease recurrence and cancer-specific mortality. In patients with organ-confined disease, p21 remained independently associated with disease recurrence and bladder cancer-specific death. In addition, the authors found that p21 has cooperative/synergistic action with p53, p27, and pRB.49 Conversely, in a study of 80 patients with pT1N0 bladder cancer who underwent cystectomy, p21 was not an independent predictor of disease recurrence or cancer-specific mortality.57 Similarly, p21 was not an independent predictor in patients with advanced disease (T4, N positive).45,55 p21 may be most useful in patients with T2, T3, node-negative disease especially in combination with other markers.49

3. p21

The product of the p21 gene binds to and inhibits the activity of cyclin-dependent kinase 2 or cyclin-dependent kinase 4 complexes, and thus functions as a regulator of cell cycle progression at G1.65 In a large immunohistochemical study of p21 and p53 expression in 242 patients, a multivariate analysis showed that p21 status was an independent predictor of tumor recurrence and survival after radical cystectomy.36 Moreover, patients with p53-altered/p21-altered tumors demonstrated a higher rate of disease relapse and worse cancer-specific survival, compared with those with p53-altered/p21-normal tumors.36

The value of p21 expression depends on the stage and management of bladder cancer patients. In a study of 49 patients with carcinoma in situ only, altered p21 expression was independently associated with bladder cancer recurrence and progression.46 Patients with carcinoma in situ and altered expression for both p53 and p21 are at the greatest risk of bladder cancer recurrence, progression, and, most importantly, mortality, suggesting a potential rationale for early definitive therapy in these patients. On the other hand, an intact pathway at the level of p21 seems to abrogate the detrimental effects of altered p53 immunoreactivity on the outcome of bladder carcinoma in situ. In another study of 74 patients with non-muscle-invasive papillary bladder cancer, p21 was independently associated with tumor progression. Combination of p21 with p53, pRB, and p27 stratified patients into statistically significantly different risk groups for disease recurrence and progression in patients with non-invasive disease.43

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4. p27

p27Kip1 is a member of the Cip/Kip family of Cdk inhibitors, which binds to Cdk2 (and to other Cdks) and potently inhibits Cdk2 kinase activity,66 potentiating cell-cycle arrest in the G1 phase. In quiescent cells (G0 phase), p27 levels are high concomitant with low Cdk activity. As cells progress through the cell cycle and enter S phase, p27 levels decrease, allowing the kinase activity of Cdks to increase.

Two studies have found limited predictive value for p27 in patients with non-muscle-invasive bladder cancer. However, in patients with muscle-invasive disease treated with radical cystectomy, p27 significantly improved prediction of bladder cancer recurrence and survival. In patients treated with radical cystectomy, p27 is a key component of a panel of immunohistochemical markers which improved predictive value of a nomogram based on standard clinical and pathological characteristics both in patients with broad stage characteristics (pT1-3N0M0) and in a more select population of pT1 patients. Furthermore, p27 was independently associated with disease recurrence and progression.

5. Cyclins

The deregulation of the G1/S transition is a hallmark of cancer, allowing uncontrolled cell proliferation. Cyclins D and E are responsible for the initial and terminal phases of G1, respectively. Cyclin E1 is the predominant regulatory protein active at the G1/S transition and its alteration significantly affects carcinogenesis. Normal bladder urothelium expresses cyclin E1 only in the umbrella cells, while cancer cells already expressed cyclin E1 in the earliest stages of the disease process.53 Cyclin E1 expression was significantly decreased in patients with features of biologically and clinically aggressive bladder cancer; decreased expression of cyclin E1
Caspase-3 is a protease that acts as an apoptosis effector by cleaving multiple cellular components. [74] Giannopoulou et al studied caspase-3 expression in 53 patients with bladder cancer and did not find a correlation between caspase-3 expression and tumor grade or stage. [75] Burton et al [76] evaluated caspase-3 expression in 34 patients with carcinoma in situ, of whom 41% developed invasive bladder cancer. They reported that activated caspase-3 overexpression was associated with higher rates of disease invasiveness. Conversely, a more recent study by Karam et al [54] involving 226 consecutive patients treated with radical cystectomy reported that 49% of the patients had loss of caspase-3 expression, which was associated with higher pathologic grade and stage, and presence of lymph node metastasis. Moreover, loss of caspase-3 was an independent predictor of bladder cancer-specific survival after radical cystectomy. [54]

c) Bcl-2

Bcl-2 is an anti-apoptotic protein present in intracellular membranes, and controls cytochrome c location, caspase status, and ion channels involved in apoptosis. [77] Overexpression of bcl-2 was found in 32% of radical cystectomy specimens, and correlated with higher pathologic stage, disease recurrence, and cancer-specific mortality. [54] In agreement with these findings, two other groups reported that over-expression of bcl-2 was associated with worse all-cause survival and lower response rates to chemotherapy. [79]

d) Survivin

Survivin is a member of the Inhibitor of Apoptosis (IAP) family, and inhibits apoptosis, at least partly, by blocking downstream caspase activity. Survivin also controls mitotic progression and induces changes in gene expression that are associated with tumor cell invasion. Survivin mRNA is selectively expressed during embryonic and fetal development, [84] becomes undetectable or expressed at low levels in most differentiated normal adult tissues, and is overexpressed in human cancers. [83] In bladder cancer, survivin expression, both at the protein and the mRNA level, is associated with cancer presence, higher tumor grade, and advanced pathologic stage. [85-87] Survivin overexpression was present in 63% of bladder cancer specimens, and was associated with higher pathologic stage, presence of lymphovascular invasion, lymph node metastasis, bladder cancer recurrence, and bladder cancer-specific survival in 219 patients treated with radical cystectomy. [54] In addition, the proportion of specimens with survivin overexpression increased gradually from non-muscle-invasive bladder cancer to advanced bladder cancer and to metastatic lymph node tissue. [88] In a large multicenter validation study, addition of survivin improved the accuracy of standard clinicopathologic features for prediction of
disease recurrence and cancer-specific survival in a subgroup of patients with pT1-3N0M0 disease.[89] Survivin is a highly promising marker that deserves further investigation as a prognostic/predictive marker as well as a target for therapy.[90]

4. ANGIOGENESIS

Angiogenesis, the process of new blood vessel formation, is a critical event in the initiation and progression of solid malignancies. Angiogenesis has been traditionally quantified by measuring microvessel density. However, a variety of molecular markers are also associated with angiogenesis-related events.

a) Microvessel density

Bochner et al[91] evaluated 164 bladder cancer specimens and reported that patients with high microvessel density (>100 microvessels per hpf) were at highest risk of disease recurrence (68% at 5 years) and cancer-specific mortality (66% at 5 years) compared to patients with lower microvessel density (MVD). In addition, MVD was an independent prognostic factor when adjusted for the effect of tumor stage, grade, and lymph node status. However, other investigators could not confirm the prognostic value of MVD.[92-94] In 204 patients treated with radical cystectomy, Shariat et al failed to detect an association between MVD and prognosis, but they found that MVD was higher in patients with lymph node metastasis.[94] Jaeger et al examined 41 muscle-invasive tumors following radical cystectomy, demonstrating higher MVD in the primary tumor if LN metastases were present.[95] Explanations for these discrepancies in prognostic value of MVD include differences in the choice of antibody used for immunohistochemistry, as well as staining and scoring protocols. For example, the endothelium of tumor and normal tissues is heterogeneous. Thus, pan-endothelial antibodies such as CD31 may not stain tumor vessels to the same degree and may generally react better with larger vessels.[96]

b) Thrombospondin-1

Thrombospondin-1, an important component of the extracellular matrix, has been implicated in the regulation of cell growth and proliferation, cell motility, cytoskeletal organization, inflammation and wound healing, and the development and differentiation of cell types. Recently, it has been shown to be a potent inhibitor of angiogenesis in vitro and in vivo, and its expression is inversely related to microvessel density.[97] Grossfeld et al previously reported that altered thrombospondin-1 expression was independently associated with an increased risk of disease recurrence and all cause mortality in 163 patients treated with radical cystectomy.[98] However, the prognostic value of thrombospondin-1 was not independent of p53 expression status since these 2 molecular markers were strongly correlated. These findings were independently confirmed in a study of 204 patients with muscle-invasive disease treated with radical cystectomy.[99] Decreased thrombospondin-1 was independently associated with disease recurrence and cancer-specific survival. Moreover, loss of thrombospondin-1 expression was associated with alterations in other cell cycle regulators such as p21 and p27.

c) Vascular Endothelial Growth Factor

Of the various angiogenic factors, VEGF has been identified as a crucial regulator of normal and pathologic angiogenesis. VEGF produces a number of important biological effects such as endothelial migration, extracellular matrix remodeling via induction of proteases, increased vascular permeability, and maintenance of newly formed vasculature. Several members of the VEGF family have been characterized. In a small study of 45 patients, VEGF-C expression was localized to the cytoplasm of bladder cancer cells, with minimal expression in normal bladder epithelium.[100] VEGF-C expression was significantly associated with tumor size, pathologic stage and grade, lymphovascular invasion, and pelvic lymph node metastasis. In multivariable analysis, VEGF-C expression was an independent predictor of pelvic lymph node metastasis.[100] In addition, patients with high VEGF-C expression had a worse prognosis compared to those with low VEGF-C expression. In a separate study of 126 patients treated with transurethral resection of bladder cancer, higher expression of VEGF-A, VEGF-C, and VEGF-D were all associated with increasing tumor stage and grade.[101] VEGF-C expression was also associated with higher microvessel density. In a study of 204 patients treated with radical cystectomy and bilateral pelvic lymphadenectomy, VEGF-C was over-expressed in 86% of patients, supporting its role in bladder tumorigenesis and identifying it as a potential target for therapy.[94]

In addition, VEGF overexpression was associated with pathologic features, and altered expression of p21, p27, pRB, cyclin E1 and Ki-67, suggesting complex interactions between different bladder cancer-associated molecules. While these associations are important, VEGF expression had no independent prognostic value. Increased VEGF levels can result in increased vascular permeability and interstitial fluid pressure, impairing chemotherapy delivery. Thus, adding anti-VEGF to chemotherapy regimens for bladder cancer might lead to improved responses.

d) Basic Fibroblast Growth Factor

Similar to VEGF, bFGF is a potent pro-angiogenic growth factor. It has been hypothesized that during wound healing and tumor development bFGF is activated, thereby mediating the formation of new
blood vessels. bFGF may behave as a transforming/oncogenic factor inducing cell proliferation and motility. The interaction with specific receptors may lead to unchecked proliferation via the Ras-MAPK pathway. The most common oncogenes and some of the tumor suppressor genes relevant to bladder cancer are components of this pathway.

bFGF has been evaluated as a potential urinary molecular marker in bladder cancer. Higher levels of bFGF were found in urine samples from patients with bladder cancer compared with those with benign disease or a history of urothelial carcinoma but no current tumor.[104] Others have measured urinary bFGF in patients with various grades and stages of urothelial carcinoma, and noted a correlation of increased bFGF with advanced disease.[105] In a tissue microarray study of 204 radical cystectomy patients, bFGF was associated with established features of biologically aggressive bladder cancer such as pathologic stage, lymphovascular invasion, lymph node metastasis, molecular markers commonly altered in bladder cancer (i.e., p27, pRb, and Ki-67) and disease recurrence. In addition, altered bFGF expression has been associated with resistance to cisplatin in human bladder cancer cell lines.[106] Since bFGF may also contribute to bladder cancer progression via its extracellular matrix involvement, bFGF could be a candidate for therapeutic targeting.

5. SIGNALING PROTEINS

Many receptor tyrosine kinases and their downstream effectors and regulators have genetic alteration and/or altered expression in bladder cancer. Several of these are oncogenes that have a dominant effect on cell phenotype and these may represent particularly good therapeutic targets.

a) ERBB Family Receptors

Receptor tyrosine kinases are attractive therapeutic targets and currently there is much effort to target these either with antibodies or small molecules. Epidermal growth factor receptor (EGFR) is a receptor tyrosine kinase implicated in the pathogenesis of a variety of human cancers. Overexpression of EGFR in bladder cancer was identified more than 20 years ago[107]. The mechanism for upregulation is unknown but is not related to gene amplification. There are several approved drugs (antibodies and small molecules) that interfere with signaling via this receptor and there are now several ongoing clinical studies in bladder cancer. However, large trials in non-small cell carcinoma of the lung have not shown significant benefit. And although there is some success in specific organs, it is difficult to predict response as this is not related directly to expression levels. In non-small cell carcinoma of the lung, activating mutation of the receptor has been shown to be predictive of response. But such mutations are not found in bladder cancer[108].

The effect of inhibition of EGFR signaling in urothelial cells is cystostatic.[109] Therefore, although combination therapies with conventional cytotoxic agents are underway, the requirement for cell division to allow some agents to exert their effects may be problematic and timing of delivery may be critical. Inhibitors of EGFR are available and have potential clinical efficacy. Overexpression of EGFR was associated with disease progression of pT1 high grade urothelial carcinoma of the bladder and decreased survival.[110] Consequently, gefitinib, which targets EGFR, was studied in preclinical in vitro and subcutaneous in vivo models of urothelial carcinoma of the bladder with promising results.[111] Unfortunately, a clinical phase II trial (CALGB 90102) investigating the treatment of measurable metastatic urothelial carcinoma of the bladder found a high toxicity and no survival benefit when gefitinib was added to gemcitabine and cisplatin chemotherapy.[112]

Patient response is clearly correlated to the presence of activating mutations in the kinase domain or a variant of EGFR (known as EGFRvIII). Importantly, several studies have demonstrated that mutations within the tyrosine kinase domain of EGFR and expression of EGFRvIII are rare events in bladder cancer, these likely limiting the utility of EGFR as a prognostic marker or therapeutic target.

b) RAS

Approximately 13% of bladder cancers of all grades and stages contain a mutation in one of the RAS genes (HRAS, NRAS, KRAS2).[114] This implicates the RAS-MAP kinase (RAS-MAPK) pathway and potentially the PI3K pathway in these tumors. Although the RAS proteins themselves have proven difficult to target, there is currently much interest in developing small molecule inhibitors of other key proteins in these pathways that may be applicable to RAS-mutant bladder cancers. Further confirmation of the activation status and examination of the relationship to RAS and other mutations, including FGFR3 and PIK3CA mutations (see below), will be required to allow rational selection of patients for these types of therapy.

c) PI3K Pathway Genes

Several genes in the PI3K pathway are implicated in bladder cancer. PTEN, a lipid phosphatase that removes phosphate from phosphatidylinositol 3,4,5-trisphosphate produced by PI3K, is commonly deleted in muscle-invasive tumors. In some cases, bi-allelic inactivation by mutation in the retained allele or homozygous deletion has been found.[115-117] Recent studies have identified activating point mutations in the alpha catalytic subunit of PI3 kinase p110alpha (PIK3CA) in bladder cancer, with highest frequency in non-invasive papillary tumors.[118] This
mutational activation of PI3K results in phosphorylation of AKT, which in turn regulates many cellular activities including cell proliferation, stimulation of protein synthesis via the mTOR pathway, effects on metabolism and evasion of apoptosis [119].

TSC1 acts in the mTOR pathway downstream of AKT and this pathway is activated in bladder cancer via mutational inactivation of TSC1. Inhibitors of mTOR (rapamycin and analogues) are approved for clinical use in kidney cancer and other malignancies but not yet tested in bladder cancer. Inhibitors of other pathway molecules are in development and some show promising activity. For example, there are reports of successful inhibition of tumor growth in preclinical mouse models by a dual inhibitor of p110alpha and mTOR. For rational selection of appropriate inhibitors in the future, it will be important to determine the relationship of different molecular lesions in the pathway to tumor phenotype and clinical outcome and to test the relative sensitivity of cells with specific pathway alterations in preclinical models.

d) Fibroblast Growth Factor Receptor 3

Fibroblast growth factor receptor 3 (FGFR3) belongs to a tyrosine kinase receptor family and regulates diverse cellular processes including growth, differentiation, and angiogenesis. It is activated by a point mutation in bladder cancer. [122] Activating FGFR3 mutations are present in up to 60% of bladder tumors, and are characteristic of papillary, non-muscle-invasive bladder cancer. [122] Surprisingly, FGFR3 mutations were found to be related to favorable disease with 84% of pTaG1 tumors having a mutation as compared to 7% of pT2G3 or higher stage tumors. [123] In general, the FGFR3 mutation represents a subset of low grade, low stage tumors that rarely progress and hence have a good prognosis.[122-124]

Lindgren et al used expression profiling, mutation analysis, and loss of heterozygosity to molecularly characterize a cohort of 75 Ta and T1 bladder cancers.[125] They confirmed that low grade, low stage bladder cancer is characterized by FGFR3 receptor activity, high protein synthesis, and low cell-cycle activity. Using screening for FGFR3 mutations by direct bidirectional sequencing and for genome-wide molecular changes with microarray technology of 35 low grade Ta and 50 T1 or grade 3 tumors, Zieger et al found that FGFR3-mutated non-muscle-invasive tumors can progress and retain their mutation and chromosomal instability patterns during progression.[126] Their results suggest that the decreasing frequency of FGFR3 mutations in later stages of tumor development is caused by the emergence of tumors following a different molecular pathway with no FGFR3 mutations. Tumors of this latter pathway were associated with carcinoma in situ. This molecular evidence for the clinical two-pathway model in bladder cancer (Figure 5) is further substantiated by the absence of FGFR3 mutations in 20 cases of CIS[123] and the mutually exclusive occurrence of FGFR3 mutations and altered expression of Ki-67, p53, and p27.

FGFR3 mutations were found to protect against progression of non-muscle-invasive bladder cancer. However, a combination of FGFR3 with another molecular marker associated with worse prognosis if positive, like Ki-67, seemed to confer a more accurate prediction of progression and disease-specific survival than FGFR3 or Ki-67 alone. Molecular grade (mG) based on FGFR3 mutation status and Ki-67 expression was proposed as an alternative to pathologic grade.[127] Using these 2 molecular markers, a 3-tier grading system was developed covering all cases: mG1 (mutation; normal expression), favorable prognosis; mG2 (no mutation; normal expression or mutation; high expression), intermediate prognosis; mG3 (no mutation; high expression), poor prognosis.[124] A recent study compared the reproducibility of pathological grading and mG on the same series of patients.[127] The reproducibility of mG was almost perfect (kappa: 0.76), whereas reproducibility for pathologic grade was only fair to substantial (kappa: 0.17-0.58). In addition, combining the EORTC risk scores and mG led to a more accurate prediction of progression in patients with intermediate and high-risk EORTC scores.[127] In this recent study with long-term follow-up, EORTC high-risk combined with mG3 showed 50% (15/30) progression as opposed to 20% (6/29) progression in EORTC high-risk combined with mG1-2. Taken together, mG (composed of 3 mGs) proved more reproducible than pathological grade assessment, making it a reliable and robust tool to assess progression in non-muscle-invasive bladder cancer. An independent prospective analysis of mG has to be done to confirm the promising retrospective data described in this paragraph.

It is clear that the FGFR3 gene plays a major role in the development of low-grade non-muscle-invasive bladder tumors; however, there is little evidence that it plays any role in the development of invasive cancer or in the progression of non-muscle-invasive to invasive disease. One of the most important clinical questions remains whether FGFR3 can help risk stratify the heterogeneous group of T1 grade 3 bladder cancers. As illustrated above, a combination of FGFR3 with another molecular marker associated with worse clinical features may be the answer.

6. HORMONE RECEPTORS

a) Human Epidermal Growth Factor Receptor 2

Human epidermal growth factor receptor 2 (HER-2) is a tyrosine kinase in the EGFR family that can promote oncogenesis. HER-2 has been
best characterized in breast cancer, in which overexpression of HER-2 is a poor prognostic factor and inhibition of HER-2 function has proven to be an effective approach for the treatment of breast cancer cells that overexpress HER-2. Conflicting data exists regarding the expression and significance of HER-2 in bladder cancer.

A number of studies have shown limited or no prognostic value of examining HER-2 expression. For instance, Kassouf et al reported no significant correlation between HER-2 expression status and clinical outcome in 184 patients with primary bladder cancer, and another study found that HER-2/neu overexpression in primary or metastatic tumors did not predict survival in a cohort of 80 consecutive patients with muscle-invasive bladder cancers. However, other studies have reported that higher HER-2 expression levels are associated with poor prognosis. Recently, a study of 198 patients observed on multivariable analyses that HER-2 positive patients were at increased risk for both bladder cancer recurrence and cancer-specific mortality compared with patients with negative HER-2 expression.

These conflicting data may be partially explained by differences in patient populations and techniques of HER-2 analysis and immunostaining among the various studies. Clearly, additional data is necessary from prospective studies using standardized analytical techniques for HER-2 expression. Clinical trials have been initiated to investigate the efficacy of anti-HER-2 therapy in patients with advanced bladder cancer, and these will provide further insight to the role of HER-2 in disease progression.

**b) Androgen Receptor**

The androgen receptor (AR) is a nuclear receptor and ligand-dependent transcription factor that mediates the biologic effects of androgens. Boorjian et al reported that expression of androgen receptor was inversely correlated with pathological stage in a series of 49 patients with bladder cancer; 75% of non-muscle-invasive tumors expressed the AR compared with 21.4% of muscle-invasive tumors. Similarly, another study confirmed that loss of AR expression was associated with higher grade and invasive tumors; however, no association was found with patient outcomes.

Although several groups have argued for a role for AR in pathogenesis of bladder cancer, evidence for using androgen receptor as either a prognostic marker or therapeutic target in bladder cancer remains limited. In a study comprising 472 patients with urothelial bladder carcinoma from two centers, the authors did not observe any association between AR protein expression and bladder cancer stage, grade, or outcomes. Further data did not suggest that loss of AR expression is gender-related. The authors used tissue microarrays and different antibodies, correlated in a blinded fashion with results observed in two centers and included automated and manual scoring systems. Results were further validated and confirmed on a small representative sample population analyzed in a previous positive study to show similar findings, despite antibody epitope, reagents, and laboratories.

**c) Estrogen Receptor and Progesterone Receptor**

Like AR, the estrogen receptor (ER) is a member of the nuclear receptor superfamily, and acts as a transcription factor after binding to estrogens and translocation to the nucleus. Two subtypes of ER exist, with varying expression and functional profiles: estrogen receptor alpha (ERalpha) and estrogen receptor beta (ERbeta). ER is expressed in a subset of bladder tumors; however, the prognostic and functional significance remains unclear. ERalpha is rarely expressed by bladder cancer specimens. It has been reported that expression of ERbeta is associated with pathologic characteristics of bladder cancer (stage and grade). However, several studies have shown limited or no impact of ER expression on prognosis of patients with bladder cancer.

The progesterone receptor (PR) is another intracellular steroid receptor that acts by a mechanism similar to that of AR and ER; however, a recent report indicates it is not expressed in bladder cancer.

**7. COMBINATION OF TISSUE-BASED MOLECULAR MARKERS**

Given the complexity of the molecular abnormalities associated with bladder cancer, it is improbable that a single marker can accurately segregate tumors of similar clinicopathologic phenotypes into distinct prognostic categories. A marker may reflect disruption of a biochemical pathway by a particular mechanism but not by another. Therefore, as previously shown, combinations of independent, complementary markers may provide a more accurate prediction of outcome compared to a single marker.

Karam and coworkers found that p53, Bcl-2, caspase-3, and survivin display distinct association patterns with tumor stage and grade, lymphovascular invasion, and carcinoma in situ. The number of simultaneously altered apoptosis markers was an important prognostic indicator for disease recurrence and bladder cancer-specific survival in patients treated by radical cystectomy. Changes in expression of markers were frequent in individuals with bladder cancer, with only 22 patients (10%) showing normal expression of all 4 markers. Alteration of fewer than 4 apoptosis markers did not provide independent prognostic information after controlling for the
effects of standard pathologic features; only when all 4 markers were altered was significance reached. This is explained by the fact that Bcl-2, caspase-3, p53, and survivin have not only interrelated but also independent roles in the apoptotic pathway.

Analysis of any combination of cell cycle regulators (i.e., p53, pRB, p21, p27, cyclin D1, and/or cyclin E1) provides additional prognostic information beyond that obtained from any single molecular marker or combination of 2 or 3 molecular markers. This makes sense because it investigates multiple pathways including downstream effectors rather than a single crossroad in a pathway. Higher total number of altered molecular markers was associated with a progressive, proportional increase in the risk of advanced pathologic tumor stage, lymphovascular invasion, lymph node metastases, disease recurrence, and death from bladder cancer. These molecular markers had a cooperative or synergistic role in the biologic behavior of bladder cancer. Furthermore, examining how many markers are altered and adding this information to a nomogram of clinicopathologic criteria significantly improved predictive accuracy for disease recurrence and cancer-specific mortality. Other studies have confirmed this principle in selected patient populations; addition of a number of altered molecular markers to a base predictive model significantly improved predictive accuracy for 80 patients with T1 disease, 324 patients with organ-confined bladder cancer, and 692 patients with advanced bladder cancer.

Because tumorigenesis and progression is a process involving multiple genetic defects, it is likely that alterations in other pathways will also affect bladder cancer progression and metastasis. These data, together with the current paradigm that bladder cancer develops along multiple molecular pathways, suggest that including multiple molecular markers in models designed to predict outcomes could enhance their predictive power. Therefore, use of multiple molecular markers likely represents the future of risk stratification and should be used to guide patient counseling and management decisions such as neoadjuvant and adjuvant therapy.

IV. PROMISING BLOOD-BASED PROGNOSTIC MOLECULAR MARKERS

The use of biomarkers in the blood offers several advantages over tissue samples, such as that of higher sample homogeneity and its minimally invasive nature. Furthermore, blood samples provide information that can be known at any disease stage, offering an alternative to surgical and clinical decision-making. However, whether further value exists in regards to the clinical applicability of these blood-based biomarkers remains to be tested and proven in large multi-institutional prospective controlled trials.

1. PLASMA-INSULIN GROWTH FACTOR BINDING PROTEIN (IGFBP)-3

Insulin growth factor (IGFs) and IGFBPs have a central role in the regulation of growth, cellular proliferation and transformation, and apoptosis. IGFBP-3 belongs to a family of high affinity IGFBPs, which directly mediate IGF-independent actions, such as regulation of cell growth and induction of apoptosis, through binding to its own putative receptor. However, evidence also suggests that IGFBP-3 has its own pro-apoptotic effects, independent of its ability to modulate IGF bioavailability. The activities of IGFBP-3 are regulated in a complex manner, such as IGFBP-3 proteases like kallikreins, cathepsin, and matrix metalloproteinases, which release IGFs from IGFBP-3. Equally noteworthy is that several studies have found that IGFBP-3 is capable of mediating the antiproliferative effects of tumor suppressor protein p53, transforming growth factor-beta (TGF-β1), retinoic acid, vitamin D, antiestrogens, and tumor necrosis factor-alpha. Previous investigators collected preoperative plasma levels of IGFBP-3 measured using DSL-enzyme-linked immunosorbent assays in a group of 51 patients who underwent radical cystectomy and compared it to the levels in blood from 44 healthy controls. The association between IGFBP-3 and IGF-I was also tested, and authors found that both levels were strongly correlated with one another and among patients with bladder cancer (r=0.568, p<0.001). Preoperative plasma IGFBP-3 concentration level was lower in patients with regional lymph node metastases (p=0.047) and was a significant predictor of lymph node involvement, independent of clinical stage and grade (HR: 0.9, p=0.047). This confirms the speculations that a relationship between circulatory IGFBP-3 levels and metastasis may exist. Moreover, authors of that study revealed that low levels of IGFBP-3 portended an increased risk of disease recurrence (HR: 0.9, p=0.049) and cancer-specific mortality (HR: 0.9, p=0.04) in the preoperative setting after adjusting for the effects of clinical stage and grade. A better understanding of the biologic mechanisms and the role of IGFBP-3 in bladder cancer is worthy of investigation.

2. TRANSFORMING GROWTH FACTOR (TGF)-B1

TGF-β1 inhibits cell growth in cellular proliferation, chemotaxis, cellular differentiation, immune response, and angiogenesis. Loss of response to the antiproliferative effects of TGF-β1 is associated with the progressive stages of carcinogenesis. The effects of TGF-β1 are mediated by membrane-bound serine-threonine kinase receptors, otherwise known as TGF-β1 receptor types I and II (TGF-
β1-R1 and TGF-β1-R1I). Alteration of TGF-β1 is common in bladder cancer and overexpression of TGF-β1 is associated with the loss of expression of its receptors.[151] An increased expression of TGF-β1 has also been linked with features of advanced bladder cancer such as tumor grade, stage, and lymphovascular invasion.[151-153] Elevated plasma TGF-β1 levels (n=51) have been associated with an increased probability of regional and distant lymph node metastasis even after adjusting for clinical stage and grade (odds ratio [OR]: 12.8, p=0.03). [153] However, others could not confirm this finding. [152] Elevated levels of TGF-β1 were associated with an increased risk of disease recurrence and cancer-specific mortality both in the preoperative (HR: 1.6, p=0.009 and HR: 2.9, p=0.02, respectively) and postoperative settings (HR: 3.1, p=0.01 and HR: 3.0, p=0.02, respectively). [153]

3. MATRIX METALLOPROTEINASE (MMP)

MMP is a family of zinc-dependent proteases involved in the breakdown and remodeling of extracellular matrix. A degradation of extracellular matrix is vital in normal physiological processes, as well as in pathological processes such as tumor progression and metastasis. [154] In addition, MMPs can induce several molecular processes implicated in tumor progression through their cleaving activities. MMPs can mobilize pro-angiogenic factors, but are also capable of generating angiogenic inhibitors, such as endostatin and angiostatin. [155-157] In bladder cancer, MMP expression has been associated with more advanced stage and grade.[158-162] Plasma MMP concentrations (-2, -3, -7, -8, and -9) collected from 135 patients with high grade T1 or higher stage bladder cancer[163] revealed that MMP-7 was elevated in patients with advanced clinical stage (p=0.02). Moreover, patients with MMP-7 levels above the median (300 pg/mL) were at increased risk of cancer-specific mortality compared to patients with MMP-7 below the median (5-year survival estimates: 48% vs. 74%, p=0.01). After adjusting for the effects of clinical grade, MMP-7 remained an independent predictor of cancer-specific mortality (HR: 2.2, p=0.02).

Szarvas et al confirmed these results in 79 serum samples from bladder cancer patients and 19 healthy individuals.[164] Higher levels of serum MMP-7 were associated with bladder cancer presence (p<0.001), lymph node metastasis (p=0.002), overall (p=0.008), and cancer-specific mortality (p=0.006). However, MMP-7 was not associated with tumor stage (p=0.1) or grade (p=0.2). In multivariable analyses, higher serum MMP-7 remained associated with metastatic cancer (HR: 2.5, p=0.048) and cancer-specific mortality (HR: 2.0, p=0.04). Interestingly, serum levels of MMP-7 decreased significantly after surgery in 75% of cases suggesting that the higher circulating MMP-7 in bladder cancer patients might originate at least partly from the primary bladder cancer cells. Nonetheless, further studies with larger sample sizes are needed to better understand the biologic and prognostic role of MMP-7 in bladder cancer.

Limited data exist on other circulating MMPs in patients with bladder cancer. Some reported elevated concentrations of MMP-2 and MMP-3 in patients with advanced bladder cancer (pathological T2-4, N+, M+) compared to those in patients with non-muscle-invasive bladder cancer (Ta-T1, N0, M0). Lower levels of plasma MMP-2 (p=0.03) have been associated with more advanced tumor stage and grade.[163] Moreover, it appears that the tissue inhibitor of metalloproteinases-(TIMP) 2, which inhibits protease activity of MMP-2, could also suppress invasion, metastasis, neovascularization, and growth in some human tumors, and that the ratio of MMP-2 and TIMP-2 is considered an independent predictor of cancer recurrence.[167] Increased MMP-9 serum levels have also been found in patients with advanced clinical stage and grade.[168]

4. UROKINASE PLASMINOGEN ACTIVATION (UPA)

uPA is a serine protease involved in the formation and regulation of blood vessels and clots, bone modeling, and activation of metalloproteinases and growth factors. It holds an important role in tumor invasion and metastasis by accelerating the conversion of plasminogen to plasmin. Subsequently, the plasmin cleaves to components of the basement membrane and extracellular matrix to allow tumor cells to access lymph vessels and vasculature. The inactive precursor of uPA is activated by binding to a specific membrane-bound or soluble cell surface receptor (uPAR). This hastens the conversion of plasminogen into plasmin.

In bladder cancer cells, the presence of both uPA and uPAR were necessary for in vitro invasion, and invasive potential was reduced when their interaction was interrupted. [171] Plasma levels of uPA and uPAR were significantly higher in bladder cancer patients (n=51) compared to healthy subjects (n=44, p<0.001). [172] Higher uPA concentration was associated with lymphovascular invasion (p=0.02) and regional lymph node metastases (p=0.02), while higher uPAR concentration was associated with distant lymph node metastasis (p=0.04). In the preoperative multivariable model, only uPA emerged as an independent predictor of disease recurrence (HR: 3.7, p=0.03) and cancer-specific mortality (HR: 3.7, p=0.04). After validation, these markers may be useful in selecting patients most likely to benefit from intensified follow-up and therapy. These markers should also be considered for integration in prediction tools.
5. INTERLEUKIN-6 (IL-6) AND IL-6 SOLUBLE RECEPTOR (IL-6sR)

IL-6 is a cytokine that plays a role in the regulation of the immune system via the proliferation and activation of cytotoxic T cells, proliferation and differentiation of B cells, and production of acute phase proteins. IL-6 signaling is initiated when IL-6 binds to the ligand specific non-signaling receptor IL-6R, which also exists in soluble form as IL-6sR. The latter arises from 1 or 2 independent cellular processes, namely differential mRNA splicing or proteolytic cleavage of membrane bound IL-6 receptors. Previous data support the hypothesis that bladder cancer cell lines produce more IL-6 than normal urothelial cells.[173]

It seems that IL-6 confers a selective advantage for certain disseminated cells to develop into metastatic tumors. In a prospective study of 51 bladder cancer patients, elevated IL-6 and IL-6sR levels were associated with more advanced pathological stage, lymphovascular invasion, and regional and distant lymph node metastases.[174] Only IL-6 was correlated with clinical stage and tumor grade. Both IL-6 and IL-6sR were independent predictors of lymph node metastasis, disease recurrence, and cancer-specific mortality after adjusting for the effects of clinical stage and grade.

6. SOLUBLE E-CADHERIN (SE-CADHERIN)

E-cadherin is a member of the family of transmembrane glycoproteins involved in calcium dependent intercellular adhesion. [175] Normal E-cadherin expression suppresses tumor progression. When altered, it allows cancer cells to detach, invade, and access the lymphatic and vascular system. In bladder cancer, as in other malignancies, a decrease in E-cadherin expression has been linked with an increased risk of metastases, tumor progression, and cancer-specific mortality. [177-182] sE-cadherin is the degradation product of cellular E-cadherin, generated by Ca²⁺ ion dependent proteolytic activity. Several authors have found increased serum levels of sE-cadherin in bladder cancer patients compared to non-cancer subjects. Moreover, sE-cadherin was significantly associated with regional lymph node metastasis as well as disease recurrence. However, sE-cadherin failed to achieve statistical significance when cancer-specific mortality was the endpoint of interest.

V. HIGH-THROUIGHPUT TUMOR PROFILING

As our understanding of the individuality of cancers evolves, we will rely on molecular fingerprints to tailor management and therapeutic approaches to the clinical, morphological, and molecular features of each patient. High-throughput genomic, transcriptomic, and proteomic assays, with appropriate database and bioinformatic support, will be effective tools to screen for novel markers and to fingerprint each cancer. Indeed, the advent of high-throughput methods of molecular analysis has allowed the comprehensive survey of the genetic profiles characteristic of distinct tumor types and identification of targets and pathways that may underlie particular clinical behavior. Several groups also have used gene expression profiling of bladder cancer tissues to identify signature genes that distinguish bladder cancer subclasses and genetic pathways underlying bladder cancer progression. Such signature genes ideally would provide a molecular basis for classification and also yield insight into the molecular events underlying different bladder cancer clinical phenotypes.

Microarray-based approaches have been used extensively to look for expression profiles that could sub-classify bladder cancers. Dyrskjot et al used high-density oligonucleotide microarrays to identify a 45-gene signature of disease progression in a training set of 29 bladder cancer patients.[126] This signature was then examined using an independent test set (74 superficial tumor samples) revealing a significant correlation between gene expression classifications and clinical outcome.

Blaveri et al used cDNA microarrays (10,368 genes) to identify differentially expressed genes along the course of disease progression in 80 bladder tumors, 9 bladder cancer cell lines, and 3 normal bladder samples.[187] Unsupervised hierarchical clustering successfully separated the samples into 2 subgroups containing non-muscle-invasive versus muscle-invasive tumors, supported by a 90.5% success rate. Tumors could also be classified into transitional versus squamous subtypes (89% success rate) and good versus bad prognosis (78% success rate). Sanchez-Carbayo et al used oligonucleotide arrays to identify genetic signatures characteristic of aggressive clinical behavior in advanced bladder tumors by transcript profiling of 52 normal urothelium, 33 superficial, and 72 invasive tumors.[188] Unsupervised clustering classified them with 82.2% accuracy, while predictive algorithms rendered an 89% correct rate for tumor staging using genes differentially expressed between superficial and invasive tumors. Accuracies of 82% and 90% were obtained for predicting overall survival when considering all patients with bladder cancer or only patients with invasive disease, respectively.

Target validation of synuclein by immunohistochemistry on tissue arrays (N=294) sustained its association with tumor staging and outcome. Lindgren et al successfully used this approach to distinguish specific molecular subtypes of bladder cancer and define gene signatures that can classify bladder cancer by grade as well as muscle-invasion status. Furthermore, they reported a gene expression sig-
nature that is associated with both metastasis and survival. Takata et al examined expression profiles of 27,648 genes in 27 cases of bladder cancer to predict response to a neoadjuvant methotrexate, vinblastine, doxorubicin, and cisplatin (M-VAC) chemotherapy regimen.[190] They identified 14 genes with a correct prediction in 8 out of 9 patients. These studies suggest that defining gene expression signatures may be a relevant complement to standard clinical and pathological risk stratification. However, current costs associated with examination of such a large number of genes make transition to the clinical realm difficult.

CONCLUSIONS

Bladder cancer is an especially complex and heterogeneous disease with a broad spectrum of histologic findings. Molecular medicine holds the promise that clinical outcomes will be improved by directing therapy toward the mechanisms and targets associated with the growth of an individual patient’s tumor. The advent of high-throughput technologies is allowing comprehensive identification of molecular targets and molecular markers specific for bladder cancer. Such identification processes may provide a better understanding of the biology associated with tumorigenesis and tumor progression. However, further research is warranted in the field to translate the identification of these molecular targets into potential predictive molecular markers. The challenge remains to optimize measurement of these targets, evaluate the impact of such targets for therapeutic drug development, and translate molecular markers into improved clinical management of bladder cancer patients.

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Committee 4

Low Grade Ta Urothelial Carcinoma of the Bladder

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Low Grade Ta Urothelial Carcinoma of the Bladder

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In this section we have attempted to review all the literature pertaining to non-muscle-invasive bladder cancer and cull out the facts specifically pertaining to low grade Ta (LG Ta) urothelial carcinoma. The evidence available is often buried in broad studies of all non-muscle-invasive bladder cancer and hence the patients with LGTa urothelial carcinoma constitute a smaller subgroup. Such subgroup analyses may be inadequately powered, given the original primary endpoints of many of the studies which would have taken into account sample sizes for all non-muscle-invasive bladder cancer together. The evidence available was analyzed using the Oxford method of assigning the levels of evidence and summary recommendations based on these levels of evidence were graded as advised by the Oxford Centre for Evidence-based Medicine, which are similar to the GRADE working group recommendations [1]. At the end of each section, a summary of the recommendations and a ready reference table with the recommendations and the levels of evidence as well as the grade of the recommendation are provided.

The initial diagnosis of LG Ta urothelial carcinoma requires the performance of a transurethral resection or biopsy. It is recommended that the presence of muscle on the initial resection specimen be documented to ensure accurate stage designation as Ta. It is not required that biopsies for recurrent LG Ta urothelial carcinoma have muscle present in the specimen. This may be particularly the case with office biopsies under local anesthesia where a deep specimen will be difficult to obtain. Forcep biopsies can only be pursued in patients with a documented history of recurrent LG Ta urothelial carcinoma and not for the initial presentation of bladder tumor.

I. Urinary Cytology, Urinary Markers and the Follow-Up of Low Grade Non Muscle Invasive Bladder Tumors

Extensive laboratory research has led to the development of numerous urinary markers for diagnosis of bladder cancer. The number of publications identified through a PubMed search are enormous when “bladder cancer” and “biomarkers” or “molecular markers” are searched [2]. Many of them exhibit sensitivity superior to urine cytology, often with lower specificity. A few of them have been applied clinically, but none has been accepted as a standard diagnostic test in routine urology or included in published guidelines to date. Insufficient and inconsistent evidence for the use of such markers in surveillance of non-muscle-invasive bladder cancer is the reason for this [2,3].

The aim of surveillance in LG Ta tumors is mainly for the timely detection of recurrences. LG Ta tumors progress to more aggressive tumors in less than 1% of the cases. Recurrences are frequent, and the main prognostic factors are multiplicity of the tumors and rapid recurrence. Most guidelines advocate cystoscopy at 3 months after initial resection in order to detect rapid recurrence but subsequent cystoscopy at yearly intervals thereafter if no tumor is detected on first post-resection cystoscopy [4]. Besides that, office fulguration of small, isolated recurrences is an acceptable and widely used method for the treatment of recurrent LG Ta tumors.

What is the role of urinary cytology and markers in this context?
Requirements for a good marker in this context follow:

1. It must detect all high grade tumors while they are still amenable to curative treatment. Urinary cytology is highly sensitive in this regard and most commercially available urinary markers are even slightly more sensitive. The problem with cytology is interobserver variability [5,6] due to the subjectivity of the test. Urinary markers are more objective. The problem with the urinary markers is the frequent occurrence of false positive tests and thus the lack of specificity. As the likelihood of LG Ta to high grade tumors is low, cytology and markers are of limited value in this regard.

2. In order to be able to replace cystoscopy, a urinary marker should be able to detect recurrent tumors before they are large and numerous. Cytology performs poorly in this context. Several urinary markers do better but still do not detect a large proportion of the low grade tumors detectable by cystoscopy. Among the commercially available urinary markers, some of the best results for detecting recurrent LG Ta tumors have been obtained using immunocytology (uCyt). But even this test has not demonstrated adequate consistency and reliability to be able to replace cystoscopy. One potential role for urinary markers in the setting of LG Ta tumors is for reducing the frequency of cystoscopy wherein these markers can be utilized alternatively or interspersed with cystoscopy for surveillance. Most protein-based urinary markers such as NMP22 are affected by the volume of the tumor, but recurrent low grade tumors often are small. Larger, multiple LG Ta tumors could be better identified by urinary markers. Hence, urinary markers may have a role in a low intensity surveillance program where the cystoscopy interval is longer, such as 1 year, to monitor for larger, recurrent LG Ta tumors during the intervals. Large prospective randomized studies of alternative surveillance regimens incorporating urinary markers for low grade tumors are required to definitely establish the utility of such markers in the surveillance of LG Ta tumors.

3. The test should also be well accepted by the patient, regarding the risk of overlooking a tumor versus the discomfort and slight risks of the cystoscopy.

4. Preferentially tests should be point-of-care test, with results available readily, easy to perform, with a short learning curve, widely available, and not too expensive. Table 1 [7] gives an overview of how far the available urinary markers correspond to these criteria.

Numerous reviews on urinary markers have appeared in the last several years supporting the statements made above [8-14]. They have all come to the conclusion that urinary markers are insufficiently tested in surveillance of non-muscle-invasive bladder cancer and that cystoscopy cannot yet be omitted but at best can perhaps be delayed.

About the existing markers we can conclude the following: The BTA test has a very limited role because of its high false positive rate and low sensitivity in low grade tumors [15,16]. NMP22 similarly suffers from high false positive rate but may have higher sensitivity than cytology, and

### Table 1. Summary of main urinary markers that could be used in LG Ta UC

<table>
<thead>
<tr>
<th>Markers</th>
<th>Overall sensitivity (%)</th>
<th>Overall specificity (%)</th>
<th>Interference by BCG and other bladder conditions</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>UroVysion®</td>
<td>30-72</td>
<td>63-95</td>
<td>No</td>
<td>Expensive and laborious</td>
</tr>
<tr>
<td>Microsatellite analysis</td>
<td>58</td>
<td>73</td>
<td>No</td>
<td>Expensive and laborious</td>
</tr>
<tr>
<td>Gene microarray</td>
<td>80-90</td>
<td>62-65</td>
<td>No</td>
<td>Expensive and laborious</td>
</tr>
<tr>
<td>Immunocyty/ uCyt+</td>
<td>76-85</td>
<td>63-75</td>
<td>Yes</td>
<td>Good sensitivity in low-grade tumors</td>
</tr>
<tr>
<td>Nuclear matrix protein 22</td>
<td>49-68</td>
<td>85.8-87.5</td>
<td>Yes</td>
<td>Low sensitivity,</td>
</tr>
<tr>
<td>BTA stat</td>
<td>57-83</td>
<td>68-85.7</td>
<td>Yes</td>
<td>Low sensitivity</td>
</tr>
<tr>
<td>BTA TRAK</td>
<td>53.8-91</td>
<td>28.3-83.9</td>
<td>Yes</td>
<td>Low sensitivity</td>
</tr>
<tr>
<td>Cytokeratins</td>
<td>12.1-85</td>
<td>75-97.4</td>
<td>Yes</td>
<td>Low sensitivity</td>
</tr>
<tr>
<td>Survivin</td>
<td>53-90.4</td>
<td>88-100</td>
<td>No</td>
<td>Low sensitivity, expensive and laborious</td>
</tr>
</tbody>
</table>
with selection of patients the specificity can be improved [17-19]. Because of its high negative predictive value, it can be used to prolong the interval between cystoscopies. ImmunoCyt has the highest sensitivity in detection of low grade tumors and is less minimally affected by other urological diseases [20], but with a 60% detection rate of low grade tumors, the test remains largely insufficient to replace cystoscopy. The combination of ImmunoCyt with cytology appears to improve sensitivity and negative predictive value, which can allow for more accurate identification of those individuals who will have a negative cystoscopy [21].

Urovysion/FISH adds little in the surveillance of low grade tumors but can perhaps be used to adjudicate inconclusive results of urinary cytology (e.g., atypical) in order to prevent excessive work-up of such patients [22]. FISH may have a larger role in high grade and higher stage tumors as it can detect occult disease and identify those patients who are likely to recur and may be useful for predicting response to intravesical therapy [23,24]. Microsatellite analysis holds promise for predicting recurrences of low grade tumors, as it appears to be able to identify such recurrences in up to 80% of the cases but is lacking in sensitivity [25,26].

More recently, photodynamic diagnosis or fluorescent cystoscopy has been shown to be able to detect additional lesions compared to white light cystoscopy. In at least one study, photodynamic diagnosis using Hexvix was able to detect 25 additional LG Ta lesions in a cohort of 108 patients with Ta bladder tumors [27]. Several randomized studies have demonstrated the ability of fluorescent cystoscopy-aided TUR to reduce recurrences as well as improve recurrence-free survival. However, these data do not specifically pertain to those with LG Ta tumors but pertain to all non-muscle-invasive bladder cancer [27]. At this time, the precise role of photodynamic diagnosis in the diagnosis and follow-up of LG Ta tumors is evolving.

**SUMMARY**

Protein based urinary markers such as BTA and NMP22 may have better sensitivity than cytology for LG Ta tumors, but their specificity is too low to allow them to replace cystoscopy. ImmunoCyt has the best sensitivity for LG Ta tumors and can be used to prolong intervals between cystoscopy but cannot replace cystoscopy. FISH analysis does not have a clear role in diagnosis of LG Ta tumors. Photodynamic diagnosis may have benefit in enhanced detection of LG Ta tumors but is limited by low specificity and need for rigid cystoscopy.

**RECOMMENDATION**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Level of evidence</th>
<th>Grade of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>• BTA has little role in diagnosis of LG Ta tumors.</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>• NMP22 has better sensitivity than cytology but cannot replace cystoscopy.</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>• ImmunoCyt has good sensitivity for LG Ta tumors and can be used to prolong intervals between cystoscopy.</td>
<td>2a</td>
<td>B</td>
</tr>
<tr>
<td>• UroVysion/FISH has no role in diagnosis of LG Ta tumors.</td>
<td>2b</td>
<td>B</td>
</tr>
</tbody>
</table>

### II. UPPER TRACT STUDIES IN PATIENTS WITH LG Ta UROTHELIAL CARCINOMA

1. **UPPER TRACT STUDIES AT THE TIME OF DIAGNOSIS OF LG TA UROTHELIAL CARCINOMA OF THE BLADDER**

Urothelial carcinomas of the urinary tract exhibit a well-known tendency for multifocal growth. Despite this, the use of imaging to detect synchronous renal or ureteric urothelial tumors at the time of diagnosis of LG Ta urothelial carcinoma of the bladder is controversial. Some authors advocate routine imaging of the upper tracts while others suggest restricting such imaging to high risk patients, including those with multiple bladder lesions [28-31]. In addition, the optimal imaging technique remains undetermined.

Information regarding the incidence of synchronous upper tract urothelial carcinoma in patients with noninvasive urothelial carcinoma is difficult to interpret because most reports include patients with high risk disease such as carcinoma in situ in addition to those patients with low grade disease. Bajaj et al reported that 4 of 120 (3.3%) patients with Ta bladder tumors were diagnosed with a synchronous upper tract tumor [28]. Palou et al, in a retrospective analysis of 1529 patients with noninvasive urothelial carcinoma, found 6 synchronous upper tract tumors in 547 (1.1%) patients with LG Ta disease [29]. Goessl et al reported no synchronous upper tract tumors in 207 patients with noninvasive bladder cancer [30].

Little information is available regarding the clinicopathological features of low grade bladder cancers most likely to be associated with a synchronous upper tract urothelial carcinoma. It has...
been suggested that multifocal non-invasive bladder cancer is associated with a higher risk of concomitant upper tract disease but there is no evidence that this is the case if the bladder cancer is low grade [32]. Palou et al reported that only trigonal involvement was associated with upper tract urothelial carcinoma at diagnosis [29]. However, in this study low grade tumors were not analyzed in isolation and it is therefore possible that trigonal tumors were in fact high grade.

Intravenous urography (IVU) has traditionally been the gold standard in the detection of upper tract urothelial carcinoma. More recently, CT urography has emerged as a technique to evaluate the upper tract [33-35]. CT urography has a higher sensitivity and specificity compared with IVU and provides additional staging information, including imaging of pelvic lymph nodes and the detection of other intra-abdominal abnormalities. The positive predictive value of CT urography is over 80% for lesions greater than 5 mm [33].

**SUMMARY**

Synchronous upper tract urothelial carcinoma is rare in patients with LG Ta urothelial carcinoma. Routine IVU or CT urography is not recommended for these patients at the time of diagnosis. However, thorough upper tract evaluation is required for patients presenting with gross hematuria and/or unexplained positive urine cytology in the presence or absence of a low grade noninvasive bladder tumor.

**RECOMMENDATION**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Level of evidence</th>
<th>Grade of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Routine upper tract studies are not recommended for patients with LG Ta tumors at diagnosis of index tumor.</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>• Upper tract evaluation in patients with LG Ta urothelial carcinoma is recommended in the presence of:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>o gross hematuria</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>o unexplained positive urine cytology</td>
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</tr>
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</table>

**2. UPPER TRACT SURVEILLANCE OF PATIENTS WITH LOW GRADE Ta UROTHELIAL CANCER**

The presence of UC in the bladder is a well-recognized risk factor for the subsequent diagnosis of upper tract urothelial cancer [36]. Nevertheless, there remains considerable uncertainty regarding the value of routine upper tract imaging in the follow-up of patients with non-invasive urothelial carcinoma. Some investigators have recommended annual or biennial IVU, while others have concluded that there is no need for regular monitoring of the upper tracts [37-40]. This uncertainty is reflected in the wide variance in practice of community urologists [41].

**a) Incidence and Risk factors**

In a retrospective review of 375 patients with Ta urothelial carcinoma followed for a median of 6 years, Canales et al reported a subsequent upper tract tumor in 13 (3.4%) patients [36]. The risk of upper tract recurrence was the same regardless of the grade or number of initial Ta bladder tumor(s). Upper tract tumors were diagnosed at an average of 22 months after initial bladder tumor diagnosis. In the largest ever review investigating metachronous upper tract urothelial carcinoma in patients with bladder cancer, Wright et al studied almost 100,000 patients in the Surveillance, Epidemiology and End Results (SEER) registry [42]. Of 56,271 patients with a Ta bladder tumor at diagnosis, 472 (0.3%) were subsequently diagnosed with an upper tract urothelial carcinoma. This report is especially significant as it reflects the risk of recurrence in patients in community practice rather than from tertiary centers alone. The SEER analysis found that patients with Ta bladder cancer were more likely to be diagnosed with an upper tract recurrence than those with muscle-invasive bladder cancer, although this may reflect poorer overall survival in the latter group. The mean time to upper tract recurrence in the entire cohort was 33 months. Other reports place the risk of upper tract urothelial carcinoma in patients with Ta bladder cancer at 0.6-2.5% [40,42-45], with a wide range of upper tract recurrence intervals from 5 months to 6.2 years [38,39,46].

Canales et al used multivariate analysis to determine predictors of upper tract urothelial carcinoma in their cohort of patients with Ta bladder cancer [36]. They found that only patients with 2 or more recurrences within 12 months of diagnosis were at higher risk of upper tract tumor. Other studies group patients with Ta and high grade T1 disease together, making the data very difficult to interpret. These studies suggest
a weak link between tumor multiplicity, vesicoureteric reflux, and upper tract recurrence in non-muscle-invasive bladder cancer [38,42,47,48].

There is no evidence that the prognosis of patients with upper tract urothelial carcinoma after Ta bladder cancer is improved by early detection using routine surveillance IVU, compared to patients presenting with symptoms such as flank pain or gross hematuria [36,48,49]. This is also the case for high grade non-invasive bladder cancer requiring BCG [49,50]. Hence routine upper tract surveillance does not appear to have a clear benefit in patients with high grade lesions, and therefore can be expected to have even less relevance for those with low grade lesions. Such routine surveillance would only add cost and inconvenience to patients and not yield demonstrable benefit. Hence the strategy of routine upper tract surveillance for LG Ta urothelial carcinoma cannot be recommended.

**SUMMARY**

The incidence of metachronous upper tract urothelial carcinoma in patients treated for low grade, noninvasive bladder cancer is low, particularly in population-based analyses. There is no consistent risk factor for upper tract recurrence, which may occur years after initial diagnosis. There is no evidence that upper tract lesions detected on routine imaging are associated with a more favorable prognosis. Therefore, routine upper tract surveillance in patients with low grade Ta bladder cancer is not recommended.

### RECOMMENDATION

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Level of evidence</th>
<th>Grade of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routine upper tract studies are not recommended for surveillance of patients with LG Ta tumors during follow-up.</td>
<td>2b</td>
<td>B</td>
</tr>
</tbody>
</table>

### III. EXPECTANT MANAGEMENT OF LG Ta UROTHELIAL CARCINOMA

Complete transurethral resection is still considered to be the gold standard in managing noninvasive bladder tumors. Indeed, EAU guidelines note that the goal of TURBT in Ta tumors is to “make the correct diagnosis and remove all visible lesions,” and NCCN guidelines explicitly state that TURBT is the “standard treatment for cTa, low grade tumors.”[51,52] Current AUA guidelines also suggest that TURBT is the treatment of choice for most non-invasive bladder tumors, but go on to acknowledge the potential role of conservative management for certain patients with recurrent low risk noninvasive disease.[53]

In this section, we will address the potential role of observation of low risk bladder tumors by evaluating the rationale for such an approach as well as the clinical experience and reported evidence to date. The terms “observation,” “expectant management,” and “active surveillance” will be used interchangeably for these discussions and recommendations.

**Rationale**

Approximately 50% of newly diagnosed cases of bladder cancer are low risk papillary tumors (LG Ta) [54]. Although the majority of these patients will recur after initial TURBT, few will demonstrate grade or stage progression [55-57]. These frequent recurrences often result in repeat TURBTs, because urologists are taught to remove tumors when they are identified in accordance to past teachings and guideline recommendations. In other words, past and present practice has suggested that many patients will undergo multiple TURBTs to manage these small, recurrent, low-risk tumors.

In deciding treatment options, other important aspects are not only tumor recurrence rates but also grade and stage progression, as this denotes a decidedly poorer prognosis in bladder cancer. The natural history of low risk bladder tumors is well-established, and the rates of progression and mortality from bladder cancer in patients with this type of tumor are extremely low [55-58]. This is regardless of age at presentation. The low likelihood of progression and the indolent nature of certain types of bladder tumors may therefore have a negligible effect on survival in select patients who will die with their disease and not from it. [55]

Furthermore, though tumor resection is usually well-tolerated, it is not without risks, especially in the elderly or those with significant medical comorbidities. These patients face greater risks with regional or general anesthesia and often require postoperative hospital stays, both of which increase cost and the burden to our health care systems. [59] Complications directly associated with TURBT must also be acknowledged,
including bleeding and perforation in the short-term, and bladder contracture and urethral stricture in the long-term. [60]

Consequently, some have recently questioned as to whether such an aggressive follow-up and treatment regimen is warranted for these low risk patients. Surveillance for bladder tumors, as compared to prostate cancer or renal masses, is relatively easy to perform, as the clinician has direct ways to monitor the bladder urothelium through cytology and cystoscopy. Indeed, it has been shown in a study by Herr et al that low grade papillary tumors were accurately identified at cystoscopy 93% of the time, and when information from urine cytology was added, the accuracy increased to 99%. [61] Furthermore, the cystoscopic findings of bladder cancer are accurate in predicting muscle-invasive disease as well. [62] If staging and grading can be accurately performed by cystoscopy, many patients may be spared unnecessary trips to the operating room.

Therefore, the rationale for observation of low risk bladder tumors is to spare patients the morbidity and inherent risks of repeat TURBT. Short- or long-term surveillance of tumors has the potential to reduce the number of resections that patients would undergo in their lifetime. For the bladder cancer patient and the treating urologist, the proper balance must be found between the risk of progression and the patient’s current state of health and medical comorbidities. The decision to observe versus intervene is a balance between the morbidity of treatment and follow-up versus the risks of progression in each individual patient. As has been suggested by Soloway, “the emphasis should be to do no harm and to avoid over treatment.” [63]

Published Data

Soloway et al were the first to expectantly observe patients with low risk disease. They observed that in 32 patients with stage Ta or T1 tumors, only 3 (9%) progressed in either stage or grade, and none had progression to stage T2 disease. [64] Similarly, Gofrit et al also demonstrated that expectant management may be an acceptable course in patients with low risk disease. [65] They followed 28 patients for 38 observation periods. Although 30 of these periods were terminated because of recurrence or additional growth, all resected tumors were found to be Ta and grade 1 or 2 (i.e., none had grade or stage progression). They also observed that initial tumor diameter was predictive of tumor growth during the observation period.

Pruthi et al showed that the majority of patients with low-risk disease had no evidence of stage or grade progression on a surveillance program. [66] Two men (9%) were observed to have grade progression of their disease, with 1 (4.5%) having stage progression as well. Both men had evidence of moderate tumor growth and suspicious or malignant cytology heralding such progression and resulting in repeat TURBT. However, similar to the results of Soloway et al, neither of these tumors progressed to muscle-invasive disease. [64,66] Interestingly, these 2 men had prolonged histories of recurrent LG Ta disease before progression, thus demonstrating the ability of low risk tumors to progress even at distant follow-up. Accordingly, the recommendations for lifelong surveillance of all bladder tumor patients seem justified. In what appears to be the largest case series, Hernandez et al recently published their experience with observation in 66 patients with low risk bladder tumors. [67] In this series, the authors selected patients with smaller tumors (less than 1 cm), but also included patients with T1a disease, which are generally accepted as being higher risk than LG Ta tumors. Despite this, at a median follow-up of over 10 months, the majority of patients had neither stage (94%) nor grade (84%) progression, and, like the prior studies, no patient progressed to muscle-invasive disease.

From these series, there does not appear to be any clear patient selection criteria aside from the low risk features that were observed in the majority of patients. [64-67] Common findings in these studies included patients with Ta tumors, low grade disease, and low tumor burden (smaller tumors, fewer lesions). The studies often recommend careful and individualized patient selection. In fact, in the studies of Soloway et al and Pruthi et al, only a small percentage of their patient population were included into an observation protocol (8% and 13%, respectively). [44,66] Furthermore, most recommend detailed discussion with patients as to the rationale and strategy of observation. Indeed, in the study by Hernandez, the authors note that once the treatment alternatives were explained, a high percentage of patients preferred to undergo close monitoring by cystoscopy and to delay the surgery for as long as possible. [67]

There also exists a growing body of evidence as to the potential use of office fulguration for low risk tumors, i.e. partial or total tumor ablation during local cystoscopy, often at the time of surveillance. Although the present discussion is focused on the potential role of observation, office fulguration may serve as an appropriate alternative to formal TURBT in select patients. [68-70]

As urologists, we must weigh the risks and benefits of aggressive versus conservative treatment in dealing with non-invasive bladder tumors. The goal of TURBT is to eliminate any visible tumor, and this is the most assured way to prevent disease progression. However, it does so with an increased surgical and perioperative risk and cost. A balance must be found between the risk of progression and
the patient’s current state of health and medical comorbidities. Although expectant management appears to be a safe treatment option, it is likely not the best choice for everyone.

Of note, observation (or office fulguration), should not replace formal TURBT with the patient under anesthesia as primary treatment for the initial tumor or for recurrence suspected on gross inspection to represent a change in tumor stage or grade. TURBT not only establishes the clinical stage of the tumor, but it also serves as the basis for adjuvant treatment decisions and surveillance intervals. Whenever there is clinical doubt whether a patient is a candidate for observation or fulguration, the patient should always undergo a formal TURBT.

We must acknowledge several possible shortcomings of the data available in regard to the expectant management of LG Ta urothelial carcinoma. Most of the current evidence is from retrospective observational case series that do not have the strength of a randomized control trial, the gold standard of evaluating treatment efficacy and superiority. Accordingly, there have been no clear and uniform selection criteria for expectant management. In addition, certain assessments in the reported case series were of a subjective nature, including tumor growth assessments, decisions to intervene, and subsequent management. Nevertheless, qualitative assessments of tumor change combined with more quantitative evaluations of urine cytopathology seem to best reflect the tools used in everyday clinical practice. Such tools combined with the ability for urologists to appropriately determine, cystoscopically, when a recurrent tumor has progressed (without the need for TURBT or biopsy) as demonstrated by Herr et al, appear to be adequate in identifying early disease progression before muscle-invasive disease occurs. [61]

Future investigation should involve better quality studies with higher levels of evidence to evaluate 1) oncologic appropriateness of expectant management, 2) the impact of surveillance programs on the overall health status and survival of the patients (including potential benefits of avoiding repeated operating room procedures), 3) effects on quality of life in patients undergoing tumor observation versus repeat TURBTs, and 4) potential impact of surveillance programs on the economic costs and utilization of our health care systems.

**SUMMARY**

Observation can be considered for patients with recurrent LGTa urothelial carcinoma (or PUNLMP) as proven by prior TURBT. Optimal tumor characteristics include those with low tumor burden. Optimal patient characteristics include those with advanced age and comorbidities, those with frequent recurrences, and those without symptoms. Younger patients can also be offered observation as long as they are aware of the risks and benefits of immediate TUR vs. observation. Observation includes cystoscopy and urinary cytology at routine surveillance intervals. Patients should be appropriately counseled as to the treatment strategy and rationale, as well as to the potential risks inherent with observation of a malignant tumor. If the cytology is suspicious or positive, the patient should be taken to the operating room for a formal TURBT and other appropriate evaluation under anesthesia. If there is increase in the size and number of lesions, or other concerning changes on gross appearance of the urothelium, then the patient should be taken to the operating room for a formal TURBT under anesthesia. For small lesions (less than 1 cm) associated with negative cytology, office fulguration is also an option. This can be followed by immediate instillation of intravesical chemotherapy to prevent recurrence (see below).

**RECOMMENDATION**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Level of evidence</th>
<th>Grade of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Expectant management should be pursued only in patients with an established history of LG Ta urothelial carcinoma.</td>
<td>3</td>
<td>B</td>
</tr>
<tr>
<td>• Optimal tumor characteristics include low tumor burden.</td>
<td>3</td>
<td>B</td>
</tr>
<tr>
<td>• Observation is particularly applicable to those with advanced age or comorbidity, but can be offered to younger patients after careful and thorough discussion.</td>
<td>4</td>
<td>C</td>
</tr>
<tr>
<td>• Surveillance includes periodic cystoscopy and cytology.</td>
<td>3</td>
<td>B</td>
</tr>
<tr>
<td>• Patients who demonstrate increase in size, number or appearance of tumor(s), or develop positive urine cytology should cease expectant management and undergo formal TUR and further evaluation.</td>
<td>3</td>
<td>B</td>
</tr>
<tr>
<td>• Office fulguration is a good option for patients with small LG Ta urothelial carcinoma. This can be followed by immediate instillation of intravesical chemotherapy.</td>
<td>3</td>
<td>B</td>
</tr>
</tbody>
</table>
IV. INTRAVESICAL TREATMENT FOR LG Ta TUMORS

1. INTRAVESICAL CHEMOTHERAPY

In most cases of non-muscle-invasive bladder cancers, TURBT plays an essential diagnostic and therapeutic role, and this is certainly the case for LG Ta tumors. A careful cystoscopic evaluation and eradication of tumor is an important initial therapeutic intervention. While in some cases tumor ablation may suffice as initial therapy, intravesical chemotherapy plays an important role in decreasing the recurrence rates of these tumors.[71-73]

The rationale for perioperative instillation includes the destruction of residual microscopic tumor at the site of TURBT and of floating cells, thereby preventing reimplantation at the time of TURBT. Intravesical therapy can also be employed in a maintenance fashion as opposed to an induction course alone to prolong the beneficial effects of the chemotherapy.

Chemotherapeutic Agents

Chemotherapeutic agents include thiotepa, an alkylating agent that cross-links with nucleic acids; mitomycin, an antibiotic that inhibits DNA synthesis; epirubicin, doxorubicin, and valrubicin, intercalating agents that inhibit DNA synthesis; gemcitabine, a deoxyctydine analog that inhibits DNA synthesis.

a) Thiotepa

Introduced in 1961, thiotepa is the oldest and one of the least expensive of the intravesical drugs. Doses range from 30 mg in 30 mL of sterile water or saline to 60 mg in 60 mL of water or saline. The usual regimen consists of 6 to 8 weekly instillations followed by monthly instillations for 1 year, but there is no standard regimen. A low molecular weight of 189 KD increases possible systemic toxicity, and myelosuppression is a risk. Importantly, the 2007 AUA Guidelines do not recommend thiotepa as an effective chemotherapy agent. [74]

b) Mitomycin C

This agent has a molecular weight of 329 KD, and the side effect of myelosuppression is less likely. Although the optimal method of mitomycin C administration is uncertain, Au et al [75] have demonstrated improved recurrence-free survival and a prolonged median time to recurrence using methods to enhance the effectiveness of this medication. The strategy consisted of a period of dehydration (no fluids for 8 hours prior to treatment), urinary alkalization (1.3 g NaHC03 by mouth, the night prior, the morning of, and 30 minutes prior to the intravesical therapy), confirmed complete bladder drainage prior to intravesical instillation of mitomycin C (post void residual less than 10 mL by ultrasound bladder scanner), and a higher mitomycin C concentration (40 mg in 20 mL of sterile water). Other methods exist but have been examined in higher risk individuals.

c) Intercalating Agents (Doxorubicin, Epirubicin, and Valrubicin)

Because of its high molecular weight of 580 kD, absorption and systemic toxicity of the anthracycline derivative doxorubicin are extremely rare. Doses vary widely, from 10 mg to 100 mg, in instillation schedules that range from 3 times a week to once a month. Epirubicin is related chemically to doxorubicin and has been used in multiple studies for initial post-TUR instillation as well as for multi-dose intravesical chemotherapy. It appears to have a favorable toxicity profile and good efficacy. It offers an attractive alternative to mitomycin C. Valrubicin, a semi-synthetic analog of doxorubicin, was approved by the US FDA in 1998 for the treatment of BCG-refractory carcinoma in situ of the bladder in patients who are medically unfit or refuse a cystectomy.

d) Gemcitabine

Gemcitabine has a broad spectrum of antitumor activity and intravesical gemcitabine has been shown to have activity in non-muscle-invasive bladder cancer in intermediate risk and high risk patients. Typical intravesical doses employed include 2 g in 50 to 100 mL of saline given weekly for 6 weeks with 2 hour dwell times. Gemcitabine is currently being tested for post-TUR instillation in all tumors as part of a study sponsored by the Southwest Oncology Group in the US. In a randomized placebo controlled study, Bohle et al [76] compared post-TUR instillation of gemcitabine to bladder irrigation with saline and found no difference in recurrence rates for tumors of all stages/grades. Hence immediate post-TUR instillation of gemcitabine does not appear to yield any benefit over bladder irrigation in preventing recurrences in patients with LG Ta urothelial carcinoma.

e) Therapeutic Schedules

The ideal intravesical chemotherapy regimen would maximize effectiveness while decreasing the number of therapies and maintaining a favorable side effect profile. Data, although sometimes conflicting, is available regarding the likelihood of treatment efficacy for these agents. Recent meta-analyses have attempted to clarify a sometimes murky picture. Further clouding the situation is the fact that most studies do not focus solely on LG Ta tumors but instead on higher risk tumors.

f) Perioperative Chemotherapy

A European Organisation for Research and Treatment of Cancer (EORTC) study comparing epirubicin to water immediately following TURBT demonstrated
that patients with primary and solitary recurrent Ta tumors had a 50% decrease in recurrence with epirubicin. [77]

In a meta-analysis performed by the AUA Guidelines Panel in 2007, a statistically significant 17% decrease (95% CI 8-28%) in median recurrence rate was found. No effect on progression was noted [4]. Two trials were identified by the AUA Panel as suitable for meta-analysis and included a combined 427 patients. In the larger trial by Tolley et al [78], 60% of the subjects treated with TURBT alone had recurrences at 5 years compared to 45% of those receiving a single, postoperative instillation of 40 mg of mitomycin in 40 mL of water. Solsona et al [79] reported a statistically significant decrease in early recurrence of up to 2 years in patients who received the single dose of mitomycin C. This study did focus on lower risk patients; all patients had a 3 cm or less single, papillary, primary, or recurrent tumor and were disease-free for more than 1 year. Patients with muscular invasion, G3 tumor, or bladder carcinoma in situ on pathologic examination were excluded from this study.

Another large meta-analysis confirms the effectiveness of single perioperative chemotherapy versus TURBT alone for decreasing recurrence. This meta-analysis was performed including 7 randomized trials, each evaluating the clinical value of a single immediate instillation of various chemotherapeutic agents, and reported a 39% decrease in the odds of recurrence compared to placebo, i.e., TUR alone [80]. In recurrent and multiple tumors, the benefit of the early instillation is insufficiently proven by a lack of statistical power and therefore challenged [81]. To be effective, the instillation should be performed on the same day as the TUR, as delayed instillation does not appear to yield similar benefits.

In a recent randomized placebo-controlled trial, the efficacy of a single postoperative instillation of gemcitabine (2 g/100 mL of saline) was examined. In this study of 355 patients with primary or recurrent Ta or T1, grade1-3 tumors, gemcitabine was not superior to saline bladder irrigation in terms of recurrence-free survival [76]. The recurrence rate was very low, suggesting that the bladder irrigation plays a role in prevention of recurrence, an observation that needs further exploration.

The most common side effect of intravesical chemotherapy is some form of lower urinary tract symptoms (dysuria, frequency, and urgency) and hematuria. **Perioperative mitomycin C should not be administered to patients with a known or suspected bladder perforation following TURBT as a small number of serious complications related to mitomycin C extravasation have been reported** [82].

**g) Induction Chemotherapy**

At this point, it is unclear if any chemotherapeutic agent holds superiority over another. A recent trial advocated the superiority of gemcitabine over mitomycin C, but the dosing schedule used was different from those employed in prior studies [83]. Importantly, although maintenance regimens are essential in higher risk disease such as CIS, there is no evidence that multiple adjuvant instillations of either BCG or chemotherapy have additional benefit in patients at initial diagnosis of LG Ta urothelial carcinoma [74]. Thus, for initial LG Ta tumors, **it is difficult to justify long-term and/or maintenance doses of therapy.** Therapy should be individualized based on the prognostic factors of the patient’s tumor.

**SUMMARY**

A well-performed, complete transurethral resection of the bladder tumor is a critical initial step in the management of LG Ta tumors and prevention of recurrences. Immediate post-TUR instillation of intravesical mitomycin C or epirubicin is recommended, as it has been shown to prevent recurrences. Induction with or without maintenance intravesical chemotherapy for LG Ta tumors may have benefit, but this has not been established unequivocally. Given that these patients have a very low risk of progression and metastases, the risks of repeated courses of intravesical chemotherapy have to be weighed against the benefit. Hence we recommend an extremely judicious and limited use of repeated courses of intravesical chemotherapy in this population.

**RECOMMENDATION**

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<td>• The initial step in management is complete TUR.</td>
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<td>• Immediate post-TUR instillation of intravesical chemotherapy in the form of mitomycin C or epirubicin is recommended as it can prevent recurrences.</td>
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<td>• Induction chemotherapy with or without maintenance has unclear but potential benefit.</td>
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<td>• The risks of repeated courses of intravesical chemotherapy have to be weighed against the benefit.</td>
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I. IMMUNOTHERAPY (BCG) IN LG Ta PATIENTS

Low risk non-muscle-invasive bladder tumors are characterized by a moderate recurrence rate from 24-37% but with very low progression rates from 0-1.7% [4]. Taking these figures into account the primary therapeutic objective for low risk patients is to reduce recurrence rate and the secondary objective is early detection of progression. To decrease progression rates in these patients would mean an overtreatment including unnecessary side effects, as the vast majority of patients will never develop progression, so this is not a realistic objective for these patients. To reach an appropriate balance between efficacy of the different therapeutic approaches and their potential toxicity is the main goal for patients with LG Ta disease.

In several comprehensive studies comparing the efficacy of intravesical chemotherapy [84,85] or BCG [86] versus observation, there was a significant reduction of recurrence rate in the intervention arm compared to the observation arm and BCG was significantly superior to chemotherapy [87]. However, according to risk groups, BCG was clearly superior to intravesical chemotherapy in terms of decreasing recurrence and preventing or delaying progression, but only when BCG maintenance is applied [88-90]. However, in intermediate risk groups there is a great controversy regarding the efficacy between intravesical chemotherapy or BCG [86,91-93], but the toxicity is significantly superior for BCG. In summary, intravesical chemotherapy or BCG represent alternative approaches for these patients [4]. In low risk patients, immediate instillation of a chemotherapy agent is considered the standard of care as a meta-analysis clearly demonstrates a significant reduction in recurrence rate compared to observation [91]. However, in cases of multiple tumors, this approach is insufficient and a complete course of chemotherapy is required [80,94]. Although there is no evidence that BCG is superior to intravesical chemotherapy in this setting, intravesical BCG constitutes a clear overtreatment with unacceptable toxicity [4] following the results in the intermediate risk group as mentioned above.

Despite the significant decrease in recurrence rate with an immediate post-TUR instillation of chemotherapy and/or following a complete course of chemotherapy in patients with multiple tumors, around 30% of patients will have recurrence [4]. In these cases, a different chemotherapeutic agent can be effective in controlling recurrence. In a recent randomized trial of 96 recurrent Ta or T1 tumors, intravesical mitomycin C showed a 50% disease-free survival with a mean follow-up of 65.7 months, outlining the equivalent efficacy of intravesical chemotherapy compared to BCG therapy as rescue therapy after initial intravesical chemotherapy failure [95].

The role of intravesical BCG as rescue therapy after chemotherapy failure in low risk groups has been analyzed in a meta-analysis carried out by Shelley et al [87]. They examined 1901 patients and found no significant difference in the efficacy between intravesical BCG and mitomycin C. However, BCG was significantly superior to mitomycin C in a subgroup analysis involving patients at high risk of recurrence (p=0.0008). Corroborating these data, in a randomized trial including 174 patients with recurrent papillary Ta or T1 tumors and comparing mitomycin C versus BCG, with a median follow-up of 64 months, BCG achieved a 43% disease-free survival superior to 34% with mitomycin C but the difference was not statistically significant (p=0.22) [96]. In another randomized trial [97] including 89 patients with frequent recurrent Ta or T1 tumors without bladder Tis, at 20 years of follow-up, 80% of patients who received mitomycin C developed recurrence compared to 59.1% of those who received BCG (p=0.005). These data also show the efficacy of BCG as rescue therapy in patients with recurrent tumors and BCG appears to be superior to intravesical chemotherapy in the rescue setting.

In a randomized trial comparing intravesical BCG and mitomycin C with planned cross-over following failure of initial therapy, of 39 patients who failed mitomycin C and received rescue BCG, 19 (32%) remained disease-free. On the other hand, 21 received mitomycin C after BCG failure and 4 (19%) also remained free of disease [96]. In a meta-analysis including 9 randomized trials on 2261 patients comparing intravesical chemotherapy and BCG, Huncharek [92] observed that in patients with prior intravesical chemotherapy (1480 patients), BCG significantly reduced recurrence rate compared to intravesical chemotherapy with a reduction in tumor recurrence rates of 46%, 49%, and 57% at 1, 2, and 3 years respectively [92]. In another recent meta-analysis comparing intravesical mitomycin C and BCG, analyzing patients who received prior chemotherapy, BCG was superior to mitomycin C (p=0.0264), reducing recurrence rate. These data support the superiority of BCG as rescue therapy in cases of recurrent tumor receiving intravesical chemotherapy [89]. Whether BCG should be used as rescue therapy after intravesical chemotherapy failure or after a second line of intravesical chemotherapy is unknown. Despite the fact that many of these studies included patients of different stages and grades and were not restricted to LG Ta, it appears that BCG is effective in salvaging a response in some low risk patients who do not respond to intravesical chemotherapy.
VI. OTHER IMMUNOMODULATING THERAPIES

As BCG is generally considered to be the most effective intravesical agent for non-muscle-invasive bladder cancer (91), there has been interest in developing and testing other immunomodulating agents against this disease entity. The aim of researchers has been to search for an alternative immunological agent with one of the following properties:

- is more efficient than BCG in lowering recurrences or progression rates.
- is as effective as BCG, but has lower rates of adverse events.
- has acceptable efficacy and adverse events, but can be used as a secondary agent in patients intolerant or unresponsive to BCG.

Regarding patients with low grade Ta tumors, an agent with less adverse events but with efficacy similar to BCG would be of clinical value. Today, BCG is not recommended as a first-line therapy in this group of patients [4] given the higher risk of adverse events in comparison to recommended first-line chemotherapeutic agents, such as mitomycin C and epirubicin.

So far, despite considerable efforts, no alternative immunologic treatment has been shown to have comparable efficacy to BCG for the treatment of urothelial carcinoma. Of the several agents showing promise, few have been evaluated in clinical trials. Further, none of these agents have been specifically tested in LG Ta tumors, and, while such tumors may have been part of the cohorts tested, the value of these agents in treating patients with recurrent LG Ta tumors is unclear at this time.

Interferon-alpha and Keyhole limpet haemocyanin (KLH) have been compared to BCG in randomized clinical trials to test their utility in preventing recurrence and progression in non-muscle-invasive bladder cancer, but both were found to be significantly less effective [98, 99].

Research on alternative immunomodulating agents has primarily focused on patients with high risk of progression, that is those in whom BCG currently is recommended as a first-line treatment, which is covered in another chapter. Future immunotherapeutic efforts will undoubtedly benefit from the gradually increasing understanding of the immunobiology of bladder cancer. This will hopefully lead to new immunologic treatment alternatives for this group of patients.

SUMMARY

Secondary immunomodulating therapies do not appear to have a role in management of LG Ta urothelial carcinoma. Most of these agents have been tested in high risk non-muscle-invasive bladder cancer and hence their role and efficacy against LG Ta tumors is unclear.

RECOMMENDATION

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95. Reference needed – Solsona


97. Solsona E. Early single instillation is very beneficial and should be the standard approach in non-muscle invasive bladder cancer. Eur Urol. 2009; suppl 8: 464.

98. Reference needed – Solsona


Committee 5

High grade Ta, CIS, and T1 Urothelial Carcinoma

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High grade Ta, CIS, and T1 Urothelial Carcinoma

MAXIMILIAN BURGER, FRED WITJES
MARKO BABJK, MAURIZIO BRAUSI, CHRIS CHENG,
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I. HIGH GRADE TA UROTHELIAL CARCINOMA

1. INTRODUCTION

Stage pTa urothelial carcinoma represents the majority (60-75%) of bladder cancer cases [1]. In general, these tumors show high recurrence but low progression rates [2].

2. DIAGNOSIS

Pathologists diagnose pTa urothelial carcinoma when they find a mucosal layer of more than 8 cell lines in a resected specimen with features of anaplasia [3]. In contrast to stage T1 urothelial cancer, the basement membrane is always intact. Only about 20% of pTa cancer is high grade (grade 3) [3].

In contrast to low grade disease, the diagnosis of high grade Ta urothelial carcinoma is facilitated by urinary cytology with sensitivity and specificity rates of over 90% [4,5]. Urinary tumor markers are of limited importance for Ta tumors. Markers of the hyaluronic acid family seem to be the most promising urinary markers for this entity, exhibiting prognostic significance for recurrence [6]. Nuclear matrix protein 22 (NMP22) and other commercialized tests have not been shown to be of any advantage when compared to cystoscopy [7].

Without taking into account associated factors, patients with multifocal stage Ta high grade urothelial carcinoma have the third highest risk of both recurrence (around 40% after 1 year) and progression (5% after 1 year) [2]. While external evaluation of recurrence rates showed a good correlation with the EORTC risk tables, prediction of progression seems less concordant [8,9].

3. TREATMENT

a) Turbt

Studies on the quality of transurethral resection of bladder tumors (TURBT) showed that the residual tumor rate of Ta urothelial carcinoma was 70% 4 weeks after first resection in a high-volume department [10]. Fluorescence-guided resection has been proven to improve the detection rates of bladder tumors not only in CIS but even in papillary carcinomas of the bladder, resulting in lower residual tumor levels and a lower subsequent recurrence rate [11,12,13,14]. Improving TURBT has become a major focus of attention for two reasons. Firstly, subsequent bacillus Calmette-Guérin (BCG) and mitomycin C (MMC) instillation therapy is more effective in patients after a complete TURBT [15,16]. Secondly, an adequate TURBT, i.e., one which provides sufficient tissue for histopathological analysis, is crucial for proper staging. The presence of detrusor muscle in the TURBT specimen is regarded as a surrogate parameter of resection quality [17]. A restaging TURBT provides more tissue for pathological examination and thus allows better staging. Accordingly, repeat TURBT is advised in high risk non-muscle-invasive cases.

Equally, an adequate TURBT is crucially important in determining the optimal treatment modality for any given patient. The presence of detrusor muscle in the TURBT specimen is of particular importance for pT1 tumors. Several studies dealing with the quality of TURBT or a second TURBT also indicated that a better resection also lowers the recurrence and progression rates and improves the reaction to BCG as well as the prognosis of the patient [16-19].

b) Instillation Therapy

While one immediate instillation is sufficient in
prophylaxis of recurrence and progression for low grade Ta urothelial carcinoma, the prognosis of patients with high grade Ta disease can only be improved with maintenance BCG therapy [1]. Decreased recurrence rates subsequent to BCG maintenance have also been reported in intermediate risk tumors, although the more severe toxicity of BCG when compared with intravesical chemotherapy has to be taken into consideration [20]. The impact of maintenance BCG on progression of high grade pTa urothelial carcinoma remains unclear [21,22].

**HIGH GRADE TA UROTHELIAL CARCINOMA: RECOMMENDATIONS**

1. Suspicious urinary cytology and papillary tumor on cystoscopy are highly suggestive of high grade Ta urothelial carcinoma. (LOE 3, Grade B)

2. A complete resection has to be pursued. If there is any question regarding the completeness of the initial TURBT, repeat TURBT is advised. (LOE 2, Grade A)

3. BCG instillation therapy should be initiated in patients with high grade pTa urothelial carcinoma. (LOE 1a, Grade A)

**REFERENCES**


II. CARCINOMA IN SITU OF THE URINARY BLADDER

1. INTRODUCTION

Carcinoma in situ (CIS) is malignant neoplasia of the urothelium, which is flat and not protruding into the bladder and which does not invade the lamina propria. That being said, it is nonetheless considered to be an aggressive tumor entity due to its level of dedifferentiation. The current WHO classification defines CIS as “a non-papillary, i.e., flat, lesion in which the surface epithelium contains cells that are cytologically malignant... CIS shows nuclear anaplasia identical to high grade urothelial carcinoma” [1]. This morphological appearance is reflected in the molecular signature of CIS. While low grade non-invasive lesions are thought to derive from chromosome 9 abnormalities and mutations in the fibroblast growth factor receptor gene, CIS is marked by deletions of 19p13 resulting in TP53 mutations and chromosome 9 abnormalities and mutations in the fibroblast growth factor receptor gene, CIS is marked by deletions of 19p13 resulting in TP53 mutations and consecutive prevention of cell cycle arrest and generalized genetic instability [2]. DNA aneuploidy is found in more than 90% of CIS lesions [3].

CIS was first reported as a distinct phenomenon by Melicow in 1952. [4] Despite the non-invasive character of CIS, it was suspected to possess aggressive tumor biology and tendencies towards early progression were described [5]. This notion has been supported by the incidence of CIS. CIS is found in approximately 3% of all patients with bladder cancer, concomitantly with invasive bladder cancer in 50%, and with muscle-invasive disease in 60% [6,7,8]. As a consequence, CIS has been suggested as a precursor lesion of invasive disease [9,10] and concomitant CIS as a significant risk factor for poor outcome. The tendency towards progression to muscle-invasive stages is in part determined by the presence of CIS; the EORTC risk score by Sylvestre et al attaches significant weight to its presence [11]. While CIS is also potentially related to an adverse outcome in muscle-invasive stages, this has not been implied in current nomograms [12,13,14].

In addition to the notion that CIS conveys a poor prognosis, the initial reports also described its diffuse appearance [4,5]. Indeed, CIS is more typically related to multiple as opposed to single tumor locations. Urothelial cancer within the urinary bladder is accompanied by tumors of the prostatic urethra generally 7 times more often and by tumors of the upper urinary tract nearly 5 times more often if CIS is also present [15,16].

2. DIAGNOSIS

For most stages of bladder cancer and indeed in most cases, macroscopic hematuria is symptomatic of CIS. CIS causes irritative LUTS more often than papillary lesions. Three characteristics determine the diagnostic workup: (a) CIS lacks profound cellular cohesion within the lamina mucosa; (b) its growth pattern is flat and lacks protrusion into the bladder; and (c) it may be found throughout the urinary tract.

The lack of profound cellular cohesion prompts the use of urinary cytology to aid in the diagnosis of CIS [17]. CIS can be reliably detected and followed up by urinary cytology, and sensitivity and specificity have been reported to exceed 90% [18]. However, cytology may be hampered by inflammation (e.g., following instillation therapy) and distinguishing malignant from reactive non-neoplastic cells may become challenging [19]. Accordingly, novel tests have been described. One of the more promising is a multicolor fluorescence in situ hybridization (FISH) assay assessing chromosomal abnormalities in DNA in urine samples. While this FISH test has a low sensitivity for low grade tumors lacking chromosomal abnormalities, it detects high grade carcinomas and CIS with reliable sensitivity [20]. In contrast, its specificity does not seem to exceed that of urinary cytology significantly, and FISH has not been broadly used in the diagnosis of CIS, although a combination with cytology has been suggested as advantageous in the initial detection and follow-up of patients with CIS [21,22]. To date, no further molecular tests have been established in the diagnosis of CIS.

The second trait, i.e., its flat growth pattern, may defy cystoscopic detection. Classic white light cystoscopy has been shown to miss up to 50% of cases. Photodynamic diagnosis employs a fluorescent substance, (hexyl-)aminolevulinic acid, which accumulates fairly selectively in neoplastic cells. Blue violet light causes the photosensitizing agent to emit a reddish fluorescence [23]. Randomized trials and a recent meta-analysis show a significantly improved diagnostic accuracy of 39% for CIS [24,25,26] and its use has been suggested to be especially valuable in the detection of flat lesions when malignant cells are present in urinary cytology and there is an absence of suspicious lesions in white light cystoscopy [23,27,17]. Definitive diagnosis is based on the histopathological evaluation of tissue samples by resection or cold-cup biopsy, although...
the restrictions of inter- and intraobserver reliability also have to be taken into account [28,29].

The third trait, i.e., the presence of CIS throughout the urinary tract, warrants a workup of the entire urinary tract. Although little specific data exist, sampling the prostatic urethra and each upper urinary tract for urinary cytology needs to be considered should no lesions be found on cystoscopy or IVU, CT, or renal ultrasound[17].

Because of the high likelihood that CIS will progress, subsequent follow-up to specific therapy is generally recommended, as with patients with non-muscle-invasive bladder cancer at high risk of progression: cystoscopy and urinary cytology every 3 months for a period of 2 years, every 4 months in the third year, every 6 months in the fourth and fifth years, and annually thereafter. In addition, ultrasound, conventional IVU, or CT imaging of the upper urinary tract should be performed periodically [17,30].

3. PATHOLOGY AND RISK ASSESSMENT

As there is a frequent association with invasive disease, CIS is clinically classified into different types: (a) primary CIS—isolated with no previous or concurrent papillary tumors; (b) secondary CIS—detected during the follow-up of patients with a previous papillary tumor; and (c) concomitant CIS—in the presence of papillary tumors [31,32]. Genetic and molecular approaches have underlined the relationship between CIS and invasive carcinoma. CIS has a variable histological appearance with different morphologic subtypes, described by McKenney in 2001 [33]. All these elements are part of the prognosis and will be discussed below.

a) Clinical prognostic factors

1. Gender

Men are more likely to present with CIS (p=0.001), although gender does not seem to affect prognosis [34]. On the other hand, age does play a role, with younger patients having a better outcome [35,36].

2. Location

CIS of the bladder is also a known risk factor for developing upper urinary tract tumors after a radical cystectomy to treat urothelial carcinoma of the bladder [37]. Volkmer et al reported in a series of 1420 patients that the presence of CIS after a radical cystectomy was a risk factor for recurrence in the upper urinary tract (RiskRatio 2.3) [38]. Similarly, Youssef et al. demonstrated that bladder CIS is an independent predictor of disease recurrence and cancer-specific mortality after a radical nephroureterectomy for upper tract urothelial carcinoma (p=0.006 and p=0.045 respectively) [39]. Prostatic urethra involvement of CIS has been observed in less than one third of cystoprostatectomy specimens [40,41] and in the prostatic urethra or prostatic ducts in 15%. The latter location shows a significantly higher rate of lymph node metastasis and a lower 5-year survival rate[42]. No difference was observed in recurrence or disease-free survival for either uni- or multifocal CIS or CIS location (urethral vs. vesical) [43].

3. Chronology of CIS

In the group of patients with primary CIS, progression and death from disease seems to be rather unusual, although more common in the group with concomitant CIS [44]. Secondary CIS associated with pTa and/or high grade infiltrating tumors historically has had the worst prognosis. Recent data presented results to the contrary, with a higher rate of progression in primary CIS rather than in secondary CIS after BCG therapies [45]. In this series, the authors observed a better response to treatment in the group of primary vs. secondary CIS and the 5-year cumulative incidence of progression was also higher in the primary vs. secondary group of CIS [45].

4. Intravesical Therapy and CIS

Numerous publications have shown that response to intravesical treatment impacts prognosis. However, few data are available concerning patients who have CIS without any association with a pTa or pT1 tumor. Several small studies could not confirm a correlation between response to treatment, type of CIS, and prognosis [34,46,47,48]. One reason for this might be the frequent association of CIS with high grade tumors, which could be responsible for the difficulties in discerning an independent prognostic effect for CIS [34]. A lack of response to BCG should therefore be regarded as a poor prognosticator.

5. Molecular and Immunohistologic Parameters

Molecular signatures can be used as diagnostic or prognostic tools [49,50,51], such as p53 mutations, amongst others [52].

Aurora-A is a serine/threonine kinase that activates the centrosome, which plays a role in cell division. Aurora-A overexpression results in the misaggregation of chromosomes and chromosomal instability that eventually explains aneuploidy [53,54]. Aurora-A overexpression in CIS has been correlated to the risk of relapse and progression [55].

In accordance with the histological appearance of CIS and the discohesive pattern of cell growth, adhesion molecule expressions were evaluated. E-cadherin negative tumor cells were able to infiltrate the normal urothelium as individual cells, whereas tumor cells with a homogeneous expression of E-cadherin exhibited sharp differences with normal tissue [56,57]. Shariat showed that E-cadherin expression was independently associated with disease progression and cancer-specific survival [57].

Cyclin D3 has a pivotal role in progression from G1
to S phase in the cell cycle. Cyclin D3 expression is amplified in secondary concomitant CIS as opposed to primary isolated CIS and is related to recurrence and progression-free survival (p=0.002) [46]. In clinical use, however, no marker is used routinely, and the value of other single markers, genomic profiling, and epigenetic markers for progression in CIS remains to be determined.

6. Pathology

In 2001, Mc Kenney et al described four different morphological subtypes of CIS (large cell pleomorphic, large cell nonpleomorphic, small cell, and clinging/denuded). The most frequent pattern is the large cell pleomorphic type, with cells showing considerable nuclear variations and architecture characterized by a loss of polarity. The most difficult form to recognize is the clinging/denuded form, when the urothelium may be extensively denuded (Figure 2). In the latter case, cytology is very important, as detached malignant clusters or isolated cells in voided urine permit differential diagnosis from artifacts of biopsy or cystitis.

Mc Kenney et al suggested that denudation reflects rapid cell turnover and therefore potentially more aggressive tumors. Nevertheless, they underlined that individual patterns do not carry any known clinical significance and that subclassification might confuse urologists [33]. Molecular arguments and histological observations strongly support the hypothesis that a natural history in the development of CIS might exist. Molecular alterations precede phenotypic changes and end in morphologic changes seen on routine staining. Early alterations during mitosis, chromosomal instability and aneuploidy are reflected by nuclear atypia and chromatin densification, leading to the development of malignant urothelial cells. In a further step, polarity and cell-to-cell adherence are altered, resulting in denuded forms of CIS with detached cell clusters in cytology and few cells remaining on the surface. Eventually, via mechanisms not yet understood, CIS develops into invasive urothelial carcinoma.

Three rare subtypes of CIS must be considered separately for their potential prognostic significance. The first is non-invasive micropapillary CIS. It was recently demonstrated that CIS associated with micropapillary invasive cancer increased recurrence upon univariate and multivariate analysis. Furthermore, all superficial micropapillary CIS displayed an invasive component [58]. Another rare variant is the in situ squamous cell carcinoma (SCC). SCC is frequently associated with an invasive component. The last of these rare subtypes is in situ adenocarcinoma, which is associated with classical CIS and frequently with invasive carcinomas with a poor prognosis such as micropapillary and small cell CIS [59]. If these subtypes are reported, the urologist should be aware of their danger, rebiopsy, especially if the biopsy lacks detrusor muscle, and closely follow the patient.

CIS is an aggressive high grade disease. Pathologists should be able to recognize the different features of CIS. Bladder biopsies and cytology are a precondition for accurate diagnosis and targeted treatment. An association with urothelial carcinoma of the upper urinary tract, prostatic urethra involvement, secondary CIS associated with other urothelial tumors, multifocality, age, and non-response to BCG are all negative clinical prognostic factors. Loss of E-cadherin, MUC-1, and overexpression of Aurora-A and CyclinD3 are considered bad molecular markers for patient outcome.

4. Treatment

a) Cystectomy

In patients with CIS and concomitant muscle-invasive bladder tumors, cystectomy is the treatment of choice. A partial cystectomy or radiotherapy is insufficient. In patients with CIS with and without concomitant non-muscle-invasive (Ta or T1) papillary tumors, there is no consensus regarding the optimal course of treatment: cystectomy or a more conservative treatment strategy. There are no randomized trials that have addressed this question.

Several recent papers have discussed the cystectomy results in patients thought to have only CIS prior to cystectomy [60,61,62]. A common theme in these studies was the clinical understaging in a third or more of the patients. Although the disease-specific survival rates in these studies ranged from 85-90%, early cystectomy represented overtreatment in approximately 50% of patients.

When a conservative treatment strategy is chosen, the transurethral resection (TUR) of all concomitant papillary tumors is mandatory for correct staging and grade determination. A TUR alone is insufficient, as CIS can be missed at cystoscopy and, without further treatment, 50% or more of patients with CIS will progress to muscle-invasive disease [63,64].

b) Intravesical Chemotherapy

As previously summarized, various intravesical chemotherapeutic regimens have been compared in patients with CIS [65,66,67]. The number of patients included in these studies has often been small. Consequently, definitive conclusions cannot be drawn from the individual studies. Complete response rates approaching 50% have been observed; nonetheless, there may be important differences between these studies with respect to patient characteristics and assessment of response to treatment (level 1). Since 50% of the complete responders on chemotherapy recurred during follow-up, complete response alone is not a suitable endpoint because
of the risk of invasion and extravesical recurrence. Indirect comparisons in a meta-analysis of 355 CIS patients treated with intravesical mitomycin C (MMC), Adriamycin, epirubicin, or sequential MMC/Adriamycin suggest that long-term disease-free rates might be better with MMC [67]. However, direct randomized comparisons do not exist (level 2).

c) Intravesical BCG

Intravesical bacillus Calmette-Guérin (BCG) has been widely used in the treatment of patients with CIS. The standard induction schedule of 6 weekly instillations yields a complete response rate of approximately 70%, although complete response rates over 80% have been reported in individual studies (level 1) [65,67,68]. About 40-60% of patients who do not respond to the initial 6 instillations will respond to a second series of 6 weekly instillations (level 2) [69,66]. Based on the results of several studies and meta-analyses, 1 to 3 years of maintenance BCG therapy is recommended in complete responders (level 1) [70, 67, 71, 72, 73]. Only half of all CIS patients will remain disease-free; approximately one-third of all complete responders will eventually recur. If recurrence occurs more than 1 year after BCG treatment, a re-induction with BCG can be considered (level 3) [74].

These studies have all been carried out with “full dose” BCG. However, a study in 155 patients with high risk T1G3 and CIS disease concluded that a one-third dose was as effective as a full dose BCG course, and was associated with significantly less toxicity (level 1) [75].

d) Comparison of Intravesical BCG to Intravesical Chemotherapy

Various randomized studies in high risk patients have compared intravesical BCG to either no further treatment, intravesical chemotherapy, or other immunotherapies post TUR. Unfortunately, separate results in CIS patients are often unavailable in many of these studies that also included patients with papillary tumors. A meta-analysis of 403 patients with CIS showed that BCG reduced the risk of progression by 35% compared to either intravesical chemotherapy or a different immunotherapy (level 1). Twelve percent of patients with CIS on BCG progressed as compared to 16% of patients receiving other treatment strategies [70].

Previous reviews in 2005 identified 12 randomized trials that compared intravesical BCG to intravesical chemotherapy (MMC, Adriamycin, epirubicin, Thiotepa, sequential MMC/Adriamycin) in 845 patients with CIS [66,69]. Data for 700 patients with CIS included in 9 trials were available for inclusion in a meta-analysis [67]. Among 298 patients receiving BCG, 203 (68.1%) had a complete response as compared to 158 (51.5%) of 307 patients receiving chemotherapy (p=0.0002. After a median follow-up of 3.6 years, 161 (46.7%) of 345 patients on BCG exhibited no evidence of disease compared to 93 (26.2%) of 355 patients on chemotherapy (p<0.0001). The long-term benefit of BCG was superior to MMC in trials with maintenance BCG (p=0.04). A reduction of 26% in the risk of progression for patients on BCG when compared to those receiving chemotherapy was observed (p=0.20), consistent with the results of the meta-analysis (level 1).

More recently, in patients with high grade (grade 2 or 3) T1 tumors, BCG was found to be superior to the combination of epirubicin and interferon alpha 2b for the endpoint of disease-free survival, but only in the subgroup of 76 patients with concomitant CIS [76]. In a recent meta-analysis comparing BCG to MMC, only 12% of patients had CIS and a separate analysis of treatment efficacy was not carried out in this patient subgroup [77].

e) Comparison of Alternating or Sequential MMC/BCG to BCG alone or to MMC alone

There is only a limited amount of evidence assessing alternating MMC/BCG in patients with CIS. Alternating MMC/BCG was compared to MMC alone in 133 CIS patients in 2 studies, with higher complete response and disease-free rates on MMC/BCG [78,79]. In the largest trial comparing alternating MMC/BCG to BCG alone in patients with CIS, there was a significantly longer disease-free interval in the BCG monotherapy arm: 80 (55%) of 145 patients were disease-free on BCG alone compared to 72 (45%) of 159 patients on the alternating arm [80]. Thus, it can be concluded that an alternating schedule of MMC and BCG is not superior to BCG alone (level 1).

However, in a trial comparing sequential BCG and electromotive MMC to BCG alone in 212 patients with high grade (grade 2 or 3) T1 tumors, BCG was found to be superior to the combination of epirubicin and interferon alpha 2b for the endpoint of disease-free survival, but only in the subgroup of 76 patients with concomitant CIS [77]. In a recent meta-analysis comparing BCG to MMC, only 12% of patients had CIS and a separate analysis of treatment efficacy was not carried out in this patient subgroup [77].

f) Treatment of Extravesical CIS

No randomized trials have been carried out in patients with extravesical CIS and, as such, no definitive treatment recommendations can be provided. Intravesical BCG does not reach either the upper urinary tract or the prostatic urethra. Therefore, the treatment of CIS in the upper urinary tract involves rinsing the renal unit with BCG or chemotherapy.

CIS may be found in the prostatic urethra at various
levels: in the epithelial lining of the prostatic urethra only, in the prostatic tissue following the prostatic ducts, or in the prostatic tissue stroma (T4), carrying the worst prognosis. In the latter case, a cystoprostatectomy is advised. In the other two cases, a TUR of the prostate can be followed by intravesical BCG. Further details concerning results obtained in a small series of non-randomized studies have been summarized by van der Meijden (level 3) [69].

**g) Treatment of BCG-refractory CIS**

Up to 40-50% of patients with CIS may eventually fail intravesical BCG. These patients have a very poor prognosis, with a high risk of progression to muscle-invasive disease and death as a result of bladder cancer. The 3-year bladder cancer specific survival is 67% in patients initially presenting with muscle-invasive disease but falls to 37% in patients who progress after intravesical treatment [82]. There is no universally agreed definition of BCG failure and there are no randomized trials comparing BCG to cystectomy. However, treatment with BCG is generally considered to have failed in the following cases [83,84,85]: (1) detection of muscle-invasive disease; (2) presence of high grade papillary tumors and/or carcinoma in situ at both 3 months and 6 months; or (3) disease worsening (stage, grade, CIS) under BCG treatment. Herr et al concluded that a minimum treatment and follow-up period of 6 months is required to identify high risk, non-muscle-invasive bladder tumors as being truly BCG-refractory [85].

In BCG failures, cystectomy is the recommended treatment option (level 3). For patients who are unable or unwilling to have a cystectomy after BCG failure, various alternative treatment possibilities exist (level 3). Intravesical chemotherapy, device-assisted chemotherapy, photodynamic therapy, and BCG plus interferon alpha are the options most frequently employed [86]. After a literature review in 2005 [69], additional publications of intravesical treatment for patients with BCG-refractory CIS became available concerning BCG plus interferon alpha 2b [87], hyperthermia and MMC [88], mycobacterial cell wall-DNA complex [89], and gemcitabine [90,91]. In general, the results for conservative treatment after BCG failure are disappointing (level 3) and research to discover new treatment options in these patients is a top priority.

### CIS: RECOMMENDATIONS

1. If CIS is clinically suspected, urinary cytology should be obtained and white light cystoscopy and imaging of the upper urinary tract should be performed. (LOE 2, Grade A) In patients with positive cytology but normal white light cystoscopy, photodynamic diagnosis with hexaminolevulinic acid should be considered. (LOE 1a, Grade A)

2. Diagnosis of CIS is based on histopathological assessment of biopsy or resection specimen. Pathology need not report subtypes but should note the presence of micropapillary and small cell CIS (LOE NA, Grade A).

3. Radical cystectomy at the time of CIS diagnosis provides for excellent disease-free survival, but is overtreatment in up to 50% of the patients. (LOE 2, Grade A)

4. Intravesical BCG is recommended, as it provides the highest complete response rate as well as the highest long-term disease-free rate among intravesical treatments. (LOE 1a, Grade A)

5. Concomitant papillary tumors should be completely resected prior to the start of intravesical treatment (LOE 1b, Grade A). Following the resection, one immediate instillation of chemotherapy may be considered (LOE 3, Grade C).

6. Maintenance BCG treatment is required but the optimal maintenance schedule is unknown. In the absence of treatment failure, at least 1 year of maintenance BCG is recommended. (LOE 2, Grade A)

7. The response to intravesical BCG should be assessed 3 months after starting treatment. If no response is seen, one might offer the patient either cystectomy, another 6-week course of BCG or 3 weekly boosters. The optimal time to abandon conservative treatment and proceed to cystectomy is unknown. (LOE 2, Grade B)

8. Cystoscopy and urinary cytology should be performed every 3 months for a period of 2 years, every 4 months in the third year, every 6 months in the fourth and fifth year, and once per year thereafter. If no recurrence, imaging of the upper urinary tract by ultrasound, conventional IVU, or CT should be performed periodically. (LOE NA, Grade C)

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III. T1 UROTHELIAL CARCINOMA

1. DIAGNOSIS AND RISK ASSESSMENT

The initial assessment of T1 urothelial carcinoma does not differ decisively from Ta urothelial carcinoma. If pT1 cancer has been confirmed pathologically, there are additional considerations.

Clinical predictors, including histopathologic markers, are most useful in forecasting progression in patients with stage T1 urothelial carcinoma. Traditional factors used to predict the clinical outcome of T1 urothelial bladder carcinoma after an initial TURBT include time to recurrence, tumor grade, multiplicity, tumor extent and size, concomitant CIS, urothelial carcinoma involving the prostatic mucosa or ducts, and depth of lamina propria invasion [1]. The response to intravesical therapy is a reliable predictor of progression within 3-6 months. Eighty percent of patients found to have evidence of tumor recurrence at the time of their 3-month cystoscopy after BCG induction ultimately progressed to invasive disease [2]. The relative importance of clinical and pathologic factors varies according to adjuvant therapy. For example, T1 substaging has not been found to be useful in BCG-treated patients, and recurrence or persistence of downstaged or downgraded disease may be evidence of response in an individual patient [2]. Nevertheless, these prognostic factors are not accurate enough to predict the individual clinical behavior of T1 urothelial tumors. Therefore, more reliable indicators of biologic aggressiveness are needed.

Lotan et al examined the association of lymphovascular invasion with prognosis at radical cystectomy. Unfortunately, the role of lymphovascular invasion in patients with stage T1 urothelial carcinoma was unclear; of 111 patients with stage T1 disease who underwent radical cystectomy, only 10 (9%) had lymphovascular invasion.

A number of molecular prognostic markers have been reported for T1 urothelial carcinoma. It has been suggested that alterations of cell cycle regulatory proteins involved in the progression from G1 to S phase are among the most promising markers. The p53 tumor suppressor gene is commonly altered in human malignancies. Pretreatment p53 nuclear overexpression in non-muscle-invasive bladder tumors is associated with a high risk of disease recurrence, progression, and cancer death after BCG therapy [3]. Alterations of p53 were associated with BCG failure. Others have not found that p53 expression before BCG treatment correlated with BCG failure [2]. Controversial results have also been reported with regard to p53 expression as an independent predictor of progression [4]. While a trend towards poorer clinical outcomes in high risk patients with a p53 mutation has been observed, no significant differences were seen in clinical outcome parameters. A number of cell cycle regulators that appear to be independent predictors of the survival of patients with high grade T1 urothelial carcinoma include p27kip1 and the cyclins D1 and D3 [5]. Many other prognostic factors, including genetic alterations, cell adhesion molecules, a family of proteases, growth factors, and other molecular markers, have been studied. To date, they do not have enough specificity for clinical use in the management of T1 urothelial carcinoma. For patients with pT1 disease at cystectomy, assessment of p53, p27, and Ki-67 in bladder specimens has been shown to improve prediction of recurrence-free and disease-specific survival [6].

In summary, useful clinical prognostic factors for T1 urothelial carcinoma include tumor grade, early recurrence, multiplicity, tumor size, concomitant CIS, urothelial carcinoma involving the prostatic mucosa or ducts, and depth of lamina propria invasion. The response to intravesical therapy is a very useful clinical marker. A great number of molecular and genetic prognostic markers, including alterations of p53, have been studied for T1 urothelial carcinoma. However, most of these markers have not been validated and are not yet available for clinical use.

2. TREATMENT

a) Turbt

A restaging TURBT is warranted in patients with pT1 urothelial carcinoma. In addition to the previously stated aspects, some special considerations also apply. The rate of residual tumors is high after initial TURBT for pT1 urothelial carcinoma. Schwaibold et al [7] showed that 52% of patients had residual tumors at restaging TURBT for initial T1 urothelial...
carcinoma, of which 86% were located in the base or margins of the previous resection and 14% in other locations. The risk of residual tumor correlates with the initial tumor grading. Divrik et al [8] reported a rate of 6% for initial G1, 38% for G2, and 63% for G3 tumors. Even after fluorescence diagnosis at the first TURBT for initial high grade T1 tumors, a restaging TURBT revealed residual tumors in 12% of cases [9].

Dutta et al [10] reported a 64% risk of tumor understaging in the absence of muscle in the first TURBT specimen. As 30% of tumors were upstaged when muscle was present in the first obtained specimen, a restaging TURBT should be performed for all high grade T1 tumors. Dalbagni et al [11] also reported a rate of 20% upstaging after restaging TURBT for initial high grade T1 tumors and thus modified patient treatment strategies. A restaging TURBT also provides prognostic markers for disease outcome. In a retrospective study, Herr [12] found a significantly higher risk of tumor progression over 5 years when residual pT1 disease was found at restaging TURBT (82% vs. 19%). Thus, a restaging TURBT helps to identify patients who should be immediately referred for radical cystectomy.

b) Immediate Instillation of Chemotherapy

The European Association of Urology (EAU) guidelines recommend that all patients with non-muscle-invasive bladder cancer should receive 1 immediate instillation of chemotherapy after a TUR (Grade B recommendation) [13]. Patients with T1 urothelial carcinoma of the bladder are at least intermediate or high risk for progression, depending on the grade. After TUR, these patients should receive further adjuvant chemotherapy or immunotherapy (BCG) once a week for 6 weeks with or without maintenance. The role of one single instillation of chemotherapy immediately after TUR in these patients (T1, any grade) has been recently questioned due to the publication of new data.

In a randomized placebo-controlled phase III multicenter study, Bohle [14] compared a single postoperative instillation of gemcitabine to placebo in patients with low or intermediate risk urothelial carcinoma of the bladder. In this series, 25% and 29% of patients receiving gemcitabine and placebo, respectively, had T1 disease; 10.5% and 11.3% were high grade. In these patients, additional BCG with maintenance was also used. The results showed that after a follow-up period of 24 months, the recurrence-free survival was high in both groups (77.7% vs. 76.3%). There was no significant difference between the 2 groups. Both groups had continuous bladder irrigation for 20 hours. The authors hypothesized that improved TUR (cystoscopy) techniques may have contributed to the high recurrence-free survival in both groups.

Hendricksen [49] studied the additive effect of early instillation or maintenance instillations of adjuvant intravesical epirubicin compared to the standard schedule of epirubicin in patients with intermediate and high risk urothelial carcinoma of the bladder.

In a randomized study (n=753), 4 weekly and 5 monthly instillations of epirubicin 50 mg in 50 mL saline for 1 hour (group 1) were compared to the same schedule with an additional instillation 1) < 48 hours after TUR (group 2) and 2) following the same schedule of group 1 with additional instillations at 9 and 12 mo (maintenance schedule). The results showed that with this quasi intention-to-treat strategy there was no difference in the 5-year recurrence-free period between the treatment groups. T1 disease was present in 156 (21%) of 731 patients. Grade 2 and grade 3 disease was present in 343 (47%) and 78 (11%), respectively. The immediate instillation was given to 68% of the patients in group 2 within 24 hours. They concluded that one immediate postoperative instillation of epirubicin preceding a standard schedule also was not effective in reducing recurrences in patients with intermediate and high risk urothelial carcinoma of the bladder.

In a multicenter study in Sweden [15], 305 patients with primary or recurrent Ta or T1, G1 or G2 urothelial carcinoma of the bladder (low or intermediate risk) were randomized to receive epirubicin 80 mg in 50 mL saline within 24 hours of TURBT or TURBT alone. The results showed that after a median follow-up time of 3.9 years, the recurrence rate in the epirubicin group was 62% vs. 72% in the control group (p= 0.016). However, in a subgroup analysis, the treatment with epirubicin only had profound recurrence-reducing effect in patients with primary, single tumors, while providing no benefit in patients with recurrent or multiple Ta or T1, G1 or G2 intermediate risk tumors.

Similar findings were reported by Berrum-Svennung et al [16]. They reported on 307 evaluable patients randomized between receiving 50 mg epirubicin within 6 hours after TURBT or TURBT alone. The recurrence rate in the epirubicin group was significantly lower (51% vs. 62.5%, p=0.04), but recurrences were prevented only if initial tumors were smaller than 5 mm. The authors also concluded that an immediate single postoperative instillation was only effective in small (i.e., very low risk) tumors.

Finally, the value of a single instillation after a TURBT in high risk patients has been recently challenged by Brausi [17]. In Sylvester’s meta-analysis, the number of high risk patients who received 1 perioperative instillation and further therapy was small. The consistency of the conclusions regarding these patients was unclear.

In the literature, there are few randomized studies addressing this issue. The first was published by
Zincke in 1983 [18]. He compared 1 single instillation of Thiotepa or doxorubicin after TURBT followed by BCG therapy vs. TURBT without postoperative instillation followed by BCG in patients with CIS. The results indicated no benefit in those patients receiving a single instillation. A second prospective randomized study by Cai [19] compared 1 single instillation of epirubicin after a TURBT followed by BCG vs. TURBT without instillation and BCG in high risk tumors. No difference in the recurrence or progression rate was demonstrated between the 2 groups. The authors concluded that 1 single instillation of chemotherapy after a TURBT in high grade, high risk tumors is not effective in reducing recurrence or progression.

c) Initial Bladder-sparing Approach vs. Cystectomy

The goal for the treatment of bladder cancer is to minimize the morbidity and mortality of the disease while maximizing patient quality of life. This is particularly true for cases of new or recurrent T1 disease. The substantial majority of stage T1 bladder cancer is high grade and therefore at particular risk of progression to incurable metastases. Treatment with TURBT alone without adjuvant intravesical therapy carries an unacceptable risk of recurrence and progression. Even with optimal intravesical chemotherapy or immunotherapy, however, a substantial proportion of patients progress to incurable disease stages [20].

The 2 treatment options available today for patients with high grade Ta or T1 bladder cancer are immediate cystectomy or intravesical therapy with a delayed cystectomy for persistent or recurrent tumors. The selection of one of these options over the other is among the most difficult in bladder cancer management. Quality of life data in this area is interesting. If faced with this choice, patients are willing to accept disabilities incurred by cystectomy to avoid compromising survival.

Selection of the treatment strategy for stage T1 urothelial carcinoma requires consideration of the risks and benefits of cystectomy versus a repeat TURBT with immediate instillation of chemotherapy and BCG immunotherapy. Understaging is frequent. When a cystectomy is performed for clinical stage T1 disease, 30% of patients will be found to have unsuspected disease that is stage T2 or greater. It was recently shown that this risk increases to 49.7% in patients with clinical high grade T1 disease [21]. Cystectomy is therefore an option to be considered. However, cystectomy survival is far from optimal and around one-third of patients with pT1 urothelial carcinoma die of the disease [21]. Because of the lack of evidence from randomized trials, there is no recommendation for early cystectomy in patients with high grade T1 disease. Nevertheless there are reports of increased mortality in patients who develop muscle-invasive disease while receiving conservative treatment who then require cystectomy. Obviously, this raises concern about delaying cystectomy.

d) Intravesical Therapy

Before the advent of BCG immunotherapy, the incidence of progression in high grade, stage T1 urothelial carcinoma ranged from 27-65% with follow-up ranging from 36-84 months. Important and valid information about the prognosis of patients with non-muscle-invasive bladder cancer can be obtained from the scoring system developed by the EORTC. According to these risk tables, the risk of progression in high grade T1 tumors ranges between 17% and 45% at 5 years, depending on further variables [22]. These results, however, were before the era of a second TURBT or fluorescence-guided resection, maintenance BCG, and the use of an immediate postoperative instillation of chemotherapy.

With the advent of (maintenance) BCG, reported results of intravesical therapy in T1 disease have improved. With follow-up times ranging from 22-78 months, overall progression is in the range of 12%, varying from 0-35%. It is quite remarkable that the overall incidence of progression in patients with T1 disease is less than the incidence of occult muscle-invasive disease (up to 62%) in patients who undergo an immediate cystectomy [23,24,25].

The role of BCG in the treatment of high grade non-muscle-invasive bladder cancer is becoming clearer. Intravesical BCG is more effective than intravesical chemotherapy or TURBT alone in decreasing recurrences. This was addressed by many prospective randomized trials and meta-analyses. Unfortunately, these trials enrolled patients both with intermediate and high risk tumors. For this reason, there is no separate analysis available based on prospective randomized data that deals with the efficacy of different treatment modalities in high grade T1 tumors.

It has been confirmed in 5 meta-analyses that BCG therapy after TURBT is better than TURBT only or TURBT plus chemotherapy in preventing recurrences of non-muscle-invasive bladder tumors [26,27,28,29,40]. A recently published meta-analysis, which was based on individual data from 2820 patients from 9 randomized trials, compared the efficacy of BCG and MMC. In those trials where BCG was used with maintenance, a 32% reduction in the risk of recurrence was found (p<0.0001) [30].

Secondly, BCG lowers tumor progression in high grade non-muscle-invasive bladder cancer but has not been shown to improve survival. Patients with high grade T1 tumors are at high risk for tumor progression, which is more important and dangerous than the risk of tumor recurrence. The question...
as to whether BCG can reduce the risk of tumor progression was addressed by a meta-analysis carried out by the EORTC that evaluated data from 4863 patients enrolled in 24 randomized trials. The results demonstrated a 27% reduction in the odds of progression with BCG treatment (p=0.0001). In the 20 trials in which BCG maintenance was provided, a reduction of 37% in progression was observed (p=0.00004) [31] (Level 1). Unfortunately, 1) the median follow-up was only 2.5 years; and 2) for papillary tumors, only 7.6% had high grade disease. This individual data meta-analysis, with a median follow up of 4.4 years, compared BCG with MMC and has not confirmed any significant difference in progression and mortality rates [30].

Indeed, there are some data indicating that the long-term risk of tumor progression remains significant in spite of BCG treatment. It has been reported that after 15 years of follow-up, 53% of patients with initial high-risk non-invasive bladder cancer progressed to muscle-invasive disease, 36% eventually underwent cystectomy, and 34% died of bladder cancer [32]. Only 27% were living with an intact bladder. Similar results have been reported by Shahin et al [33] from a study with 153 patients treated with either TURBT and BCG or TURBT alone. With a median follow-up of 5.3 years, disease recurred in 70% and 75% of patients treated with BCG and TURBT alone, respectively. Progression was seen in 33% and 36% of cases, respectively. A deferred cystectomy was performed in 29% and 31% of cases, respectively. Overall and disease-specific survival for those receiving BCG compared with TURBT alone was 42% and 77% versus 48% and 79%, respectively. The investigators stated that BCG therapy is unlikely to substantially alter the final outcome for patients with high grade T1 urothelial carcinoma.

BCG instillation is associated with side effects. Up to 90% of patients have irritative lower urinary tract symptoms, and a small number of patients have serious, debilitating complications, such as sepsis and contracted bladders. Lamm [34] reported that only 16% of patients were able to tolerate a full maintenance course of BCG secondary to adverse effects, albeit in an earlier era. With increased experience in the use of BCG, the side effects now appear to be less severe. Serious side effects are encountered in less than 5% of patients and can be effectively treated in virtually all cases. [35] (Level 3).

For optimal efficacy, BCG must be given according to a maintenance schedule [29,30,31,36]. It is not possible, however, to determine which BCG maintenance schedule is the most effective [31]. In their meta-analyses, Böhle et al concluded that at least 1 year of maintenance BCG was required to show the superiority of BCG over MMC in preventing recurrence or progression [29,30,31,35,36]. Today, BCG instillations are given according to the empirical 6-weekly induction schedule introduced by Morales 30 years ago. However, many different maintenance schedules have been used, ranging from a total of 10 instillations given in 18 weeks, to 30 instillations given over 3 years according to the Southwest Oncology Group (SWOG) schedule [37]. The quality of the initial TURBT in adequate staging and optimal resection has a crucial role in providing optimal results in a bladder sparing approach to high grade T1 cases.

Conservative therapy is an attractive option for many patients with high grade non-muscle-invasive bladder cancer. There is a subgroup of patients with the highest risk of progression who benefit from early cystectomy. These may include patients with adverse factors, for example, patients with tumor multifocality, tumor size of over 3 cm, and associated CIS. It has been shown that patients with at least two of these factors could benefit from immediate cystectomy [38].

The most important prognostic factor has been shown to be the clinical response to intravesical therapy. A study of patients treated with intravesical doxorubicin found that 50% of those with stage T1 or high grade recurrent tumors progressed. [39] The pathologic tumor stage at recurrence was the only factor shown to be predictive of recurrence in this study. In 80 patients given intravesical therapy for T1 disease, Solsona et al [40] demonstrated that 78% had a complete clinical response. However, as is the case of many studies of high risk non-muscle-invasive bladder cancer, in this study, T1 tumors were not separated from CIS in the analysis of risk factors for progression. In conclusion, the absence of a 3-month clinical response seems highly predictive of progression [41]. It is not known exactly whether a cystectomy should be performed immediately at 3 months in non-responders or whether we can repeat BCG instillations and wait for a response at 6 months. There is no doubt, however, that an early cystectomy is strongly recommended in patients with persistent high grade tumors despite 3 and 6 month BCG treatments, since the prognosis for progression increases significantly [42].

e) Early Cystectomy

Disease-specific survival after cystectomy for non-muscle-invasive urothelial carcinoma is higher than for patients with muscle-invasive disease. However, the benefits must be balanced against the morbidity and mortality rates of surgery. Amling et al [43] reported on a large series of 531 patients undergoing cystectomy and found a perioperative mortality rate of 2.3% and a complication rate of 20.5% (level 3). Similar complication rates have been reported in other large cystectomy series by Stein et al [44] and Ghoneim et al [45] (level 3).
There is significant support for early cystectomy in T1 disease in view of the high rate of late failure after initially successful intravesical therapy and the good quality of life possible post-cystectomy. [46] Fritsche [21] reported on a multicenter series of 1136 patients with high grade T1 disease who underwent cystectomy without undertaking neoadjuvant chemotherapy. Upstaging to muscle-invasive disease occurred in 49.7% and 35.5% died of metastatic disease within 8 years of their cystectomies (level 3).

However, the proponents of an aggressive initial approach acknowledge that a significant number of patients will be rendered disease free with bladder-sparing strategies. Current proposed indications for immediate surgery include younger patients with T1 tumors with at least one additional bad prognostic factor including multifocality, associated CIS, prostatic involvement, and tumor at a site that is difficult to resect. Bianco et al [47] performed a multivariate analysis to identify risk factors in patients undergoing a cystectomy that influenced cancer-specific survival. They found that patients with concomitant CIS and those who had persistent disease after an initial course of BCG therapy were at significant risk (level 3). Herr and Sogani [48] retrospectively evaluated 90 patients with high-risk non-invasive bladder cancer who ultimately underwent cystectomy. These investigators reported improved 15-year disease-specific survival for those who underwent cystectomy within 2 years after an initial BCG treatment (Level 3). Moreover, those who underwent a cystectomy for recurrent non-invasive disease had an improved outcome compared to those who underwent surgery for progressive disease. The investigators thus concluded that deferring cystectomy until progression to muscle-invasive disease may decreases a patient's overall disease-specific survival. Nevertheless, 217 patients from their original cohort of 307 with high-risk non-invasive disease never required cystectomy and were thus spared the morbidity associated with cystectomy.

The presence of metastasis has the most profound impact on survival. A large series of 1054 patients who had undergone radical cystectomy was reviewed retrospectively by Stein et al [44]. The investigators identified 401 patients who had pathologically non-muscle-invasive tumors (pT0, pTa, pT1, or pTis). These patients demonstrated improved 5-year recurrence-free survival compared with those with non-organ-confined tumors (pT3b, pT4, and those with positive lymph nodes). No survival differences were observed when comparing non-invasive (pTa, pTis), lamina propria–invasive (pT1), and muscle-invasive tumors (pT2, pT3a), providing that there was no evidence of metastatic disease to the lymph nodes. The overall recurrence-free survival rates in those with organ-confined, node-negative disease were 85% and 82% at 5 and 10 years, respectively. A total of 246 patients (24%) had lymph node tumor involvement. The 5- and 10-year recurrence-free survival rates for these patients were 35% and 34%, respectively (Level 3).

Based on the current literature, patients with high risk disease should be offered an early cystectomy. Likewise, those with recurrent or persistent disease after BCG immunotherapy should also be offered cystectomy.

T1 UROTHELIAL CARCINOMA: RECOMMENDATIONS

1. The assessment of T1 urothelial carcinoma should be based on tumor grade, early recurrence, multiplicity, tumor size, concomitant CIS, urothelial carcinoma involving the prostatic mucosa or ducts, and depth of lamina propria invasion. (LOE1a, grade A).

2. The use of 1 immediate postoperative instillation of chemotherapy is not supported by consistent data and therefore it should not be recommended for standard practice. (LOE1a, grade A)

3. High risk patients and those with recurrent or persisting disease after BCG should be offered a cystectomy. (LOE2a, grade A)

4. If a bladder-sparing approach is desired, a secondary TURBT should be performed and followed with intravesical BCG therapy. (LOE3, grade B)

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IV. TREATMENT OPTIONS FOR BCG FAILURE

1. INTRODUCTION

Although BCG is an effective therapy for urothelial carcinoma, BCG failure remains a significant problem. Greater patient age, previous intravesical therapy, and failure to achieve a complete response after induction BCG are associated with an increased risk of progression or death for patients with non-muscle-invasive bladder cancer [1]. Studies using more intensive BCG treatment and extended BCG maintenance schedules tend to show better results. The median time to progression generally exceeds 12 months, with an estimated progression rate of ≤5% by 6 months. For these patients, radical cystectomy continues to be the “gold standard.” However, patients are sometimes reluctant to undergo major surgery for a condition that does not pose an immediate threat to their lives. Furthermore, radical cystectomy is not a suitable treatment option for a subset of patients with severe comorbidities. A number of alternatives have thus been developed.

2. DEFINING BCG FAILURE

In evaluating salvage therapies for use after BCG failure, Herr and Dalbagni noted that comparisons between therapies have been hampered by the lack of standard definitions for BCG failure and BCG-refractory urothelial carcinoma [2]. Some series have defined BCG failure after a single induction course of BCG, others after 2 courses [3,4,5]. In addition, result reporting methods have been inconsistent [6]. Most studies have included all patients who received 1 or more courses of BCG [7,8,9]. Investigators have often combined patients with persistent disease (nonresponders) and patients with recurrent disease after an initial response. Some studies combined patients who were BCG nonresponders and patients who could not complete BCG therapy due to the associated toxicity (BCG intolerant). Furthermore, many studies have combined all patients with papillary tumours both with and without CIS. Finally, most studies did not indicate the disease-free interval after the last BCG course. These inconsistencies have made it more difficult to compare outcomes in this very heterogeneous population.

In the most general sense, any recurrent disease after initiation of BCG therapy can be referred to as “BCG failure.” However, to provide more uniformity in reporting, the following alternative descriptive terms for specific types of BCG failure should be used whenever possible:

- BCG-refractory disease is the term used when a disease-free state is not achieved within 6 months of the initial BCG therapy with either maintenance
or retreatment at 3 months due to either persistent or rapidly recurrent disease. The definition also includes any progression in stage, grade, or disease extent within 3 months of the first BCG cycle (i.e., non-improving or worsening disease, despite BCG). BCG-resistant disease is the term used when there is recurrence or persistence of disease 3 months after the induction cycle. If it is of lesser degree, stage, or grade, and is no longer present at 6 months following BCG retreatment with or without TURBT, the disease has improved and is resolved with further BCG. BCG-relapsing disease is the term used when there is a recurrence of disease after disease-free status has been achieved within 6 months (i.e., disease resolved after BCG but subsequently returns). Relapse is further defined according to the time of recurrence as either early (within 12 months), intermediate (12 to 24 months), or late (> 24 months). There is some overlap with BCG-refractory disease, as disease relapse while on active maintenance, i.e., within, 3 months, may qualify as BCG-refractory disease. BCG-intolerant disease is the term used when disease recurs after a less-than-adequate course of therapy is applied because of a serious adverse event or symptomatic intolerance that mandates discontinuation of further BCG therapy (i.e., recurrent disease in the setting of inadequate BCG treatment because of drug toxicity).

Prophylactic use of ofloxacin has been reported to decrease incidence of moderate to severe adverse events associated with BCG intravesical therapy, but this strategy has not been widely adopted. [10]

3. TREATMENT OPTIONS

a) Cystectomy

Great variation exists in actual practice with regard to the timing of cystectomy in patients who fail induction BCG therapy. These vary from immediate surgery after the first follow-up cystoscopy if residual disease is present to delaying surgery for 6 months if a complete response is not achieved. The evidence for this interval is not well-established at the present time. There is general consensus that the prognosis for some patients with aggressive disease can be adversely affected by delaying surgery, but the prediction of this risk in individual cases is difficult. As such, alternative bladder-sparing strategies are frequently used (see below).

b) Repeat BCG Treatments

This treatment may be appropriate for both BCG-resistant and BCG-relapsing disease. However, the success of a second course of BCG for stage T1 disease has not been extensively reported, and only a few published studies have addressed this issue. Cookson and Sarosdy [11] reported an initial 69% (59 of 86) complete response to BCG in patients with any grade T1 disease; another 70% (19 of 27) responded to further TURBT and BCG, including 64% (7 of 11) with recurrent T1 disease. Similar results were reported by Brake et al [12] who found a 70% (89 of 128) enduring response after 1 BCG cycle and 51% (19 of 37) after a second BCG cycle for the remaining 37 patients (13 of whom had already progressed). Pansadoro and De Paula [13] reported that the response rate of 47 patients to TUR plus 1 cycle of 6 weekly BCG instillations was 53% (25 of 47). Of the 22 failures treated with a repeat TUR and a second cycle of BCG, 27% (6 of 22) responded, and, of the remaining 16 patients who received a third cycle of BCG, only 6% (1 of 16) responded. These results are similar to those reported in BCG studies in non–T1-restricted tumors and illustrate that a second (but not greater) course of BCG may be appropriate in select patients with original stage T1 disease who have a recurrence of non-BCG-refractory disease. Unfortunately, there are insufficient data to assess the effectiveness of repeated BCG treatments in refractory patients or those with recurrent T1 disease [14].

c) Intravesical salvage chemotherapy

Of the various standard intravesical chemotherapeutic agents (Thiotepa, doxorubicin, MMC) there is only minimal reported experience with their use in patients failing prior BCG therapy. Malmstrom et al [15] reported a 19% 3-year disease-free rate among intermediate and high risk patients treated with MMC who had failed a prior first induction cycle of BCG. The results for T1 recurrences are unknown. Similarly, there are few data on the newer anthracycline derivative valrubicin. Of 90 valrubicin-treated patients with CIS with and without papillary urothelial carcinoma who had failed 2 or more cycles of prior intravesical therapy (most commonly BCG), only 21% had a complete response at 6 months and 8% by 24 months [16]. Notably, all 5 patients with stage T1 disease (previously resected) plus CIS failed to achieve a complete response. Gemcitabine has been suggested as a potential alternative for patients intolerant to or otherwise unable to receive BCG due to its favorable toxicity profile. However, gemcitabine has been shown to have an almost two-fold recurrence rate at 44 months (53% versus 28%) when compared to BCG in a randomized prospective study [17]. Two other studies, however, suggest that gemcitabine could be used in BCG failures. Addeo et al treated 120 patients, of which 109 were assessable for response [18]. Ninety-one of these 109 patients failed previous BCG, but details on these failures were not provided. Patients were randomized between gemcitabine and MMC, with a 3-year recurrence-free survival of 72% and 61%, respectively. Progression was noted in 6 of 54 patients and 10 of 55 patients, respectively. Di Lorenzo et al [19] compared 1 year of gemcitabine to BCG Connaught. The only difference in the
treatment schedule was that the 6 week induction course was biweekly for gemcitabine in comparison to weekly for BCG. All patients had high risk non-muscle-invasive bladder cancer, having failed 1 course of BCG. The 2-year recurrence-free survival was 19% for gemcitabine versus 3% for BCG (p<0.008). Progression rates were 33% and 37.5%, respectively. In all, gemcitabine seems to have some effect in patients who have failed BCG; nevertheless, many patients experience recurrence and progression, especially in the high risk group.

Additionally, prospective evaluation has found epirubicin with interferon alpha to be inferior to BCG for prophylaxis of recurrence and therefore has a limited role in patients experiencing BCG failure [20]. Given these poor results, it appears that current intravesical salvage chemotherapy has little to offer patients who have failed BCG, especially those with stage T1 disease.

d) Interferon alpha Immunotherapy

In 2 studies, findings suggest that interferon alpha is unlikely to be of benefit in stage T1 BCG failures. The long-term (>2 years) success rate of interferon alpha monotherapy of patients who fail BCG (CIS and/or papillary urothelial carcinoma) is generally ≤15% [21]. Furthermore, in a study of interferon alpha monotherapy for primary stage T1 disease, interferon alpha was found to be no better than placebo at 43 month follow-up [22].

e) Combination BCG plus Interferon alpha

Several single institutional studies have demonstrated that the combination of low-dose BCG plus interferon alpha may be useful as a salvage regimen for BCG failures [23,24,25,26]. With follow-up times ranging from 12-30 months, disease-free rates were 50-60%, even in patients with recurrent T1 disease. Furthermore, no patient with an expedient cystectomy after BCG plus interferon alpha failure had unresectable or metastatic disease. Interim results of an even larger group of 231 patients with BCG failure in a multi-institutional study showed a disease-free rate of 42% at a median follow-up time of 24 months [27]. The efficacy results for stage T1 patients have not yet been published, but preliminary analysis reveals a similar degree of durable response among an approximate 10% progression rate (M. O’Donnell, personal communication).

f) Other Alternatives

There are no reliable data published on the use of photodynamic therapy for recurrent stage T1 cancer, although it is generally believed to be more effective with surface disease, such as CIS [28]. Likewise, although 5-year disease-free survival rates of 50-60% for radiation therapy for stage T1 disease have been reported, its role as a salvage therapy for BCG failures has not yet been established [29]. Furthermore, for T1 disease alone, local recurrence or progression occurs in approximately 50% of cases [30]. Thermo-chemotherapy has recently been reported on in patients with recurrent disease following BCG [31]. One hundred and eleven patients (29 pT1) were treated with 6 weekly induction treatments, and thereafter 4 to 6 sessions with a 6 week interval. The disease-free survival estimates were 85% and 56% after 1 and 2 years, respectively. Only 3 patients experienced progression. There was no difference between the different BCG failing groups (definitions used as outlined above), nor, for example, for Ta versus T1. Only maintenance hyperthermia treatment was associated with increased efficacy. In all, hyperthermia treatment would appear to be a possibility for these patients, although more studies are needed.

RECOMMENDATIONS FOR BCG FAILURE

1. The threat of progression remains real but comfortably low enough within the first 6 months of initiating BCG to consider alternatives to cystectomy for those patients unfit or not willing to undergo this standard management option (LOE 2, Grade B).

2. In the case of any BCG non-response or failure, cystectomy is recommended (LOE 2a, Grade A).

3. The current best option for alternative treatment includes repeat resection and repeat BCG (LOE 1a, Grade A), possibly with interferon alpha as a costimulant (LOE 2, grade C). Gemcitabine and thermo-chemotherapy have shown efficacy, but more studies are needed. There is no reported evidence of significant efficacy using current intravesical chemotherapy, interferon alpha monotherapy, photodynamic therapy, or radiation therapy.

REFERENCES


Committee 6

Muscle-invasive, Presumably Regional, Tumor

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I. OVERVIEW

A panel of an international multidisciplinary group consisting of urologists, oncologists and radio-oncologists provide data on evidence-based management of patients with muscle-invasive, clinically presumably node-negative, bladder cancer. The guidelines focus on treatment options and outcome, including radical surgery, neoadjuvant and adjuvant treatment modalities, bladder-sparing approaches, and treatment of mixed and secondary urothelial recurrences. In addition, specific recommendations are given for the surgical treatment and extent as well as for follow-up strategies after curative intent. The level of evidence and grade of recommendation given are as outlined by the Oxford Centre for Evidence-based Medicine [1].

REFERENCES


II. INDICATIONS AND ALGORITHMS OF TREATMENT

Radical cystectomy and bilateral pelvic lymphadenectomy provide excellent loco-regional control for patients with clinical stage T2-T4a, N0-NX, M0 disease. Local pelvic recurrence rates are as low as 4% in patients with node negative disease and 15-20% for patients with node metastases. [1,2] Cystectomy may also be appropriate initial treatment for some patients with first occurrence of high risk non-muscle-invasive cancer or recurrence. Patients with high grade papillary disease (Ta, T1) or carcinoma in situ that recurs following treatment with intravesical BCG or patients with intermediate...
risk papillary disease that cannot be controlled with transurethral resection and intravesical therapy alone should be offered cystectomy. Surgery should not be withheld or delayed in these patients as the long-term survival probability is decreased when there is evidence of progression to muscle-invasive cancer.[3] Morris et al studied how physician behavior affected outcomes in bladder cancer management and determined that the persistent use of conservative therapy delays necessary, aggressive treatment.[4] In this setting, changing physician decision-making and/or practice patterns may decrease mortality. Salvage cystectomy is indicated for non-responders to conservative therapy, recurrences after bladder-sparing treatments, non-urothelial carcinomas (these tumors may respond poorly to chemotherapy and radiotherapy), and as a purely palliative intervention in the setting of fistula formation, pain, or recurrent gross hematuria.

Much has been written about the timing of cystectomy and long-term survival, which is inconclusive due in part to the retrospective nature of the research and the biology and demographics of the unique patient populations studied. A recent population based study from the United States SEER Medicare database looked at patients operated on between 1992 and 2001.[5] The authors’ findings suggest that 12 weeks is the outside limit beyond which there is a negative impact on outcome (level 3b).

The goals of therapy are complete eradication of the loco-regional disease including the primary tumor and regional lymph nodes. The primary landing zone for node metastases includes the obturator and internal and external iliac lymph nodes. The incidence of node metastases increases with tumor stage. The majority of patients with node metastases have multiple positive nodes and at least one-third have node metastases in secondary landing zones including the pre-sacral and common iliac nodes. [6-8] Neoadjuvant or adjuvant chemotherapy targeting occult regional node and/or visceral metastases should be integrated with loco-regional therapy when the risk of this occurring is high enough.[9-12] Patients should have volitional control of urination via the retained urethra or by a continent catheterizable stoma (in properly selected patients) and treatment-related morbidity should be minimized wherever possible.

Radical cystectomy provides excellent local control of the primary tumor. In men, this should include the bladder and surrounding perivesical soft tissue, prostate, and seminal vesicles, and, in women, the ovaries, uterus with cervix, and anterior vagina. With the pervasive use of robotic-assisted laparoscopic radical prostatectomy, many surgeons are applying these skill sets to radical cystectomy (discussed in Section 2.1.6). Proof of concept has been demonstrated as the technical hurdles have been overcome. Several randomized clinical trials are underway comparing open versus robotic but to date there is a paucity of long-term data to provide guidance regarding long-term oncologic outcomes. Surgical modifications that spare a portion of the prostate have been developed in order to improve continence and potency following cystectomy. It is not clear that this technique offers an incremental improvement in quality of life outcomes over meticulous nerve-sparing and careful dissection of the apical prostate and membranous urethra. The oncologic risk for prostatic involvement with urothelial cancer is up to 40%. [13] The incidence of prostate adenocarcinoma is similar, and at least one-half of these cancers are considered clinically significant.[14]

In sexually active women, vaginal preservation and/or reconstruction must be discussed and planned preoperatively. Recent reports challenge the dogma of removal of the internal female organs as the rate of involvement of the uterus, cervix, and ovaries is low.[15] Preservation of the vagina and uterus provides better support for a neobladder and the pelvic floor when the extent of the cancer or the age and general health status of the patient does not warrant anterior pelvic exenteration.[16] One also needs to balance the benefits of retaining the uterus, Fallopian tubes, and ovaries versus the increased surgical risks of potentially requiring hysterectomy later after a neobladder. Involvement of the urethra or bladder neck is an absolute contraindication to urethra-sparing in women and a posterior-based invasive cancer is a relative contraindication.[17,18]

The morbidity of cystectomy can be significant though the mortality has been reduced to 2-3% in most contemporary series.[19] A recent report from Memorial Sloan Kettering Cancer Center described 1145 patients operated on between 1995 and 2005 using a modified Clavien system.[20,21] The majority of patients (64%) experienced one or more complications and the majority of these were grade 2-5. The hospital re-admission rate was 26%. The authors suggest that this degree of peri-operative morbidity may limit use of adjuvant chemotherapy in as many as 30%[20].

RECOMMENDATIONS

- Radical cystectomy is indicated for definitive loco-regional control of non-muscle-invasive urothelial cancer that is refractory to intravesical therapy or cannot be controlled with transurethral resection (LE 2b GR B).

- The most common indication is primary treatment for patients with initial occurrence of muscle-invasive cancer or progression to muscle-invasive cancer that has failed intravesical therapy (LE 2a GR B). The evidence supporting this is based on
an open surgical technique incorporating bilateral pelvic lymphadenectomy.

- Minimally-invasive techniques including robotic-assisted laparoscopic radical cystectomy have been reported in increasing numbers. Short-term outcomes, pathologic findings, and assessments of morbidity compared to the open technique have been reported. Continued research with these techniques is required and specifically results of several randomized trials underway should be reported prior to accepting this as an equivalent option to open radical cystectomy (LE 2a GR C).

- Cystectomy is also indicated as palliation for intractable pelvic pain and bleeding from locally advanced or metastatic bladder cancer (LE 4 GR C).

(Level of Evidence = LE, Grade of Recommendation = GR)

REFERENCES


III. RADICAL SURGERY

1. REMOVAL OF THE TUMOR-BEARING BLADDER

a) Background

Radical cystectomy is the standard treatment for muscle-invasive bladder cancer in most countries worldwide [1]. In the pre-cystectomy era, 5-year survival rates for patients with muscle-invasive disease rarely exceeded 3% and performing radical surgery was associated with a considerably increased perioperative morbidity and mortality [2]. In the last decades, advances in the surgical technique as well as perioperative anesthesia care have significantly
decreased the complication rates associated with this procedure and have led to radical cystectomy now being considered the mainstay of treatment for this muscle-invasive disease.

In the last decade, increased interest in quality of life issues has increased the trend toward bladder preservation with transurethral resection followed by chemotherapy and radiation therapy [3, 4, 5]. Also, performance status and age were formerly reported to influence the choice of therapy, with cystectomy being reserved for younger patients without concomitant disease and better performance status [6]. Nonetheless, recent studies have demonstrated the feasibility and safety of radical surgery in octogenarians [7]. The value of assessing overall health before recommending and proceeding with surgery was emphasized in a prior report, which demonstrated an association between comorbid illness and adverse pathological and survival outcome following radical cystectomy [5]. Similar to these results, a recent analysis from the SEER registries evaluated the impact of comorbidities on cancer-specific and other-cause mortality in a population-based competing risk analysis of more than 11,260 patients. Age was found to confer the highest risk for other-cause mortality but not for increased cancer-specific death, whereas locally advanced tumor stage was the strongest predictor for decreased cancer-specific survival [8]. Stratifying elderly patients according to their individual risk-benefit profile within a multidisciplinary team might help to select those who may benefit most from radical surgery and optimize their outcomes.

REFERENCES


b) Timing and Delay of Cystectomy

It has been suggested that delaying radical cystectomy in organ-confined disease is associated with decreased survival [1]. These concerns regard primary surgery as monotherapy; the time spent for neoadjuvant chemotherapy is another matter. Even though it is well accepted that treatment should be instituted once a diagnosis of cancer has been made, several factors play a role in delaying such treatment. Some of these factors are linked to the health care system, while others are patient-related. The question of whether there is a window of opportunity for the treatment of invasive bladder cancer remains unanswered.

Reviewing all studies on this issue, it becomes evident that there is no linear relationship between delay of radical cystectomy and prognosis. However, delays are associated with worse outcome. The majority of studies suggest that a treatment delay of more than 12 weeks from diagnosis of invasive disease to cystectomy is associated with a significantly impaired prognosis.

Lee et al [2] analyzed the outcome of 214 patients who underwent radical cystectomy for muscle-invasive bladder cancer and they observed a significant disease-specific (p=0.05) and overall survival (p=0.02) advantage in patients who underwent radical cystectomy within 3 months or less as compared to those undergoing radical cystectomy greater than 3 months after diagnosis. Interestingly, the most common factor contributing to cystectomy delay was a scheduling delay. In a similar study, Fahmy et al [3] characterized various periods of delay sustained by bladder cancer patients before radical cystectomy across Quebec. The authors analyzed the 1633 patients being treated with radical cystectomy between 1990 and 2002 and they identified a delay of more than 84 days to be associated with a 1.4 times increased risk of death from bladder cancer. Gore et al [4] examined the survival impact of a delay in radical cystectomy using nationally representative SEER data. The authors identified 441 patients with stage II bladder cancer who underwent radical cystectomy between 1990 and 2001. Delay in radical cystectomy beyond 12 weeks and 24 weeks resulted in a 2-fold increased risk for both disease-specific and overall mortality when compared to immediate radical cystectomy performed within 4 to 8 weeks after diagnosis of muscle-invasive bladder cancer. Kulkarni et al [5] identified 2535 patients who underwent radical cystectomy between 1992 and
2004 in Ontario. The median waiting time between transurethral resection and radical cystectomy was 50 days. Prolonged waiting times were significantly associated with a lower overall survival rate. A cubic splines regression analysis revealed that the risk of death began to increase after a waiting time of 40 days. Similar data were reported by Jäger et al [6] who identified a waiting time of longer than 4 months to be associated with a significantly reduced 5-year cancer specific survival of 77% versus 86% (p=0.04). Ayres et al [7] recently analyzed whether a delay to radical cystectomy affects the survival of patients with bladder cancer in England. The analysis of organ-confined bladder cancer revealed that a delay of greater than 90 days was associated with a 1.4 times increased risk of death from bladder cancer whereas there was significant correlation between delay and prognosis for patients with locally advanced disease.

There is one recent publication in the literature which does not demonstrate any correlation between the delay from the last TUR to radical cystectomy and decreased survival times [8]. The authors analyzed the outcomes of 592 patients who underwent radical cystectomy within a median time from TUR to radical cystectomy of 1.8 months. However, it has to be taken into consideration that 35% of all patients who underwent radical cystectomy demonstrated non-muscle-invasive disease on final pathology.

**RECOMMENDATIONS**

- Delay in cystectomy for muscle-invasive disease is associated with significantly reduced overall and cancer-specific survival (LE: 3, GR: B).
- Radical cystectomy in patients with muscle-invasive bladder cancer should be performed within 3 months after initial diagnosis of stage T2–T4 disease (LE: 3, GR: B)

**REFERENCES**


**c) Technique**

In male patients, the literature over the last two decades has set the standard of surgical limits for curative radical cystectomy as complete removal of the bladder with all macroscopically visible and resectable bladder perforating tumor extensions, removal of the adjacent distal ureters, and the lymph nodes corresponding to the tumor-bearing bladder.

Preservation of the anterior and membranous urethra including the rhabdosphincter in order to enable an orthotopic neobladder; parts of the prostate and seminal vesicles for reasons of fertility, potency, and continence; and intrapelvic autonomic and sensory nerves to enhance potency and continence are all technical variations to this standard that may improve patients’ quality of life but must be attentively judged against possible oncological risks [1] (Level of evidence: 3, grade of recommendation: C).

In case of leaving parts of the prostatic gland during the resection, the hazard of an unsuspected adenocarcinoma may be as high as 23-54% of which up to 29% may be clinically significant, lead to local recurrence, or even metastasis [2-4]. Furthermore, urothelial carcinoma may be present in the prostate and in some series up to 27% of patients undergoing cystoprostatectomy had prostate cancer [5]. A rather new technical variation is deliberately leaving the seminal vesicles and prostatic capsule in order to better preserve the surrounding autonomic nerves. The results regarding potency versus oncological risk in small series of selected patients are encouraging but need long-term confirmation in larger series [6, 7]. To date these technical modifications have not been documented to improve continence and they remain highly controversial regarding oncologic safety.

In female patients, standard anterior pelvic exenteration includes the entire urethra, adjacent vagina, uterus, distal ureters, and respective lymph nodes (level of evidence: 3, grade of recommendation: C). Unless the primary tumor is located at the
bladder neck or in the urethra, a major part of the functioning female urethra and, provided a complete tumor resection is possible, its autonomous nerves can be preserved in case of a planned orthotopic neobladder [8, 9, 10, 11] (level of evidence: 3, grade of recommendation: C). New data also question the necessity to remove the uterus or any portion of the vagina, arguing for a better anatomical support of the neobladder and better preservation of surrounding autonomous nerves.

In both sexes, the length of the distal ureteral segment to be removed with the bladder has not been specified and depends on oncological issues such as tumor extension or presence of carcinoma in situ and type of subsequent urinary diversion. In one recent study, frozen section of the distal ureteral margins had a sensitivity of 74% and a specificity of 99.8%, resulting in an overall accuracy of 98.3% [12]. With a serial sectioning strategy, most initially positive ureteral margins can be converted into negative final margins. Those patients were also at decreased risk of developing recurrent disease in the upper urinary tract [13, 14].

RECOMMENDATIONS

Preservation of the anterior and membranous urethra, including parts of the prostate and seminal vesicles for reasons of fertility, potency, and continence, are technical variations to the nerve-sparing approach that may improve patients’ quality of life but must be attentively judged against possible oncological risks. (LE 3, GR C)

In female patients, standard anterior pelvic exenteration includes the entire urethra, adjacent vagina, uterus, distal ureters, and respective lymph nodes (LE: 3, GR: C). Sparing the urethra-supplying autonomous nerves can be performed in case of a planned orthotopic neobladder (LE: 3, GR: C).

REFERENCES


d) Lymphadenectomy

1. Pelvic Lymphadenectomy in Bladder Cancer

Radical cystectomy with pelvic lymphadenectomy represents the treatment of choice for muscle-invasive bladder cancer. Pelvic lymphadenectomy is included as part of the surgical procedure to control loco-regional disease and to potentially improve cancer-specific survival. Survival after radical cystectomy is usually predicted by the pathologic tumor stage, status of surgical margins, and the involvement of lymph nodes.

Although earlier studies have already demonstrated a prognostic benefit of extended pelvic lymphadenectomy as compared to a limited lymphadenectomy, the anatomically adequate extent
of lymph node dissection to obtain reliable staging results is still controversial.

In a recent prospective randomized phase III trial on the clinical efficacy of neoadjuvant chemotherapy plus cystectomy [1], it was shown that surgical factors, including the extent of lymph node dissection and the individual surgeon’s experience, have a major impact on the therapeutic outcome and overall survival [2] (Level of Evidence: 1b). The data of this trial also indicate that chemotherapy was more likely to be of beneficial value if patients received a high-quality surgery by an experienced surgeon. It was concluded that it is extremely important to develop universally accepted standards for radical cystectomy and pelvic lymph node dissection in patients with invasive bladder cancer in order to improve outcome [3].

2. Threshold Number of Lymph Nodes for Accurate Staging

Recently, Capitanio et al [17] evaluated the likelihood of finding one or more positive lymph nodes (LNs) according to the number of LNs removed at radical cystectomy (Level of Evidence: 2b). Results from 731 patients who underwent radical cystectomy and bilateral pelvic lymphadenectomy at three different institutions were analyzed. ROC curve coordinates were used to determine the probability of identifying 1 or more positive LNs according to the total number of removed LNs. Lymph node metastases were present in 174 (23.8%). The mean (median, range) number of LNs removed was 18.7 [17, 1-80]. The ROC coordinate-based plots of the number of removed LNs and the probability of finding 1 or more LN metastases indicated that removing 45 LNs yielded a 90% probability. Conversely, removing either 15 or 25 LNs indicated, respectively, 50% and 75% probability of detecting 1 or more LNs metastases. These data indicate that removing 25 LNs might represent the lowest threshold for the extent of lymphadenectomy at radical cystectomy. In a similar approach, Koppie et al reported a study designed to determine if there was a minimum number of lymph nodes analyzed above which there was no improvement in survival [53] (LE: 2b). The cohort included 1121 patients from MSKCC accrued over a 14-year period. The investigators determined that there was no plateau in the dose-response curve with an increasing number of nodes up to 23 nodes, as very few had 24 or more nodes removed. The authors did not indicate the percent of patients who underwent an extended node dissection, and, in fact, 13% had no nodes identified in the pathology report. The median number of nodes removed was 9.

3. Anatomic Extent of Pelvic Lymphadenectomy

Lymph node metastases are found in 20-25% of patients who undergo radical cystectomy and pelvic lymphadenectomy for bladder cancer, and it is the most important prognostic factor in these patients, predicting significantly decreased recurrence-free survival and overall survival compared to patients without node metastasis [23, 33, 34]. In patients with negative nodes, the total number of lymph nodes removed and the anatomic extent of the node dissection are both useful measures in evaluating the proper extent of surgery and predicting outcome. In patients with nodal metastasis, the number of nodes removed and the number and percent of positive nodes may both be independent predictors of recurrence and survival [35-38].

4. Extent of Pelvic Lymphadenectomy and Therapeutic Outcome

Despite the aforementioned data which demonstrate that long-term survival is possible in patients with lymph node-positive bladder cancer, the anatomical extent of pelvic lymphadenectomy and the minimum of lymph nodes to be retrieved for an accurate staging have not been defined. Some others take the crossing of the ureters with the common iliac vessels as the most cranial limit for lymph node dissection, [9] whereas others extend lymphadenectomy up to the aortic bifurcation. It is generally agreed that the more lymph nodes are removed, the higher is the number of patients with positive lymph nodes [10] LE 3; furthermore, it has been demonstrated that survival after radical cystectomy is predicted by the pathologic stage of the primary bladder tumor and pelvic nodes. Leissner et al [11] suggested that a significant survival benefit was maintained if more than 16 lymph nodes were removed. Stein et al [12] reported that survival in patients with positive lymph node disease was better if more than 15 pelvic lymph nodes had been retrieved. On the other hand, Abdel-Latif and coworkers [13] and Herr [14] could not reproduce the relationship between survival and number of dissected lymph nodes by using multivariate statistical analysis. In this context, it has to be underlined that the number of retrieved lymph nodes can be influenced by many factors such as the surgeon[47], the extent of lymphadenectomy [9-11], presentation of the pathological specimen [16], and pathologic work-up and techniques of analysis [17]. The clinical reality, however, is significantly different: an evaluation of the SEER database in 2003 demonstrated that the majority of patients in a population-based analysis had 4 or fewer nodes removed with cystectomy [40, 41].

Despite these suboptimal clinical factors, there are a few studies having demonstrated a significant impact of the technique of pelvic lymph node dissection with regard to therapeutic outcome. Poulsen et al [8] were among the first to compare the prognostic significance of limited versus extended pelvic lymphadenectomy in a retrospective analysis of 194 patients undergoing radical cystectomy [LE 3]. Limited pelvic lymphadenectomy began at
the iliac bifurcation including the lymph nodes along the external and internal iliac artery and the obturator fossa. Extended pelvic lymphadenectomy began at the aortic bifurcation and included the common, external, and internal iliac artery and the obturator fossa. The authors observed a substantial improvement of 5-year recurrence-free survival in patients with tumors confined to the bladder wall (85% vs. 64%, p<0.02) and without lymph node involvement (90% vs. 71%, p<0.02). Five-year probability for loco-regional (7% vs. 2%) and systemic recurrences (21% vs. 10%) was reduced substantially in patients with bladder cancer confined to the bladder wall in the extended pelvic lymphadenectomy group, but did not reach statistical significance.

In another retrospective analysis of 484 patients undergoing radical cystectomy and pelvic lymphadenectomy, Leissner et al [17] demonstrated that the total number of lymph nodes retrieved had a significant impact on recurrence-free survival (p<0.01) (LE 2b). The 5-year recurrence-free survival rates were 25% and 53% in patients with 14 or fewer and 15 or more lymph nodes removed, respectively. Furthermore, the surgeon had a significant impact on the prognosis as it was shown the number of lymph nodes dissected ranged between 10.6 and 25.7 and differed significantly between the 11 different surgeons in the study. These data are further corroborated by a recent paper on the standardization of radical cystectomy and pelvic lymphadenectomy [3]. However, the authors did not demonstrate a significant overall and cancer-specific survival advantage for patients undergoing extended pelvic lymphadenectomy as compared to those undergoing limited dissection. The authors further evaluated the concept of extended pelvic lymphadenectomy in a prospective clinical trial of 290 patients [20]. The cranial limit of dissection was the inferior mesenteric artery, the lateral border was the genitofemoral nerve, and the caudal limit was the pelvic floor. A mean number of 43.1 ± 16.1 lymph nodes were removed with 27.9% of the patients having positive lymph nodes. Although the group identified a preferred pattern of metastatic spread, they were not able to identify a well-defined sentinel lymph node or lymph node area.

These data are in contrast to the recently published prospective trial of Borchner et al [21] on the evaluation of lymph node count and lymph node mapping (LE 3). One hundred forty-four consecutive patients were included in this monocentric evaluation with 56 and 88 patients undergoing standard and extended pelvic lymphadenectomy, respectively. Standard dissection included the nodal regions of the external iliac, hypogastric, and obturator fossa with the iliac bifurcation representing the cranial limit of lymph node dissection. Extended dissection included the lymph nodes at the aortic bifurcation to no more than 2 cm cranially to the bifurcation and the nodal regions of standard dissection. Although the median number of positive lymph nodes differed significantly between both groups (22.5 vs. 8), there was no difference with regard to the percentage of positive nodes, which was 21% in both groups. Interestingly, all patients with positive nodes above the aortic bifurcation also had positive nodes detected in the lower packages indicating that only extensive locoregional metastatic disease might involve the retroperitoneal areas associated with a dismal prognosis. Including the lymph nodes along the common iliac artery above the iliac bifurcation, however, appears to be of prognostic value and of clinical significance. In the study of Bochner et al [21], 4 patients had unexpected micrometastatic lymph node disease at the common iliac region only. Reflecting the survival data of patients exhibiting micrometastatic lymph node disease at time of radical cystectomy, most of these patients are expected to have a relatively favorable outcome. Morbidity of pelvic lymphadenectomy is not increased by including the common iliac region in routine pelvic lymph node dissection, so this area should be removed as a standard part of staging lymphadenectomy.

Further evidence to include the common iliac region derives from the prospective multi-institutional study published recently by Leissner et al [20], (LE 2b). Eighty-one (27.9%) patients demonstrated lymph node involvement and 35% of all positive lymph nodes derived from above the iliac bifurcation. Furthermore, 20 (6.9%) patients were shown to harbor positive lymph nodes above the bifurcation of the common iliac artery only. Although no data with regard to the prognostic significance in terms of cancer-specific or progression-free survival are available, these data strongly support the idea to include the lymph nodes of the common iliac region up to the aortic bifurcation in routine lymph node dissection for muscle-invasive bladder cancer.

In another study, Abol-Enein et al [22] evaluated the loco-regional distribution of positive pelvic lymph nodes in 200 consecutive patients undergoing radical cystectomy (LE 3). The authors also attempted to identify the probability of lymph node clearance with increasingly wide fields of node dissection. In their investigation, extended pelvic lymphadenectomy included the lymphatic tissue up to the inferior mesenteric artery and the common, external, and internal iliac region. A mean number of 50.6 lymph nodes were retrieved per patient with 48 (24%) patients exhibiting positive nodes. More than one-third of these patients (39.6%) demonstrated bilateral involvement. A single positive lymph node was identified in 22 (45.8%) patients. The authors demonstrated that close to 80% of all positive nodes could be cleared completely if the field of pelvic lymph node dissection included all lymphatic tissues along the common, external, and internal iliac region. Metastases outside the true pelvis were only
detected in multinodal disease and these metastatic deposits were always associated with metastases at the obturator fossa and/or the internal iliac region. Therefore, the authors conclude that standard lymphadenectomy in bladder cancer should always include all lymphatic tissues in the true pelvis; lymph node dissection might be extended up to the inferior mesenteric artery if frozen section examination exhibits positive lymph nodes in the sentinel region of the true pelvis.

Dhar and coworkers [23] evaluated the impact of limited and extended pelvic lymphadenectomy in a cohort of 336 and 322 patients, respectively, who were treated at 2 different institutions (LE 3). The overall lymph node positive rate was 13% for patients with limited and 26% for those who had extended pelvic lymph node dissection. The authors identified a significantly better recurrence-free survival for patients who underwent extended pelvic lymphadenectomy. These figures held true for both organ-confined and locally advanced disease. The 5-year recurrence-free survival of patients with lymph node positive disease was 7% for limited and 35% for extended pelvic lymph node dissection. The 5-year recurrence-free survival for pT2pN0 cases was 67% for limited and 77% for extended pelvic lymph node dissection, and the respective percentages for pT3pN0 cases were 23% and 57% (p<0.0001). The 5-year recurrence-free survival for pT2pN0-2 cases was 63% for limited and 71% for extended pelvic lymph node dissection, and for pT3pN0-2 cases the respective figures were 19% and 49% (p<0.0001). These data confirm that extended pelvic lymph node dissection allows for more accurate staging and improved survival of patients with non-organ confined and lymph node-positive disease.

In another single institution analysis, the clinical importance of dissecting all lymphatic tissue up to the aortic bifurcation became evident when analyzing the outcome of 336 patients who underwent radical cystectomy and extended pelvic lymphadenectomy including the common and external iliac lymph nodes and the periaortic, presacral, and obturator fossa nodes [24], (LE 3). The lymphatic tissue removed above and below the bifurcation of the common iliac vessels was submitted separately for histopathological analysis. Overall, 64 (19%) patients had lymph node metastases of whom 22 (34.4%) had lymph node involvement above the bifurcation of the common iliac vessels outside the template of the standard lymph node dissection. The median number of retrieved lymph nodes was 27 (range 7 to 78) and in those with lymph node metastases 27 (range 11 to 49) included 8 (range 0 to 17) above the bifurcation and 18 (range 8 to 41) below the bifurcation of the common iliac vessels in the true pelvis. Lymph node involvement proved a significant adverse prognostic factor with a 5-year probability of survival of 39% versus 76%. The overall 5-year survival rates were similar in patients with lymph node involvement above the bifurcation of the common iliac vessels (37%) compared to the entire population with lymph node metastasis (41%) and to those with lymphatic metastases in the true pelvis below the bifurcation of the common iliac vessels (42%). The survival rate was significantly higher in patients with 5 or fewer involved lymph nodes (50% vs. 13%, p<0.002) and in those with a lymph node density (number of lymph nodes involved/total number of lymph nodes removed) less than 20% (25% vs. 47%, p<0.05), but it did not relate to the total number of retrieved lymph nodes. These data underscore the contention that extended dissection not only provides the most accurate staging but also offers the patient the best chance of survival. Following radical cystectomy, patients can be stratified into risk groups according to tumor stage, lymph node involvement, number of metastatic nodes, and lymph node density. The results of Steven et al [24] support the idea that the benchmark for radical cystectomy should include extensive pelvic lymph node dissection with anatomic boundaries including the common iliac and presacral nodes.

5. EXTENT OF AN ANATOMICALLY ACCURATE PELVIC-STAGING LYMPHADENECTOMY IN BLADDER CANCER

As has been shown by the previous studies, the anatomic extent of pelvic lymph node dissection in patients undergoing radical cystectomy for muscle-invasive bladder cancer can be well-defined. Standard lymphadenectomy should include all lymphatic tissues around the common iliac, intercommon iliac, internal iliac, d the obturator groups bilaterally since up to one-third of all positive nodes are located around the common iliac artery. This technical variant will allow one to clear 80% of all positive nodes; if frozen section does not demonstrate positive lymph nodes in the true pelvis, lymph node dissection is not needed to be carried out further cranially. If, however, frozen section examination is not performed or if it identifies positive nodes, the inferior mesenteric artery represents the cranial border of lymph node dissection.

6. CRITICAL ISSUES IN ANATOMIC PELVIC LYMPHADENECTOMY FOR BLADDER CANCER

Although the above-cited studies have apparently demonstrated the clinical importance of extended pelvic lymph node dissection with regard to the most efficient retrieval of micrometastatic lymph nodes, there are still some unresolved critical issues.

Pathologic examination of dissected lymph node specimens in these studies has been done more thoroughly and extensively than in other studies concentrating on issues such as overall survival, cancer-specific survival, and regional versus distant failure. Therefore, some critical facts have to be considered for the general community if
extended pelvic lymphadenectomy becomes common practice in all patients undergoing radical cystectomy. Lymphatic tissues dissected from different areas should be sent separately instead of en bloc submissions for pathologic evaluation since it has been demonstrated recently that the yield of lymph nodes increases significantly thereby increasing the frequency of micrometastatic deposits [16]. Intraintitutional standardization of pelvic lymphadenectomy appears to be of utmost importance to generate reliable and reproducible results since staging lymphadenectomy is extremely surgeon-dependent, as has been demonstrated by Leissner et al. [17].

Last, but not least, although the various types of extended pelvic lymphadenectomies have been associated with an improved progression-free survival, none of the trials has demonstrated an advantage with regard to cancer-specific survival. Benefit in terms of progression-free survival might be just due to a stage migration associated with extensive lymph node dissection. The majority of patients with positive lymph nodes will die due to distant metastatic spread in the long run and only the few patients with a single or two metastatic lymph nodes might benefit from the extended variant of lymphadenectomy. In order to solve this question, the Association of Urological Oncology of the German Cancer Society has initiated a prospective randomized clinical phase III trial to evaluate the true clinical efficacy of extended pelvic lymphadenectomy.

In bladder cancer, the biological aggressiveness of a particular cancer may have already been expressed at time of diagnosis and the impact of less or more extensive surgery in terms of recurrence and survival might be completely underestimated. For the future, it will be necessary to shed light on the important clinical questions of the biologic role of lymph node metastases for the likelihood of synchronous or metachronous distant metastases. It will be necessary to evaluate the expression of various growth factors and mediators of systemic spread on patients with lymph node metastases and to correlate these findings with clinically important end points such as cancer-specific survival, overall survival, and locoregional versus systemic recurrence.

**RECOMMENDATIONS**

The extent of lymph node dissection and the individual surgeon’s experience has a major impact on the therapeutic outcome and overall survival [2] (LE: 1b, GR: A.)

The more lymph nodes removed, the higher is the probability to detect at least 1 positive lymph node. However, there is no defined threshold of the numbers of lymph nodes that need to be removed [4, 5] (LE: 2b, GR: B)
1. **Introduction**

Literature on a minimally invasive approach to radical cystectomy has evolved since 1993.[1] Over the past decade, laparoscopic and robot-assisted approaches have been seen as alternatives to open radical cystectomy with the possible advantages of decreased postoperative pain and quicker return to normal day-to-day activity. The robotic approach is similar to laparoscopic with the added benefits of improved range of motion of instruments and 3-dimensional vision, affording a less steep learning curve.

2. **Patient Selection**

Decreased blood loss and need for transfusion, less opioid requirement, and shortened length of stay, with comparable complications to open radical cystectomy has led to radical cystectomy being performed in a minimally invasive fashion. Meanwhile, immediate oncologic results are acceptable, while mature data on long-term oncologic results are still awaited. Patients with clinical T3 and T4 disease should be carefully selected for such approach following consideration for neoadjuvant chemotherapy.[2]

Due to concerns for oncologic control and technical difficulty, surgeons should selectively choose their patients for this approach early in their experience.

As minimally invasive approach has evolved since 1993, key progress has been achieved with adoption of the robot-assisted approach. Despite recent advances, approximately 50% of all patients undergoing radical cystectomy experience recurrence and subsequent mortality.[3]

3. **Surgical Margins**

Despite advantages with magnified 3-dimensional vision and precision achieved by robotic instruments, in robotic interface the lack of tactile feedback has created concerns about adequacy of wider excision in advanced disease and avoiding soft tissue surgical margins. Positive soft tissue surgical margins are associated with high local recurrence, resulting in poor overall survival. Open expert consensus in 2005 recommended less than 10% of all cases and less than 15% for bulky tumors as acceptable positive soft tissue surgical margins rates in radical cystectomy.[6]

Data from the International Laparoscopic Cystectomy Registry in 2008 revealed a soft tissue surgical margin rate of 2%. The International Robotic Cystectomy Consortium, which is a consortium of over 20 robotic surgeons from 15 institutions, demonstrated in 513 patients an overall positive soft tissue surgical margin rate of 6.8%. Advanced stage was independently associated with increased likelihood of a positive margin while case number and institution volume associated with high local recurrence, resulting in poor overall survival. Open expert consensus in 2005 recommended less than 10% of all cases and less than 15% for bulky tumors as acceptable positive soft tissue surgical margins rates in radical cystectomy.[6]

Data from the International Laparoscopic Cystectomy Registry in 2008 revealed a soft tissue surgical margin rate of 2%. The International Robotic Cystectomy Consortium, which is a consortium of over 20 robotic surgeons from 15 institutions, demonstrated in 513 patients an overall positive soft tissue surgical margin rate of 6.8%. Advanced stage was independently associated with increased likelihood of a positive margin while case number and institution volume were not.[8] These rates are similar to larger open series. These findings suggest that positive margins are associated with infiltration of the soft tissue boundaries of the bladder rather than learning curve and surgical error. In patients with large volume tumors and/or suspected extravesical disease, wide dissection of the perivesical tissue is recommended to reduce positive soft tissue surgical margin rates.

9 Collection of data based on surgical pathology rather than clinical stage and absence of centralized pathology review might skew the results from the International Robotic Cystectomy Consortium.

4. **Lymph Node Yield**

Bilateral extended pelvic lymphadenectomy is a
crucial part of radical cystectomy. The incidence of positive nodes at the time of radical cystectomy is in excess of 20%.\[5\] Based on the observed therapeutic and prognostic advantages, experts suggest removal of a minimum of 10-15 lymph nodes and its adequacy has been criticized in the minimally invasive approach. (see discussion chapter 3.1.4) Guru et al reported the feasibility and safety of performing adequate robot-assisted lymph node dissection and demonstrated higher yield with increasing case volume.\[11\] In direct comparison, Wang and colleagues found no difference in the number of lymph nodes retrieved via open or robotic approach (20 vs. 17).\[12\] A recent prospective, randomized, non-inferiority study by Nix et al. demonstrated a mean lymph node yield of 19 in the robotic-assisted group vs. 18 in the open group.\[13\] Second look [open] lymphadenectomy by a different experienced open surgeon showed minimal additional lymph node yield (range 0 – 8) to the previous median 43 lymph nodes removed by a robot-assisted approach.\[14\] Collaborative evaluation by the International Robotic Cystectomy Consortium, has demonstrated a mean lymph node yield of 19 with high volume centers (>100 cases per year) having the highest yields and high surgeon volume (>50 cases) independently predicting extended (rather than standard) lymphadenectomy.\[15\]

The number of lymph nodes retrieved depends on node viability, method of submission (en bloc or separately), and the processing technique. In conclusion, a thorough anatomical dissection around the pelvic vessels and complete clearance of all nodal tissue within the anatomical boundaries using a minimally invasive approach is advocated.

5. Complications

Despite preoperative optimization, advances in surgical techniques, and postoperative care, radical cystectomy remains a morbid operation with complication rates of up to 26–64% and mortality rates of 1-7%.\[16-19\] Radical cystectomy readmission rates are high with bowel-related and urinary infectious complications being most common.\[20\] One of the major attractions towards a minimally invasive approach to radical cystectomy is that the morbidity of this procedure could possibly be reduced. Estimated blood loss reported in minimally invasive series ranges from 100–1100 mL, with most series reporting a mean of less than 500 mL and transfusion rates below 2%. Reported complication rates following a robot-assisted approach are similar to an open approach at 6-65%. Two small prospective comparisons of open and robot-assisted cases showed similar complication rates between the two approaches. In a prospective comparison of complications in 187 consecutive patients who underwent radical cystectomy with either open or robot-assisted approach, the robot-assisted group experienced significantly fewer total complications and major complications at 30 and 90 days.\[26\] Moreover, being operated with robot-assistance was an independent predictor of fewer overall and major complications.

Regardless, published series are limited in patient number and long-term follow-up. Although the only randomized controlled trial of radical cystectomy was designed as a non-inferiority study regarding lymphadenectomy and node retrieval, it also reported no difference in complications between the 2 small groups (n=20).\[13\] although in this study this endpoint was underpowered to clearly define this relationship. Reporting of complications following cystectomy is also limited by patient selection bias, possible under-reporting, and non-standardized documentation.\[28\] In an attempt to overcome these biases, a group from MSKCC reported complications on 156 consecutive (non-selected) patients who underwent robot-assisted radical cystectomy using standardized methodology and fulfilling the Martin criteria for adequate reporting of adverse events following surgery. The 90-day complication rate of 52% and overall complication rate of 65% at median follow-up of 9 months are similar to open series.\[27\] The 90-day complication-related mortality rate was 2.6% and the majority of complications were low grade (63%). Careful reporting of complications following the robot-assisted approach revealed rates similar to high volume open cystectomy centers.

6. Quality of Life

Health-related quality of life (HRQoL) outcomes after surgery remain critical for measuring the impact of any surgical modality. Studies investigating HRQoL in patients undergoing radical cystectomy and urinary diversion are lacking proper credence and power.\[30\] Many of the studies are retrospective or cross-sectional by design and do not use validated questionnaires, while lacking baseline or preoperative assessment.

Gilbert et al evaluated HRQoL outcomes for patients with bladder cancer using Bladder Cancer Index (BCI) in 315 patients. Domains of the BCI included urinary, sexual, and bowel function and bother domain.\[31\] Patients undergoing radical cystectomy had lower sexual function scores than patients who kept their native bladder. The difference in urinary and bowel domains between cystectomy and non-cystectomy patients differed by type of urinary diversion, ileal conduit or neobladder.

As robot-assisted radical cystectomy is a relatively new technique, there is a paucity of literature evaluating HRLQoL in patients undergoing this treatment modality. Yuh et al prospectively evaluated short-term HRQoL outcomes after robot-assisted radical cystectomy and ileal conduit diversion using the FACT-BL questionnaire.\[32\] The FACT-
Thirty-seven percent (288) of those patients had rates of 82% and 68% at 1 and 2 years, respectively.

The Consortium of 820 patients revealed overall survival reports from the International Robotic Cystectomy are similar to those described by Martin.[29] Recent 74%, 85%, and 79%, respectively. These outcomes cancer-specific, and overall survival rates were of minimally invasive approaches.

It is important to keep in mind that much of the long-term morbidity of radical cystectomy is associated with urinary diversion, not extirpation. There is currently no evidence regarding quality of life after intracorporeal urinary diversion.

7. Oncologic Outcomes

The long-term oncologic efficacy of robot-assisted radical cystectomy has yet to be determined, however, surrogate markers of oncologic outcomes which include margin status and lymph node yield have been described earlier in this text. Similar to laparoscopic radical cystectomy, early studies of the robot-assisted approach suffer from selection bias including younger patients, lower stage, and minimal comorbidities compared to most contemporary open series.[33-35] That selection bias makes interpretation of oncologic outcomes difficult.

Previous open series have reported that patients who experience recurrence after cystectomy do so at a median of 12 months.[3] Martin described short-term survival of patients undergoing robot-assisted radical cystectomy. Fifty-nine patients with at least 6-month follow-up were included in that study with mean follow-up of 25 months. Clinical characteristics of these patients appear to be similar to that of open series with 27% of patients having extravesical disease and 34% of patients having lymph node positive disease.[29] Overall survival at 12, 24, and 36 months was 82, 72%, and 72%, respectively. Recurrence-free survival was 82%, 72%, and 72%, respectively. This is comparable to early results of modern open series studies. The retrospective nature of this study with potential selection bias hampers direct comparisons at this time and further studies will need to be performed to evaluate the oncologic outcomes of minimally invasive approaches.

Kaufmann et al described early oncologic outcomes of 85 patients who underwent robot-assisted radical cystectomy.[37] Two-year recurrence-free survival, cancer-specific, and overall survival rates were 74%, 85%, and 79%, respectively. These outcomes are similar to those described by Martin.[29] Recent reports from the International Robotic Cystectomy Consortium of 820 patients revealed overall survival rates of 82% and 68% at 1 and 2 years, respectively. Thirty-seven percent (288) of those patients had extravesical disease and 26% (195) had positive lymph nodes.[38]

8. Intracorporeal Urinary Diversion

Haber et al compared outcomes of patients undergoing complete laparoscopic intracorporeal conduit and their modified “open assisted laparoscopic approach.”[39] Specific technical difficulties with the completely intracorporeal group included a high anastomotic leak rate and long operative times (mean 9.3 hours). This approach was eventually abandoned for an open-assisted laparoscopic approach.

Robot-assisted surgery has helped overcome some of the difficulties in performing intracorporeal urinary diversion. Two small series have described robot-assisted radical cystectomy with the creation of an intracorporeal ileal conduit. The construction of an intracorporeal conduit was performed with combination of both robotic and laparoscopic techniques. The robot was undocked after completion of the radical cystectomy and construction of the ileal conduit was performed in a pure laparoscopic fashion. The robot was repositioned and used to perform the ureterointestinal anastomosis. When the series are combined, ileus was the only postoperative complication in 1 of 5 patients. Operative times ranged from 10-13 hours and stay ranged from 5-10 days (mean 6.8).

Hayn et al recently presented a series of 96 patients who underwent robot-assisted radical cystectomy with creation of either an extracorporeal or intracorporeal ileal conduit.[42] There were no differences in age, body mass index, ASA score, estimated blood loss, or pathologic stage between the two groups. Mean diversion time was similar between the intracorporeal and extracorporeal group (123 vs. 136 min) although mean overall operative time was shorter in the intracorporeal group (390 vs. 356 min). Thirty and ninety-day complication rates were similar between the two groups and there was no difference in the grade of complications. There were no statistically significant differences in bowel-related complications between the extracorporeal and intracorporeal groups (25% and 12%, respectively). Patients in the intracorporeal group, however, had better short-term body image scores compared to the extracorporeal group.

Even smaller series have reported the creation of urinary diversions performed in an intracorporeal fashion. Intracorporeal continent cutaneous diversions and pouches have been reported but are rare. Gaboardi, in 2002, described the first intracorporeal neobladder.[43]

Pruthi et al described a series of 8 ileal conduits and 3 orthotopic neobladders performed intracorporeally. Estimated blood loss, recovery of bowel function, and time to discharge were all comparable to their series of extracorporeal urinary diversions [44].
A recent study of intracorporeal urinary diversions from the International Robotic Cystectomy Consortium included 73 patients who underwent ileal conduit formation and 61 patients who underwent neobladder creation.[45] The mean age of those patients undergoing intracorporeal neobladder was 60. Mean diversion time was longer in the neobladder group compared to the conduit group (224 min vs. 138 min). The 90-day complication rate was 42% for both groups with the majority of the complications being low grade. The neobladder group had a lower risk of both overall complications and high grade complications. Improvements in technology and intracorporeal techniques may allow urologists to become more facile with completely intracorporeal urinary diversion, thus improving outcomes in the future.

RECOMMENDATIONS:

• Robot-assisted radical cystectomy is a surgical option for locally advanced bladder cancer. Larger series and long-term oncologic data are still awaited and will define its permanent role in urologic oncology. (LE 2a, GR: B)

• High volume centers with dedicated minimally invasive surgical teams have shown better results than smaller centers. (LE: 2c, GR: C)

REFERENCES


2. SURGICAL OUTCOME: MORBIDITY AND MORTALITY

a) Introduction

Complications related to radical cystectomy may be directly related to pre-existing patient comorbidities, the surgical procedure, the bowel anastomosis, or the urinary diversion. Variables such as hospital volume, case mix, and surgeon skill and experience influence the rate, type, and severity of surgical complications. Other factors, including the availability and breadth of consultative, diagnostic, and ancillary services, may explain the association between cystectomy volume and short-term surgical outcomes.[1]

When reporting surgical complications during cystectomy, regardless of the technique, a standardized and reproducible classification of surgical complications is applied. The modified Clavien system is one such paradigm and has been used to evaluate complications in more than 6300 surgical procedures.[2] Recently, complications of both open [3] and laparoscopic radical cystectomy[4] have been reported using the modified Clavien system. When possible, overall mortality in the perioperative period should be captured and reported for both the 30- and 90-day postoperative period.[5] Morbidity occurring within 90 days should be considered an early complication, while those complications after 90 days are considered late.[6,7] Despite improvements in surgical technique, anesthetic delivery, and peri-operative care, radical cystectomy remains a challenging procedure. Adverse events of any grade may occur in up to 58% of patients and mortality rates up to 3.9% occur at 30 days after cystectomy. [8, 9, 10, 11]

The following will detail rates of morbidity and mortality associated with cystectomy and urinary diversion, as well as candidate quality of care indicators for treatment of bladder cancer and recommendations from the literature to minimize complications.

b) Morbidities

1. COMORBIDITIES

There is a significant body of literature evaluating...
patient age as a prognostic indicator for radical cystectomy. [12,13] In general, advanced age is a risk factor for the development of complications due to radical cystectomy. However, chronologic age is less the determinant than physiologic age. Other risk factors for morbidity include female gender, prior abdominal surgery, extravesical disease, and prior radiotherapy.[11] Furthermore, elevated body mass index is associated with an increased rate of wound dehiscence and hernia.[14] Unfortunately, most series evaluating radical cystectomy do not include indices of morbidity in the patient evaluation. Suffice it to say, patients with pre-existing neurologic disease, cardiopulmonary compromise, renal insufficiency, autoimmune disease, and bowel disease experience higher rates of complication. [11]

2. PERIOPERATIVE COMPLICATIONS

Intraoperative complications may include acute blood loss requiring transfusion and injury to adjacent structures. Acute bleeding during radical cystectomy is common and is typically associated with ligation of the bladder pedicles or dorsal vein of the prostate in men and excision of the anterior vagina in women. The development of bipolar cautery devices, surgical staplers, and improved understanding of the prostatic anatomy have helped to reduce blood loss during cystectomy. Regardless, average blood loss during the procedure ranges from 600 mL to 1700 mL in large series. [14, 15, 16] Transfusion rates are as high as 66% in some series. [17] Injuries to associated structures, such as the rectum, may occur in as many as 1.7% of procedures.[18]

Medical complications comprise a large proportion of the morbidity experienced by patients after radical cystectomy. These complications include thromboembolic, cardiac, pulmonary, infectious, and renal adverse events. The rates of deep venous thrombosis (DVT) and pulmonary embolus (PE) are up to 5%. [19] Prophylaxis in the form of low molecular weight heparin has been shown to reduce the rates of both DVT and PE. [20] Cardiac events such as congestive heart failure, arrhythmia, and myocardial infarction occur in as many as 7% of patients. [16] Pulmonary compromise in the form of acute respiratory distress, reintubation, or pneumonia complicate the postoperative course of up to 7.8% of cystectomy patients. [21] As many as 13% of radical cystectomy patients develop an infectious complication such as pyelonephritis, sepsis, wound infection, or UTI.[20] It is quite common for patients to have a colonized urine specimen. However, symptomatic urinary tract infections and pouchitis require treatment with appropriate antibiotics. Lastly, renal insufficiency requiring dialysis may occur in as many as 7% of patients in some series. [17]

Surgical complications may arise from the cystectomy, the pelvic lymph node dissection, the bowel anastomosis, or the diversion. Paralytic ileus is quite common during the postoperative course of many cystectomy patients, plugging patients as much as 22.7% of the time. [22] Fortunately, true small bowel obstructions or anastomotic leak are less common, but do occur in up to 8.7% of patients. [17] Lymphocele rates vary on the degree of dissection utilized during pelvic lymph node dissection. With that said, an appropriate lymph node dissection may carry a risk of symptomatic lymphocele in up to 5% of patients. [18] Rates of wound infection, incisional hernia, pelvic hematoma, and fascial dehiscence are widely variable, but may occur in as many as 9% of patients. [23]

3. LAPAROSCOPIC RADICAL CYSTECTOMY

Data from laparoscopic and robotic cystectomy series are relatively immature and with small patient populations. Nonetheless, complication rates are similar to open series and demonstrate similar short-term oncologic control. Adverse events are typically of the same variety as those that occur during open surgery. The typical rate of any form of complication is 30-35% in the literature. [4,24] Not surprisingly, in some series, there does appear to be a slightly greater rate of higher grade complications earlier in a surgeon’s experience. [24]

4. URINARY DIVERSION

Complications due to the urinary diversion vary depending on the type of diversion and may occur in either an early or late fashion. Early complications may occur in the form of urine leak, pouch leak, excessive mucus, urethro-enteric stricture, and ureteroenteric stricture. Urine leak from either a pouch or ureteroenteric anastomosis is noted in as many as 7.7% of patients. [25] Typically, prevention involves the placement of suction drains or ureteral catheters until adequate time for healing. However, there is debate regarding the necessity of routine use and duration of ureteral catheters. Ureteral stricture may be an early or late complication and has occurred in up to 14% of patients in some series. [26] The etiology of the stricture may be benign or, more concerning, a malignant recurrence. Methods for treatment may include percutaneous nephrostomy with antegrade stenting, ureteroscopic balloon dilation, or open revision. The type of anastomosis (Bricker vs. Wallace), does not appear to affect the incidence of ureteroenteric stricture. [27, 28]

The urinary diversion may be the etiology of a variety of late complications in the radical cystectomy patient, which may be benign due to scar from ischemia, technical error, or recurrent tumor. Stomal stenosis has been described in as many as 1.7% of patients and is likely related to ischemia to the conduit. Stomal hernia is a more common occurrence, occurring in up to 5.2% of cases. [21] Both entities may require open revision; the latter may require
transfer to the contralateral side or reinforcement with mesh. Worsening renal function, hydronephrosis, and ureteral reflux may occur in as many as 50% of patients at 15 years. This suggests the importance of long-term follow-up, serial imaging, and laboratory assessments. Metabolic changes are noted in up to 3% of patients with urinary diversions and include Vitamin B12 deficiency, metabolic acidosis, and electrolyte derangements. Concomitant urinary stone disease may occur due to these metabolic changes. Furthermore, chronic bacterial colonization, mucus production, urinary retention, and enteric hyperoxaluria may exacerbate stone formation in patients with urinary diversions. Rates of stone formation may approach 30% in some series. [25]

5. Mortality

Clearly, given the surgical complexity and high rates of surgical morbidity, it is not surprising that mortality from radical cystectomy ranges as high as 3.9% in larger series. Additionally, the rate of mortality climbs for those patients with greater morbidity or advanced age. Recently, Morgan and colleagues performed a retrospective analysis of 220 patients over the age of 75 who underwent radical cystectomy at a high volume center. They noted a sobering 90-day mortality rate of 12.7%. In the multivariate analysis, preoperative albumin was as great a predictor of patient outcome as patient age. [29]

6. Quality of Care Indicators

The treatment and management of bladder cancer is complex and challenging. Metrics are being developed to measure the quality of healthcare provided by physicians and will likely play an increasing role in healthcare delivery in the future. Cooperberg and colleagues recently defined candidate measures for quality of care in the treatment of bladder cancer and their relationship to surgical outcomes.[30] They note that time to cystectomy after diagnosis, hospital volume, surgeon volume, nodal yield, and utilization of orthotopic diversion are associated with improved healthcare outcomes in patients receiving radical cystectomy. However, despite clear recommendations from multiple urologic associations, compliance with treatment guidelines range from a dismal 3% for postoperative mitomycin C to 20% for surveillance cystoscopy and cytology. [31] Likely, improved adherence to recommended guidelines and recognition of important quality of care measures can reduce the substantial morbidity of radical cystectomy for bladder cancer.

RECOMMENDATIONS

- Surgical complications associated with radical cystectomy and urinary diversion should be reported in a uniform grading system. Currently the best adapted graded system for cystectomy is the Clavien grading system \( \text{LE}: 2, \text{GR}: B \).
- Surgical complications associated with radical cystectomy and urinary diversion should include the length of follow-up for the patient cohort and a minimum of 30-day, but preferably 90-day, reported outcome \( \text{LE} 3, \text{GR} C \).
- ASA score, age, previous treatment for bladder cancer or other pelvic diseases, surgeon and hospital volume of radical cystectomy, and type of urinary diversion influence surgical outcome. \( \text{LE} 3, \text{GR}: C \)
- Reduction in blood loss and blood transfusion is afforded by meticulous technique, use of modern surgical devices, and improved understanding of pelvic anatomy. \( \text{LE} 3, \text{GR}: C \)
- Reduction of urinary extravasation and leak can be achieved with careful closure of anastomosis or pouch, stenting of the ureteroenteric anastomosis, and maintenance of appropriate drainage. \( \text{LE} 3, \text{GR}: C \)
- Reduction of symptomatic lymphocele formation can be achieved with appropriate identification of lymphatic channels, careful surgical technique, and an open peritoneal window. Initial treatment should begin with percutaneous drainage. \( \text{LE} 3, \text{GR}: C \)
- Reduction of anastomotic strictures requires meticulous surgical technique, minimal ureteral dissection, well-perfused segment, copious spatulation, and careful apical suture placement. \( \text{LE} 3, \text{GR}: C \)
- Reduction of metabolic disorders after urinary diversion requires preservation of distal ileum, serial monitoring of electrolytes and vitamin B12 levels, understanding of bowel segment physiology, and appropriate emptying of urinary diversion. \( \text{LE} 3, \text{GR}: C \)
- Reduction of DVT and PE can be achieved with use of low molecular weight heparin, early ambulation, and sequential compression devices. \( \text{LE} 1B, \text{GR}: B \)

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3. ONCOLOGICAL OUTCOME OF RADICAL SURGERY ACCORDING TO TNM STAGING

a) Survival According to AJCC/TNM Staging

Long-term oncological outcome of radical cystectomy has been investigated in a multitude of studies which derive mainly from high volume centers across Europe, North Africa, and North America [1-3]. The oncological outcomes reported in these series are based on the TNM staging system, which consists of three important parameters for survival. These parameters are local tumor invasiveness (T-tumor stage), presence of positive lymph nodes (N-nodal stage), and distant metastatic disease (M-metastasis). Based on this concept, patients can be categorized according to six prognostic groups (0a, 0is, I, II, III, IV) as proposed by the American Joint Committee on Cancer (AJCC) [4, 5]. The TNM staging system can be used for determining the clinical and pathological stage of patients with invasive bladder cancer. Tables 1 and 2 list the current 2009 TNM staging system with the corresponding AJCC prognostic groups [6].

One of the largest retrospective single-center series reported oncological long-term outcomes in a total of 1054 patients treated with radical cystectomy and pelvic lymphadenectomy[1]. In the entire cohort, after a median follow-up of 10.2 years, recurrence-free and overall survival rates at 5 years were 68%
and 66%, respectively, and at 10 years 60% and 43%, respectively. In organ-confined disease (pTa-T2b N0; AJCC stages 0a, 0is, I, and II) recurrence-free and overall survival rates at 5 years were 80% and 74%, respectively, and 77% and 54% at 10 years, respectively. By contrast, in extravesical, node-negative disease (pT3a-4a, pN0; AJCC stage III), recurrence-free and overall survival at 5 years dropped to 58% and 47%, respectively, and to 55% and 27% after 10 years, respectively. Among 236 patients with histologically confirmed lymph-node-positive bladder cancer (stage IV according to AJCC) the 5-/10-year recurrence-free and overall survival were only 35%/34% and 31%/23%, respectively [1]. In the meantime, similar single- and multicenter series have confirmed these first cutting-edge results and led to conclude that radical cystectomy is the mainstay of treatment in patients with muscle-invasive bladder cancer [2, 3, 7].

b) Controversial Issues of the Current TNM Staging System

1. pT2 Substaging

In 1997, the AJCC updated the TNM staging system and introduced new substagings for the tumor stages T2 and T3 [5]. The latest version was published in 2009 but without any changes to the former version of 2002 [6]. Both stratifications were thought to provide a better risk assessment for follow-up strategies and improve counseling of patients for adjuvant treatment options [4]. However, in patients with node-negative, pT2a-T2b bladder cancer, classified as AJCC stage II (4), recent retrospective studies have challenged the prognostic importance of substratifying pT2 tumors into those involving the inner (T2a) or outer half of the detrusor muscle (T2b) and suggested consolidating both substages into one [8-10]. The largest of these series included 311 patients with pT2 bladder cancer but found that pT2b classified patients still had a higher risk for lymph node tumor involvement than pT2a classified patients [10]. Furthermore, limitations of these studies were that the extent of lymphadenectomy and number of retrieved lymph nodes were not exactly reported, which might have biased the final survival analysis [10]. Additionally, patients with non-urothelial cell carcinoma or those who underwent neoadjuvant chemotherapy were not excluded from analysis [8, 9].

Therefore, a recent multicenter series on 565 patients with pT2 urothelial carcinoma of the bladder has attempted to overcome these limitations and reported significant differences in survival between both substages in node-negative pT2 disease [11]. These findings were also confirmed in a mixed cohort of 1737 patients with pT2 bladder cancer of whom 54% had squamous cell carcinoma [7]. In this study, the
5-year disease-free survival was significantly higher for patients with pT2aN0 (mean±SE: 76.6±2.2%) compared to those with pT2bN0 bladder cancer (58.3±1.6%). In a recent series, this significant difference in recurrence-free and cancer-specific survival was also confirmed for patients with pT2 urothelial carcinoma of the bladder who were treated with an extended pelvic lymphadenectomy approach [12]. Moreover, another recent multicenter study proposed a weighted prognostic model for patients with node-negative pT2 bladder cancer. Among different independent risk factors (presence of high grade disease or lymphovascular invasion), pT2 substaging was the strongest one for recurrence-free survival [13]. In conclusion, these data support the prognostic importance of the current substratification in node-negative pT2 bladder cancer.

2. Definition of Organ-confined Bladder Cancer

The definition of organ-confined bladder cancer has been controversially discussed in recent literature. A prior series assumed that microscopic extension of the tumor into the perivesical fat (pT3a) does not significantly confer a higher risk for lymph node involvement and decreased survival compared to muscle-invasive bladder cancer [14]. This study included 381 patients (pT2: 172 patients, pT3a: 88 patients, pT3b: 121 patients) and found no significant difference for recurrence-free survival between the stages pT2 versus pT3a, but for the stages pT2 versus pT3b. However, a trend towards significance was reported for cancer-specific survival between patients with pT2 versus pT3a disease (p=0.06) [14]. By contrast, in another series with 134 pT2b patients and 236 patients with pT3a or T3b bladder cancer, recurrence-free and cancer-specific survival was significantly improved for pT2b compared to pT3a patients [15]. Moreover, a current study of the SEER database analyzed the outcomes of 2238 patients with pT2b-T3b bladder cancer and found a significantly higher rate of node-positive disease and all-cause mortality in patients with node-negative pT3a versus pT2b bladder cancer [16]. Regarding these data, it seems anatomically intuitive to define organ-confined muscle-invasive bladder cancer as stages pT2bpN0cM0 or less.

3. pT3 Substaging

The prognostic significance of substaging patients with pT3 bladder cancer into those with microscopic (pT3a) and macroscopic (pT3b) perivesical fat invasion as implemented by the 2002 TNM staging system is also controversially discussed. Most larger series found that the risk of lymph node metastases was significantly higher for patients with pT3b versus pT3a classified disease [15-17] while some smaller series did not [18]. A recent single-center analysis focused on outcomes in 75 patients with node-negative pT3 bladder cancer [19]. Actuarial

5-year recurrence-free survival and cause-specific survival for patients with pT3apN0 versus pT3bpN0 classified disease were not significantly different with 68% versus 72% and 54% versus 42%, respectively. However, a larger multicenter study on 808 patients with pT3N0 bladder cancer (median follow-up 43 months) treated with radical cystectomy without any neoadjuvant modality reported significantly improved 5-year recurrence-free survival (61% vs. 48%) and cause-specific survival (64% vs. 55%) rates for patients with pT3a versus pT3b disease [17]. This assumption is further supported by another multicenter study in which a weighted prognostic model was constructed for 578 patients with node-negative pT3 bladder cancer. pT3 substaging was found to independently contribute to a 2.05-fold increase in the relative risk of decreased recurrence-free survival [20]. In conclusion, the present data do support the current concept of substaging in node-negative pT3 bladder cancer whereas in node-positive pT3 disease a prognostic significance cannot be attributed to this substratification [15, 18].

4. Prognostication in Lymph Node Positive Bladder Cancer

Oncological outcome in patients with node-positive bladder cancer at radical cystectomy is reported to be generally poor with a 5-year recurrence-free survival ranging from 34-43% [1,3, 21]. Nonetheless, long-term survival has been described especially in patients with low-volume lymph node metastasis [21-23]. The following pathological and clinical parameters have been investigated as critical determinants for survival in node-positive disease: number and size of positive lymph nodes [22], extracapsular extension of lymph node metastasis [24], number of retrieved lymph nodes [25], aggregate lymph node metastasis diameter [26], and the anatomic extent of lymphadenectomy reflecting the surgical meticulousness of the lymph node removal [27]. The current pTNM staging system differentiates lymph node tumor involvement according to the number and size of positive lymph nodes (see table 1) but does not reflect sufficiently the surgeon’s capability of removing all the affected nodal tissue.

With growing evidence of the prognostic role of the extent of lymphadenectomy for improving outcomes in invasive bladder cancer [22, 27], the concept of lymph node density (LND) has been proposed [28, 29]. It is defined as the number of positive lymph nodes divided by the overall number of retrieved lymph nodes. In most series, a cut-off value of 20% has been reported to statistically optimally distinguish between different outcomes [25, 30, 31]. Various studies also found that LND outperformed the pTNM based predictions (pN1-N3) in terms of recurrence-free and disease-specific survival [28, 29, 31]. Even more, LND was a superior prognosticator in node-positive patients after adjusting for the
use of adjuvant chemotherapy [31, 32]. On the contrary, Fleischmann et al. reported that LND lost its independent prognostic value after accounting for the presence of extracapsular extension of lymph node metastasis [24]. Although the concept of LND seems to be a promising alternative for improving the prognostication of patients with lymph-node positive bladder cancer, there are several unresolved issues which hinder its unquestionable adoption into clinical practice. Besides the retrospective design of the studies in favor of the concept of LND, the proposed cut-off values are based on statistical calculations and are highly dependent on the surgical extent and meticulousness of lymphadenectomy. Even when considering a defined anatomical template of extended pelvic lymphadenectomy, the number of retrieved lymph nodes can vary between individuals significantly [27] and this might have implications on the proposed cut-off values. Furthermore, different techniques in the pathological processing and evaluation of lymph nodes have to be taken into account [33]. Moreover, in the neoadjuvant setting, LND was not found to be of prognostic value [34]. In this respect, prospective trials are certainly needed to address more specifically the role of LND in patients with lymph-node positive bladder cancer.

c) Outcomes of Patients with Stage pT0 or Carcinoma-in-situ-only Disease

The percentage of patients without evidence of the primary tumor (classified as pT0) at radical cystectomy has been shown to range from 5-7% with a risk of concomitant lymph node metastasis of approximately 3-7.5% [35, 36]. In one study, the following clinical stages were reported at preoperative transurethral resection in 56 patients with final pT0 disease: Tis in 5 (9%), Ta in 2 (4%), T1 in 18 (32%), T2 in 29 (52%), and T3 in 2 (4%) (36). The probability of remaining disease-free at 5 years in patients with invasive bladder cancer (pT1-T2) staged pT0 at radical cystectomy is approximately 89-90% and is significantly higher than in cases with residual pT1-T2 bladder cancer [35, 36]. In a large international study of 228 patients with pT0 bladder cancer at final pathologic analysis, risk factors which independently correlated with decreased survival were the presence of lymph node metastasis and female gender [35].

For patients with carcinoma in situ only, who had undergone radical cystectomy due to refractory conservative treatment, the overall disease-free and cancer-specific survivals were 74% and 85%, respectively. However, 36% of these patients experienced disease upstaging (≥pT1) at radical cystectomy. Similar to patients with pT0 disease, risk factors for decreased cancer-specific survival were found to be the presence of lymph node metastases, lymphovascular invasion, and female gender [37].

d) Stage pT4 Bladder Cancer

Radical cystectomy in patients with T4 bladder cancer has been shown to be a feasible option in terms of therapy-related morbidity [38]. Nevertheless, the oncological outcome of these patients treated without neoadjuvant therapy is generally poor, although some patients may achieve long-term survival. Risk factors that determine independently an adverse oncological outcome are the presence of positive soft tissue surgical margins, lymph node metastasis, lymphovascular invasion, tumors infiltrating the abdominal or pelvic wall (staged as pT4b), and female patients [39]. In this respect, several series have demonstrated that a positive soft tissue surgical margin per se is a strong independent risk factor for decreased recurrence-free and cancer-specific survival [40, 41]. Especially female patients are at increased risk for positive soft tissue surgical margins at radical cystectomy [42]. However, since complete tumor removal cannot be achieved by surgery alone in case of abdominal or pelvic wall infiltration, cystectomy should be preserved in this stage for symptom relief, such as recurrent gross hematuria, pain, fistula formation, and therapy-refractory urgency [43].

e) Impact of Lymphovascular Invasion on Oncological Outcomes

Lymphovascular invasion in pathologically node-negative bladder cancer was found to independently predict worse cancer-specific and overall survival after radical cystectomy, whereas in node-positive disease its independent prognostic significance was not confirmed [44, 45]. Therefore, in node-negative disease, its presence might indicate micrometastasis and, thus, help to improve risk assessment and guide clinicians for counseling patients for adjuvant treatment options or clinical trials [46]. However, when assessing lymphovascular invasion on conventional histological sections, its accurate detection can be hampered due to retraction artifacts and difficulties in identifying small lymphatic or blood vessels [47] which, in turn, limits its prognostic value and stresses the importance of additional immunohistochemical studies.

f) Molecular Markers and Outcome

The predictive value of molecular markers for risk assessment in invasive bladder cancer has been evaluated in a subset of series. These markers play an important role in cell-cycle regulatory or angiogenic mechanisms. The following markers have been recently investigated: E-cadherin, pRB, survivin, p53, p16, p21, p27, cyclin E, and Ki-67 [48-50]. Expression levels of these markers are assessed in cystectomy specimens by immunohistochemical methods and the combination of different markers have been shown to improve the predictive accuracy of standard clinical and pathological risk factors [49].
A recent analysis incorporated serum preoperative C-reactive protein concentration as a serological marker in a new predictive model, termed TNR-C score, and showed that increased levels were not only associated with decreased cancer-specific survival but also with an increase in the predictive ability of standard pathologic risk factors including tumor stage, lymph node density, and resection margin status [51]. Nonetheless, up to now, there are no established molecular markers that can be unequivocally recommended for risk assessment in invasive bladder cancer on a routine basis.

g) Impact of Clinical Parameters on Outcome: Follow-up Duration, Surgical Expertise, and Age

An ongoing discussion in invasive bladder cancer is the validity of the reported survival analyses of retrospective studies with short or intermediate follow-up time interval. Considering the fact that the median time to local or distant recurrence after radical cystectomy in studies with a median follow-up of more than 10 years ranges from 7-18 months [1], a recent study was set up to investigate the validity of disease-free survival rates reported at 2 or 3 years after radical cystectomy. This study found that disease-free survival rates reported at 2 or 3 years correlated well with the 5-year overall survival regardless of the use of adjuvant chemotherapy [52].

Another important parameter that might influence the outcomes of bladder cancer patients is surgical expertise. A recent meta-analysis addressed the ongoing debate on the relationship between high-volume centers and oncologic outcome. A positive significant association on improved survival was not found for hospital (HR 0.89; p=0.06) or for surgeon volume (HR 0.83; p=0.26) [53].

Nonetheless, older patients might derive the highest benefit when treated in a high-volume center [54]. In this respect, the largest series on cystectomy to date from the SEER database analyzed the outcomes of 13,796 bladder cancer patients and demonstrated that patients above 80 years had an increased risk for postoperative morbidity but not mortality. The ability of patients older than 80 years to undergo cystectomy had the highest impact on risk reduction of cancer-related and non-cancer-related mortality [43].

h) Nomograms

In 2006, bladder cancer nomograms were published from the Bladder Cancer Research Consortium (BCRC) and the International Bladder Cancer Nomogram Consortium (IBCNC), and are freely available on the Internet [55-57]. The BCRC nomogram is based on a total of 731 patients treated in 3 North American institutions. In this nomogram, the standard predictors of the AJCC based prediction model, the pT and pN stage, were complemented by the following parameters: age, gender, tumor grade at cystectomy, presence of lymphovascular invasion, presence of carcinoma in situ, neoadjuvant chemotherapy, and adjuvant chemo- and radiotherapy. The addition of these parameters increased significantly the predictive accuracy of the BCRC nomogram by 3.2% as compared to the AJCC-based predictions [56].

By contrast, the IBCNC nomogram relies on more than 9000 cystectomy patients who were treated in 12 international centers worldwide. In this nomogram, the following parameters have been added to the pT and pN stage: age, gender, tumor grade, number of days from diagnosis to cystectomy, and final histology. This nomogram has shown to improve the AJCC based predictions by approximately 7% [55]. The original data sets of both nomograms used 200-bootstrap resamples for reducing overfit bias and for interval validation. Currently, only a few smaller series have externally validated these data but have confirmed an approximately 4% improvement in the predictive accuracy for both nomograms [58].

Nevertheless, some limitations must be taken into account when addressing the patient’s individual risk of recurrence and death by the use of these nomograms. In the IBCNC nomogram, a considerable number of patients with squamous cell carcinomas were included but their primary clinical and pathological parameters were not published, which makes its general applicability difficult [55]. In this respect, the BCRC nomogram provides detailed patient data but the number of included patients is relatively low. In addition, the independent prognostic relevance of some of the included parameters (i.e., adjuvant treatment modalities) currently is controversial (see subsection 4.2). Nonetheless, both nomograms can be regarded as an important tool for estimation of outcomes in patients treated with radical surgery.

RECOMMENDATIONS

The AJCC substratifications in node-negative pT2 and pT3 bladder cancer are of prognostic value (LE: 3, GR: C).

According to the TNM staging system, organ-confined bladder cancer has to be defined as pT2bN0M0 or less (LE: 3, GR: B).

Nomograms provide improved prognostic information for oncological outcomes after radical surgery as compared to the pTNM stage predictions. However, its general applicability has not been established sufficiently by external validation (LE: 3, GR: B).
In patients older than 80 years, radical cystectomy is associated with the highest risk reduction on cancer-related and non-cancer-related mortality (LE: 3, GR: C).

Based on the scarce data available, the routine use of molecular markers for risk assessment after radical cystectomy in invasive bladder cannot be recommended (LE: 3, GR: B).

REFERENCES


IV. PERIOPERATIVE CHEMOTHERAPY

1. APPLICATION OF CHEMOTHERAPEUTIC AGENTS IN BLADDER CANCER: NEOADJUVANT CHEMOTHERAPY

a) Introduction

Radical cystectomy is considered to be the “gold standard” of treatment for patients with clinically localized muscle-invasive bladder cancer. However, despite potentially curative surgery, approximately one-half of patients with deep, muscle-invasive urothelial carcinoma (stages T2b-4) develop metastatic disease within 2 years.[1] At 5 years, the survival rate after cystectomy is at best 65%, ranging from 36-48% (level 3) [2-4] depending on the presence of extravesical extension (pT3) and lymph node metastases (N1-N3). Both factors are associated with an increased risk for recurrence following cystectomy. In contemporary series, 5-year overall survival rates up to 57% have been reported in patients with clinically unsuspected N1 disease, as compared to 0-27% for those with larger volume N2 or N3 disease [3, 5, 6].

b) Rationale for Perioperative Therapy: Advantages and Disadvantages of Neoadjuvant Chemotherapy

Neoadjuvant or adjuvant chemotherapy has the potential of eradicating micrometastases and improving survival in patients with muscle-invasive urothelial carcinoma. This seems to be particularly true for patients with pathologic extravesical and lymph node-positive disease. [7]

Administration of chemotherapy prior to surgery versus after (adjuvant) offers several potential advantages. Patients may be able to tolerate treatment better and the response of the primary tumor to chemotherapy can be assessed [8-12], providing prognostic significance. In a study of patients treated with neoadjuvant cisplatin-based therapy followed by definitive surgery, 91% of patients who responded to chemotherapy (defined as pathologic stage ≤ T1) were alive at a median follow-up of 25 months in contrast to 37% of non-responders [10].

Downstaging of the tumor may provide an indication of the activity of neoadjuvant chemotherapy, especially in patients who have a pathologic complete response and in patients who are pT1 stage after therapy. Those patients with residual disease at radical cystectomy should probably be offered clinical trials evaluating non-cross-resistant alternative agents. A complete response after neoadjuvant therapy may also permit consideration of organ preservation in selected cases. The standard of care is that the majority of patients require and undergo cystectomy or radical radiotherapy.

An important potential disadvantage of neoadjuvant chemotherapy is the discordance between clinical and pathologic staging. In a study reported by Scher et al, [13] while 57% of patients achieved a clinical and cystoscopic complete response following neoadjuvant M-VAC, only 30% had a pathologic complete response at subsequent cystectomy.

A potential disadvantage of neoadjuvant chemotherapy is that patients achieving a complete clinical response at the transurethral resection of bladder tumor after chemotherapy may refuse cystectomy. Another theoretical disadvantage of the neoadjuvant approach is the possibility that some low-stage, low-risk patients may unnecessarily receive neoadjuvant chemotherapy. Conversely, delay of definitive local treatment could potentially be associated with disease progression [14].

The primary disadvantage of the adjuvant chemotherapy paradigm may be that it does not appear feasible in a third of patients within 90 days after radical cystectomy due to postoperative complications or slow recovery of functional status.
Also, approximately 40% of patients who would be candidates for neoadjuvant chemotherapy may not be candidates for postoperative cisplatin because of a perioperative decline in renal function.

Besides all these pros and cons, both approaches are targeting microscopic disease and the question is to know what the best option for an individual patient is. No published trials have directly compared pure populations of neoadjuvant versus adjuvant chemotherapy. In the absence of a specific randomized trial that has compared optimal neoadjuvant and adjuvant chemotherapy regimens in association with cystectomy, it is not possible to make a definitive recommendation about the utility of adjuvant chemotherapy as compared to neoadjuvant treatment. This will be further discussed in the subsequent section of adjuvant chemotherapy.

Before reviewing the accumulating data from controlled, prospective trials on neoadjuvant chemotherapy for bladder cancer, it is beneficial to acknowledge a growing consensus among many investigators for at least selective use of neoadjuvant chemotherapy in subgroups of patients who are known to be at high risk for micrometastatic disease including those with bulky primary tumors, hydronephrosis due to the primary tumor, mixed histology, and possibly lymphovascular invasion within the primary tumor.

**c) Data Supporting a Survival Benefit for Neoadjuvant Chemotherapy: Randomized Trials of Neoadjuvant Chemotherapy**

Neoadjuvant chemotherapy theoretically should provide benefit to patients, whether it is given before cystectomy or before radiotherapy. In the United States, radical cystectomy is preferred for patients who have a good performance status. In most of Europe, radical cystectomy is also the preferred option, although some institutions consider local radical radiotherapy as an alternative.

Several randomized trials have explored whether neoadjuvant chemotherapy improves survival in bladder cancer. The results of these randomized trials are presented in **Table 3** [18, 19]. Some studies suffered from small sample size, suboptimal chemotherapy, premature closure, or inadequate follow-up [20]. Among these trials, single agent regimens failed to show a survival benefit from neoadjuvant therapy [21]. However, well-designed multi-agent chemotherapy trials utilizing effective chemotherapeutic regimens have demonstrated an improvement in survival. These trials have shifted the treatment paradigm in muscle-invasive disease favoring more the use of neoadjuvant chemotherapy [18, 22].

The SWOG Intergroup Trial 0080 randomized patients with T2-T4a urothelial carcinoma of the bladder to radical cystectomy alone (154 patients) versus 3 cycles of M-VAC followed by radical cystectomy (153 patients) [22]. The use of neoadjuvant chemotherapy was associated with a higher rate of complete pathologic response (38% versus 15%, p<0.001). At a median follow-up of 8.7 years, improvements in median survival (77 versus 46 months, p=0.06) and 5-year survival (57% versus 43%, p=0.06) favored the neoadjuvant M-VAC arm. Because of its size, this trial had limited potential to discern a clinically meaningful difference. This trend...
toward improved survival favoring M-VAC–treated patients with an estimated reduction in the risk of death by 25% (hazard ratio [HR], 1.33) provides some evidence of the benefit (level 1) [22]. There were no treatment-related deaths and neoadjuvant chemotherapy did not adversely impact the ability to proceed with radical cystectomy or increase adverse events related to surgery.

Several studies have been published based on retrospective analysis of this trial database. As an example, surgical factors were evaluated in 268 patients with muscle-invasive bladder cancer who underwent radical cystectomy in this Intergroup trial [23]. Cystectomies were performed by 106 surgeons at 109 institutions. Half of the patients received neoadjuvant M-VAC. The 5-year post-cystectomy survival and local recurrence rates in all patients who underwent cystectomy were 54% and 15%, respectively. Surgical variables associated with longer post-cystectomy survival were negative margins (hazard ratio 0.37; p=0.0007) and removal of 10 or more nodes (hazard ratio 0.51; p=0.0001). These associations did not differ by treatment arm (p=0.21 for all tests of interactions between treatment and surgical variables). Predictors of local recurrence were positive margins (odds ratio 11.2; p=0.0001) and removal of fewer than 10 nodes (odds ratio 5.1; P = 0.002). The quality of surgery was an independent prognostic factor for outcome after adjustments were made for pathologic factors and neoadjuvant chemotherapy usage (LE 2).

Another recent analysis evaluated the impact of histology when neoadjuvant M-VAC was given in this trial. There was evidence of a survival benefit from chemotherapy in patients with mixed tumors [24]. Presence of squamous or glandular differentiation in locally advanced urothelial carcinoma of the bladder does not seem to confer resistance to M-VAC and in fact may be an indication for the use of neoadjuvant chemotherapy before radical cystectomy.

The MRC/EORTC performed a large trial in which 976 patients were enrolled and randomized to neoadjuvant CMV (cisplatin - methotrexate - vinblastin) (491 patients) or no neoadjuvant chemotherapy (485 patients) over a 5.5-year period from 106 institutions. This trial was performed more or less during the same time as the SWOG trial. The results of this trial were updated at a median follow-up of approximately 7 years [18]. Management of the primary tumor involved cystectomy, radiation therapy, or both and was left to the choice of investigators. An initial 8% improvement in time to progression and a 5.5% difference in absolute 3-year survival (HR=0.85; 95% CI 0.71-1.02) favoring the neoadjuvant chemotherapy arm was reported. When results were published in 1999, a non-significant trend toward improvement in survival was observed in patients in the CMV arm. In a 2002 update from the American Society of Clinical Oncology (ASCO), with follow-up of 7.4 years, a statistically significant improvement in survival was observed for patients who received neoadjuvant chemotherapy (p=0.048; HR=0.85; 95% CI 0.72-1.0). This trial, well-powered and with adequate follow-up, demonstrated both a survival benefit and improved loco-regional control with neoadjuvant CMV chemotherapy, however, the predefined endpoint with an improvement in survival of 10% was in fact not reached. Survival at 5 years was 50% with CMV compared with 44% with radiotherapy; at 8 years, it was 43% with CMV and 37% with radiotherapy. (level 1).

A trial that was almost identical to the SWOG study was performed by the Gruppo Uro-Oncologico Nord Est (GUONE) cooperative group in Italy [25]. Over a 6.5-year period, 206 patients were randomly assigned to neoadjuvant M-VAC before cystectomy or to cystectomy alone. No clear differences in survival were demonstrated; as 3-year survival was 62% for the M-VAC–treated patients and 68% for patients in the cystectomy alone arm (LE 2).

The Nordic cystectomy I trial evaluated neoadjuvant doxorubicin, cisplatin, and preoperative radiotherapy before cystectomy versus preoperative radiotherapy and cystectomy alone. A 15% survival difference in favor of patients treated with chemoradiotherapy was seen in only a subset analysis of patients with T3 or T4 disease. Investigators were unable to confirm this survival advantage in the subsequent Nordic cystectomy II trial, in which 317 patients were randomly assigned cystectomy or cystectomy preceded by methotrexate and cisplatin (without radiotherapy) [26]. However, combining the 2 trials provided positive results in favor of neoadjuvant chemotherapy (LE 2) [27].

d) Meta-Analysis

Because of the uncertainties of the definitive value of neoadjuvant chemotherapy in terms of survival, a meta-analysis of neoadjuvant chemotherapy trials was performed [28]. Data from 2688 patients treated in 10 randomized trials evaluating neoadjuvant chemotherapy for invasive urothelial carcinoma was reviewed. Of note, this analysis did not include data from the SWOG Intergroup trial. Compared to local treatment alone, neoadjuvant platinum-based combination chemotherapy was associated with a significant benefit in overall survival [HR=0.87 (95% CI 0.78-0.98, p=0.016)], a 13% decrease in the risk of death, and a 5% absolute survival benefit at 5 years (overall survival increased from 45-50%). When trials utilizing single-agent cisplatin were included, the survival benefit did not achieve statistical significance [HR=0.91 (95% CI 0.83-1.01, p=0.084)]. (LE 2). However, single-agent cisplatin did not show an improvement in survival (p=0.26) compared with no neoadjuvant therapy. As all platinum-based combination trials were analyzed as a group, it is not
possible to discern the best combination for use in neoadjuvant therapy.

A subsequently reported meta-analysis that included individual patient data from 3005 individuals enrolled in 11 randomized trials, including the SWOG data extrapolated from the published report[22], confirmed the survival benefit for neoadjuvant cisplatin-based compared to local therapy alone [28, 29].

A very similar meta-analysis of neoadjuvant randomized controlled trials was conducted in Canada.[30] A total of 16 eligible trials that included 3315 patients were identified, and 2605 patients provided data suitable for a meta-analysis of overall survival. The pooled HR was 0.90 (95% CI 82% to 99%; \( P=0.02 \)). Eight trials used cisplatin-based combination chemotherapy and the pooled HR was 0.87 (95% CI 78% to 96%; \( P=0.006 \), consistent with an absolute overall survival benefit of 6.5% from 50% to 56.5% (95% CI 2% to 11%). A major pathologic response was associated with improved overall survival in 4 trials. Neoadjuvant cisplatin-based chemotherapy improved overall survival in muscle-invasive urothelial carcinoma, but the size of the effect was modest (LE 2).

The use of perioperative chemotherapy has been limited until 2003-2005, when these meta-analyses were published. Among 7161 analyzable patients in the National Cancer Data Base with stage III bladder cancer diagnosed between 1998 and 2003, perioperative chemotherapy was administered to 11.6% of patients with 10.4% receiving adjuvant chemotherapy and 1.2% receiving neoadjuvant chemotherapy [31]. After 2003, there has been a slight increase in its use. In a more recent report on 40,388 patients 18 to 99 years old diagnosed with muscle invasive (stages II to IV) bladder cancer in 2003 to 2007 from the National Cancer Database, the incidence of those who received chemotherapy increased from 27.0% in 2003 to 34.5% in 2007 due to an increase in neoadjuvant chemotherapy and chemotherapy without surgery [32]. Clinical Practice Guidelines can help to increase the implementation of neoadjuvant chemotherapy. A Canadian study [33] has shown that neoadjuvant referral and treatment rates increased after publication of the Clinical Practice Guidelines. However, overall referral and treatment rates remained low.

Based on these observations and despite level I evidence, neoadjuvant cisplatin-based chemotherapies continue to be underutilized in the management of bladder cancer, even at high-volume tertiary centers [34].

**e) Novel Combinations as Neoadjuvant Therapy for Bladder Cancer**

The promising results from newer combinations such as gemcitabine and cisplatin/carboplatin with or without paclitaxel in patients with metastatic disease have led to their investigation in the neoadjuvant and adjuvant setting. Although these newer regimens are promising, there are no data from randomized trials supporting their use in the neoadjuvant setting [35] and limited data form phase II trials.

In a phase II trial of 68 patients with adequate renal function and clinical T3 or T2 with hydronephrosis, N0 M0 bladder cancer received 3 cycles of neoadjuvant paclitaxel, carboplatin, gemcitabine (PCaG) with a primary endpoint of pCR. Patients with T4 or node-positive disease received 6 cycles of PCaG with an endpoint of resectability [36]. The caveat is that this regimen was fairly toxic in a population with adequate baseline renal function and may often warrant prophylactc granulocyte growth factors in accordance with guidelines. **

The SWOG conducted a phase II trial of 3 cycles of neoadjuvant paclitaxel, gemcitabine, and carboplatin followed by cystoscopic surveillance or immediate radical cystectomy for patients with cT0 status after chemotherapy [37]. Patients with cT0 status could elect immediate radical cystectomy or cystoscopic surveillance, and those who did not achieve cT0 status underwent immediate cystectomy. There was an unacceptably high rate (60%) of persistent cancer at radical cystectomy in patients presumed to have pT0 status, which suggests that radical cystectomy is a critical component of therapy.

While recently, some potential benefits have been reported with the use of the triple regimen in the adjuvant setting [38], only the M-VAC regimen has been extensively evaluated. On that basis M-VAC has the strongest evidence-based data for neoadjuvant use.

While the gemcitabine/cisplatin (table 3) doublet has not been validated in the perioperative setting, recent retrospective data from the Memorial Sloan-Kettering Cancer Center (MSKCC) shows that the GC regimen produces a pCR rate of 35%, similar to M-VAC [39]. Multiple other reports on use of this doublet for metastatic disease show very similar response rates and survival to that obtained with M-VAC, and with lower toxicity. In contrast to the above MSKCC study, data from the Cleveland Clinic showed that only 7% of patients achieved a pCR with mostly GC and other non-MVC-based regimens mainly administered in community oncology practices [35].

In the absence of definitive supportive data for GC in the neoadjuvant setting, M-VAC remains the preferred regimen.

Trials are building upon combinations of GC or dose-dense M-VAC (DD-MVAC) with novel biological agents administered in 3 to 4 cycles in the neoadjuvant setting with pCR as a key intermediate endpoint [7] (Table 2).
f) Developing a Personalized Neoadjuvant Therapy: A paradigm to define risk of relapse and response to systemic therapy

The ability to predict response to a specific therapy is still a major challenge in oncology. Advances in molecular research have led to the identification of genetic markers that impact upon response to chemotherapy. Based on detailed molecular information for each individual tumor, the clinician will ultimately be able to more accurately select the appropriate therapy for each patient according to individual predicted response. This customized treatment using chemosensitivity markers such as intratumoral molecular pharmacology markers (pharmacogenomics and genetics) should aid in improving outcome [40].

Several reports have outlined a variety of potential predictive markers either in localized disease or in advanced disease. Data remains limited, but it is conceivable that in coming years a marker or a panel of markers may be available that achieves this predictive goal, allowing improved patient selection for chemotherapy.

g) Muscle-invasive urothelial carcinoma

Neoadjuvant chemotherapy followed by cystectomy improves survival compared to surgery alone. However, 20 patients must be treated to cure one additional person compared to surgery alone. To identify those patients who will derive benefit, limited studies have provided some hints on single markers and which specific treatments may be of benefit. At present, many of the published results of gene expression profiling are preliminary, based on small sample sizes, and it is not possible to make a definitive statement on the role of gene expression profiling in the molecular prognostication of invasive urothelial carcinoma. Work in this area is directed along 2 concurrent themes: risk stratification and chemotherapy response prediction.

To this point, defining risk of relapse has been dependent on clinical and imaging based staging, which often understages the patient, with resultant upstaging at surgery [41]. A recent study developed a gene expression model (GEM) in primary bladder cancer tissue to predict the presence of lymph node involvement at cystectomy in the AUO-AB-05/95 trial [42, 43]. A 20-gene signature has an Area under the Receiver Operator Curve of 0.67 for prediction of lymph node metastases and was an independent predictor of their presence in multivariate analysis with age, sex, pathological stage, and lymphovascular space invasion. The gene signature divided patients into high relative risk (1.74, 95% CI 1.03-2.93) and low relative risk (0.70, 95% CI 0.51-0.96) of node-positive disease. Further precision in determining risk of lymph node involvement has the potential to better define the subset of patients who should have neoadjuvant chemotherapy. Such signatures may provide a matrix into which chemosensitivity genes can be intercalated to prediction not only of stage variables for risk of relapse but also benefit from specific chemotherapy agents [44,45]. These hypotheses require testing and validation in neoadjuvant cohorts and more definitively in trials.

There are several studies looking at candidate markers in cohorts of patients treated with neoadjuvant chemotherapy. These are summarized below:

- **p53 aberrancy** as inferred by IHC overexpression, confers a poor prognosis in muscle-invasive bladder carcinoma [46, 47]. In one report of 90 patients undergoing neoadjuvant M-VAC chemotherapy, patients with mutant p53 were 3 times more likely to die from their disease than those with wild-type p53 [47]. The impact of p53 overexpression on survival was predominantly in T2 and T3a tumors. Conversely, a retrospective analysis of data suggested that adjuvant chemotherapy enhanced survival in patients with p53 mutant tumors [48].

- **Ki67**, **p53**, and **angiogenesis** (microvessel staining with CD34) were assessed by immunohistochemistry in 94 patients who accrued to the SWOG 8710 phase III neoadjuvant M-VAC trial [22, 49]. There was a trend toward shorter disease-free and overall survival in patients with higher Ki67 expression. Increased p53 nuclear expression was associated with a shorter overall survival but this was not statistically significant. No association or trend between microvessel density and outcome parameters was noted. The study was very limited in power given the small number of specimens available.

- **BRCA1 mRNA expression** was analyzed by quantitative PCR in tumor biopsies obtained by transurethral resection from 51 patients with locally advanced bladder cancer receiving neoadjuvant chemotherapy. A close correlation was found between BRCA1 mRNA levels and pathological response. Low levels of BRCA1 were shown to predict response to neoadjuvant cisplatin-based chemotherapy, and correlated with longer disease-free survival [50].

- In vitro, **XAF1 expression** enhances the apoptotic response of tumor cells to chemotherapeutic agents. In vivo, in a paired sample study from 14 bladder cancer patients treated with a combination of neoadjuvant gemcitabine and cisplatin, patients with high levels of XAF1 in their tumor had increased rates of response, progression-free survival (PFS), and overall survival (OS)[51].

- **Baseline tumor genomics** appear promising as predictors of pCR but limited small studies have been reported. The Takata study [52], in a retrospective study of patients with invasive...
bladder cancer who received neoadjuvant M-VAC chemotherapy, found that 14 predictive genes separated the responder group (defined as no residual muscle-invasive disease) from the non-responder group. This system accurately predicted the drug responses of 8 of 9 test cases. To further validate the clinical significance of the system, the investigators applied it to 22 additional cases of patients with bladder cancer and found that the scoring system correctly predicted clinical response for 19 of the 22 test cases [53].

In summary, 2 large randomized trials and a meta-analysis support the concept that neoadjuvant chemotherapy for patients with muscle-invasive bladder cancer provides a survival benefit greater than with surgery alone. This approach should be considered for patients who are candidates for cisplatin-based combination chemotherapy and radical cystectomy. For patients who have not received neoadjuvant chemotherapy and who have extravesical or node-positive disease following cystectomy, enrollment in a clinical trial should be encouraged. If patients are not protocol-eligible, adjuvant cisplatin-based combination chemotherapy is a reasonable consideration.

SUMMARY

Cystectomy is considered to be the “gold standard” of treatment for patients with localized muscle-invasive bladder cancer (grade B). A discrepancy between clinical/cystoscopic and pathologic staging can be anticipated after neoadjuvant chemotherapy and therefore cystectomy is not obviated by response (grade B).

Toxicity and mortality associated with neoadjuvant chemotherapy are acceptable (grade B). However, few data on quality of life are available.

Meta-analysis of cisplatin-containing combination neoadjuvant chemotherapy trials revealed a modest difference in favor of neoadjuvant chemotherapy (GR B).

We recommend using M-VAC [methotrexate, vinblastine, doxorubicin, and cisplatin, (table 2)] for appropriately selected cases as the neoadjuvant chemotherapy regimen (GR 1A).

Although other regimens, such as gemcitabine plus cisplatin (GC), have similar activity in patients with metastatic disease, there are no data from randomized trials in the neoadjuvant setting to support the use of regimens other than M-VAC. (Grade 1A)

Available data suggest that for “average-risk” cancer patients with cT2, the benefit of adding chemotherapy to local therapy is at best modest. Likewise, all available studies suggest a much more substantial benefit for patients with high-risk disease, such as cT3b cancers or those thought to have lymph node involvement (GR B).

The quality of the surgery is a confounding factor in interpreting these studies (GR B).

Following cystectomy in patients who did not receive neoadjuvant chemotherapy, we suggest consideration of adjuvant chemotherapy (see below) with a cisplatin-based regimen for patients who have perivesical tumor extension (stage T3 or higher) or regional lymph node involvement (GR 2C).

Presence of squamous or glandular differentiation in locally advanced urothelial carcinoma of the bladder does not seem to confer resistance to M-VAC and in fact may be an indication for the use of neoadjuvant chemotherapy before radical cystectomy (GR 3C).

RECOMMENDATIONS

Neoadjuvant Chemotherapy

- Cystectomy is considered the gold standard of treatment for localized muscle-invasive bladder cancer (grade B).

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2. APPLICATION OF CHEMOTHERAPEUTIC AGENTS IN BLADDER CANCER: ADJUVANT CHEMOTHERAPY

a) Introduction

Despite the high rate of down-staging and response in the neoadjuvant and metastatic setting, cisplatin-based chemotherapy is underutilized in the treatment of urothelial cancer. As a consequence, more than 50% of patients with high grade bladder cancer and muscle invasion ultimately die of disseminated disease. High-risk patients with pT3-pT4 and node negative disease have no more than a 5-year overall survival of 47% after cystectomy; patients with lymph node metastases have an overall 5-year survival rate of up to 31% after radical cystectomy [1, 2]. Despite a high risk of relapse, translating the high response seen in advanced disease into long-term survival in the locally advanced setting has proved difficult [3, 4]. The chemotherapy agents used in urothelial cancer have recently been reviewed and will not be discussed in detail here [5].

Adjuvant chemotherapy for bladder cancer is controversial. This controversy is fueled by suboptimal outcome for advanced patients treated with radical cystectomy alone, a small potential benefit of chemotherapy and a sequence of trials that have been underpowered and/or closed early due to poor accrual as well as the presence of more definitive evidence for neoadjuvant chemotherapy. Neoadjuvant cisplatin-based combination chemotherapy is the standard of care for medically fit patients with high-grade stage T2 or greater bladder cancer based on level 2B evidence for improved overall survival and is discussed in detail above. An alternative is the use of concurrent cisplatin and radiation therapy for which there is also level 2B evidence, albeit in a more highly selective cohort of patients. At this time, there is no proven value to neoadjuvant or adjuvant chemotherapy for patients undergoing definitive chemo-radiation (see discussion in the section on radiation therapy).

Despite definitive evidence for its use, relatively few patients are offered and receive neoadjuvant chemotherapy before surgery [6, 7], although this may be increasingly driven by clinical practice guidelines [8-11]. In tandem with commonly observed upstaging of bladder cancer patients at surgery [12, 13], slow adoption of neoadjuvant treatment has resulted in clinicians being confronted with patients who have not had the potential benefit of chemotherapy in combination with surgery but
who have pathological staging that portends a risk of relapse of up to 70%. This scenario begs the question as to whether patients would be better treated with immediate postoperative chemotherapy or observed for possible relapse and treated at that time. This question is currently the subject of some studies where results are awaited.

Unfortunately, there have been methodological issues with many of the studies undertaken in the postoperative chemotherapy setting and we are left with meta-analyses for our best evidence. A pooled analysis supported adjuvant chemotherapy, with a more extensive meta-analysis demonstrating a benefit to adjuvant cisplatin combination chemotherapy [14, 15]. Since these analyses were undertaken, 4 major phase III studies were commenced and closed: Spanish Oncology Genitourinary Group SOGUG 99/01 [16], CALGB, Italian Multicentric [17], and EORTC 30994 [18]. These trials continue the pattern of premature closure for poor accrual seen in earlier studies, but may contribute in composite to the field.

Recently, a large cohort analysis assessing the effect of adjuvant chemotherapy from several large centers has been published [19] suggesting the greatest impact of adjuvant chemotherapy is seen in patients with extravesical extension or N+ disease.

b) A Short History of Early Clinical Trials of Adjuvant Chemotherapy in Bladder Cancer

Multiple cisplatin-based combinations have been evaluated in the adjuvant setting (see Table 4) [20]. Logothetis et al administered CISCA to a group of 71 post-cystectomy patients with resected nodal metastases, extravesical extension, lymphovascular invasion, or pelvic visceral invasion [21]. These patients were compared in a non-randomized fashion to 62 high-risk patients and 206 low-risk patients who did not receive adjuvant chemotherapy. They concluded that adjuvant CISCA conferred a 2-year disease-free survival advantage to patients with unfavorable pathologic findings (70% vs. 30%, p=0.00012). The earliest randomized control trial of combination chemotherapy administered to patients after radical cystectomy was conducted at USC [22]. Ninety-one patients with p3, p4, or node-positive urothelial carcinoma were randomized to receive 4 cycles of CAP or to observation. Chemotherapy resulted in a significant improvement in the risk of disease recurrence at 3 years (30% vs. 54%, p=0.011, unstratified Wilcoxon test) but only a trend to benefit in the overall risk of death (34% vs. 50% p=0.099, unstratified Wilcoxon). The median survival of patients on chemotherapy was reported to be 4.25 years versus 2.4 years for patients in the observation group. This study has been criticized for the fact that only 33 out of 44 patients assigned to the chemotherapy arm received one or more cycles of CAP, for the small sample size, and for deficiencies in statistical analysis such as the use of the Wilcoxon test emphasizing early differences. Nonetheless, the study was provocative in revealing the potential benefit of adjuvant chemotherapy and in highlighting the difficulties involved in conducting such trials.

<table>
<thead>
<tr>
<th>Center</th>
<th>Regimen</th>
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<tr>
<td>University of Mainz</td>
<td>MVEC/MVAC</td>
<td>Early stopping due to interim analysis favoring chemotherapy</td>
<td>Underpowered</td>
<td>(26)</td>
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<tr>
<td>University of Southern California</td>
<td>Cisplatin-based</td>
<td>Modest benefit for chemotherapy</td>
<td>Methodological issues</td>
<td>(50) (1)</td>
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<tr>
<td>Stanford University</td>
<td>Cisplatin, methotrexate, vinblastine</td>
<td>Early stopping due to interim analysis favoring chemotherapy</td>
<td>Underpowered, delayed time to progression (p=0.01) effect on survival</td>
<td>(27)</td>
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<tr>
<td>1. SOGUG 99/01</td>
<td>Cisplatin, gemcitabine, paclitaxel vs. observation</td>
<td>Early termination due to poor accrual</td>
<td>Major benefit to chemotherapy arm</td>
<td>(16)</td>
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<td>CALGB-90104</td>
<td>Rapid sequence AG-ITP chemotherapy with G-CSF vs. cisplatin, gemcitabine</td>
<td>Early termination due to poor accrual</td>
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<td>(30)</td>
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<tr>
<td>Italian Multicentric study</td>
<td>Cisplatin, gemcitabine vs. observation</td>
<td>Early termination due to poor accrual and futility</td>
<td>Non-significant, underpowered; trend to better outcome in non-chemotherapy arm</td>
<td>(17)</td>
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<tr>
<td>EORTC 30994</td>
<td>GC, M-VAC, or DD-M-VAC vs. chemotherapy at relapse</td>
<td>Early termination due to poor accrual</td>
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A subsequent trial of adjuvant chemotherapy with 3 cycles of cisplatin alone did not result in any survival benefit in a randomized study of 77 patients [23]. Potential explanations for the lack of significant benefit include the usage of single agent cisplatin, the small sample size, the inclusion of patients with lower T stage and lymph node-negative disease, and the administration of the planned 3 cycles of chemotherapy to only 65% of patients in the treatment arm.

Given the superiority of the M-VAC combination over single agent cisplatin in the metastatic setting [24], it became important to evaluate the M-VAC or M-VEC (using epirubicin rather than Adriamycin or doxorubicin) combinations in the adjuvant setting. Stockle et al randomized patients with pT3, pT4, and or pelvic lymph nodes to 3 cycles of M-VAC or M-VEC versus observation[25, 26]. While planned to accrue 100 patients, the study was closed after an interim analysis of 49 randomized patients revealed a significant advantage in relapse-free survival with chemotherapy (p=0.0015). This trial has been interpreted with caution given its early closure and the fact that only 62% of patients randomized to chemotherapy completed the 3 cycles of treatment. Furthermore, patients in the observation arm were not offered chemotherapy at relapse. Two to three years later, the same authors reported their longer experience with adjuvant M-VAC/M-VEC in 83 patients. Forty-nine of the patients had been enrolled in the prospective trial before being closed while the remaining 38 had received M-VAC/M-VEC as a routinely recommended therapy based on the interim results of the trial. Longer follow-up of the patients (38 to 78 months) who were on the trial confirmed significant improvement in progression-free survival in the adjuvant chemotherapy group (p=0.0005). The continued advantage in progression-free survival with more mature data offered support to the beneficial role of chemotherapy.

The combination of cisplatin, vinblastine, and methotrexate was utilized as adjuvant therapy in a prospective randomized trial of 4 cycles of CMV versus observation following cystectomy at Stanford University [27]. Patients accrued to this trial had pT3b and pT4 urothelial carcinoma with or without lymph node involvement. Data was reported on 50 out of 55 enrolled patients. Twenty-two out of 25 patients randomized to adjuvant therapy received the total number of 4 planned cycles. With a median follow-up of 62 months, a significant difference in freedom from progression was noted between the chemotherapy and the observation group (median of 37 months vs. 12 months respectively, p=0.01). No significant difference in overall survival was noted.

c) Meta-analysis and Composite Analysis

In 2006, an analysis was published of both composite trials and a meta-analysis of individual trials of patients who were treated in adjuvant chemotherapy trials compared to observation studies that were published before September 2004. The analysis was limited in its ability to be definitive in most eyes, with only 491 patients from 6 randomized controlled trials included. The overall hazard ratio for survival of 0.75 (95% CI 0.60-0.96, p=0.019) suggested a 25% relative reduction in the risk of death for chemotherapy compared to controls (see Figures 1 and 2). The authors commented on the small number of patients and relative poor quality of data going into the meta-analysis and highlighted the need for accrual to ongoing phase III trials examining adjuvant therapy.

Concomitantly, Dr. Ruggeri and colleagues undertook a composite analysis from published data from all phase III studies of adjuvant chemotherapy published [14]. While less stringent than the Cochrane review, the conclusions were similar with a benefit to adjuvant chemotherapy for overall survival (RR 0.74; 95% CI 0.62-0.88 [P= 0.001]) and disease-free survival (RR 0.65; CI 0.54-0.78, [P<0.001]).

Concurrently investigators have begun to compare different adjuvant regimens. Investigators at MD Anderson presented data comparing 2 cycles of preoperative chemotherapy with M-VAC and 3 afterwards with the same chemotherapy given only postoperatively [28] in a group of patients at high risk of extravesical extension or nodal involvement at surgery. This study demonstrated a high likelihood of extravesical extension or nodal involvement in nearly 80% of patients treated with initial surgery, and no difference in survival whether the chemotherapy was given in the neoadjuvant or adjuvant setting. While there was no difference between the two approaches in terms of outcome, it did demonstrate the feasibility of preoperative chemotherapy and, in particular, that such therapy did not result in deterioration or toxicity so that the patient had delayed surgery or missed it altogether. The German Urologic Oncology groups ran a phase III trial for patients with stage pT3a-4a and/or pathologic node-positive urothelial carcinoma of the bladder after radical cystectomy, randomizing 327 patients to either cisplatin and methotrexate (CM) or methotrexate, vinblastine, epirubicin, and cisplatin (M-VEC) (29). The 5-year progression-free, tumor-specific, and overall survival rates were not significantly different between the 2 arms although patients given M-VEC had higher rates of grade 3 or 4 leukopenia (22%) than those given CM (7%, p=0.0001).

The meta-analysis and composite analysis represent a watershed in perioperative chemotherapy for bladder cancer in part because they suggested benefit from chemotherapy but highlighted the relative poor quality of the trials undertaken in the area. The advent of phase III evidence for neoadjuvant M-VAC at around this time also shaped thinking with
Figure 1. Composite Kaplan-Meier curve of overall survival in bladder cancer patients treated with adjuvant chemotherapy or observation that were included in the Cochrane individual patient data meta-analysis (15).

Figure 2. Hazard ratios for overall survival in bladder patients treated with adjuvant chemotherapy or observation that were included in the Cochrane individual patient data meta-analysis (15).
neoadjuvant therapy becoming a standard of care. Despite this, most patients were not being offered chemotherapy before surgery. When presented with the all too common upstaging and/or more definitive evidence of risk of relapse in the surgical pathology report, many clinicians and patients considered postoperative treatment despite deficiencies in evidence to support this approach.

d) More Recent Phase III Trials

Subsequently, 4 major phase III trials have been formulated and opened to accrual. They share a common theme: adjuvant chemotherapy for transitional cell-predominant urothelial cancer coupled with the acrimony of early closure for slow accrual.

The **Italian multicentric trial** saw 194 patients with pT2G3, pT3-4, N0-2 transitional cell bladder carcinoma treated with radical cystectomy who were then randomized to immediate chemotherapy or a control arm of observation and chemotherapy at relapse [17]. Patients were stratified by center and lymph node metastases. Those patients given adjuvant chemotherapy were randomized to two slightly different schedules of gemcitabine and cisplatin over a 4-week cycle given for 4 cycles. The primary endpoint was overall survival. The 3-year overall survival was 67% (± 6% SE) for chemotherapy at relapse patients and 48% (± 6% SE) for those given immediate adjuvant therapy with corresponding 3-year disease-free survival of 47% and 35%, respectively. These differences were not statistically significant. The authors concluded that there was no role for adjuvant chemotherapy after cystectomy for locally advanced bladder. The outcome data from this trial run counter to prior publication in a peer-reviewed journal with more data on surgical treatment given and chemotherapy delivery in each arm is awaited.

The **Cancer and Leukemia Group B 90104** trial saw patients with urothelial carcinoma of the bladder treated with cystectomy and with a creatinine clearance greater than 60 mL/min randomized to either a rapid cycling regimen of chemotherapy with 4 cycles of doxorubicin-gemcitabine given at 14 day intervals with granulocyte colony stimulating factor support followed by 4 cycles of paclitaxel-cisplatin given at 21 day intervals compared to adjuvant gemcitabine with cisplatin in a 4-week cycle [30]. Up to 4 cycles of 4 weeks each of each regimen were administered. Accrued patients were stratified based on pathological criteria according to primary tumor status (<T4 vs. T4), number of positive lymph nodes (0 or unknown vs. 1-5 vs. >5), and number of dissected nodes (0-10 or unknown vs. more than 10). Patients commencing chemotherapy no earlier than 42 days and no more than 3 months after surgery. The accrual target was 800 patients, however, the study was halted due to slow accrual less than 2 years after opening with fewer than 100 patients enrolled. Subsequent analysis of Memorial Sloan Kettering Cancer Center data from studies used to develop the rapid cycling regimen in more advanced disease, which also incorporated ifosfamide, suggested issues with toxicity in the accelerated therapy arm that was also an issue in this trial [31]. In retrospect, CALGB 90104 may have been overly ambitious in attempting to move a dose-dense regimen forward in the same step as the integration of newer agents. Published results from this trial are awaited.

The **Spanish Urologic Oncology Group** opened the 99/01 trial comparing 4 cycles of paclitaxel, cisplatin, and gemcitabine (PCG) to observation [16]. This regimen was used based on the results of a phase I/II trial in the advanced disease setting [32]. In a subsequent phase III trial in advanced urothelial cancer, the addition of paclitaxel increased the efficacy in terms of response rate when compared to GC with a benefit in overall survival seen only in patients having the bladder as primary (post-hoc analysis). In the intention-to-treat population, only a trend was observed (p=0.07) [33]. The adjuvant 99/01 trial accrued patients with pT3-4 and/or lymph node positive bladder cancer with a creatinine clearance greater than 50 mL/min and mandated chemotherapy commencement within 8 weeks of cystectomy, whereas prior studies had allowed up to 12 weeks after surgery. The trial enrolled 142 patients between July 2000 and July 2007 when it was closed prematurely due to poor accrual. Toxicity in the triple drug chemotherapy arm was acceptable with a single treatment-related death due to sepsis. At a median follow up of 30 months, overall survival was significantly prolonged in the PCG arm (median not reached; 5-year overall survival 60%) compared to observation (median 26 months; 5-year overall survival 31%) (p<0.0009). Disease-free survival (p<0.0001) and disease-specific survival (p<0.0002) were also superior in the PGC arm. The results from this trial raise several questions.

- Does the addition of paclitaxel increase the efficacy of PCG in this setting compared to GC or MVAC, when data for the addition of paclitaxel to GC in the advanced setting are lacking [33]?
- Did the stringency of time to commencement of chemotherapy in this trial contribute to the difference seen in overall survival?
- Given data from several centers suggesting diminished survival outcomes in patients with later commencement of chemotherapy compared to those starting earlier [28], should clinical trials and clinical practice outside trials mandate commencement within 8 weeks of surgery?
The EORTC-30994 trial accrued patients with pT3-4 and/or lymph node positive urothelial cancer and with a creatinine clearance greater than 60 mL/min to either 4 cycles of cisplatin-based combination of chemotherapy of physician preference (GC, MVAC, or Dose-Dense MVAC [34]) or chemotherapy with the same regimen at first relapse [18]. Both standard M-VAC and GC were given on a 4-week cycle whereas DD-MVAC was given every 2 weeks. Patients were stratified by pT stage and number of lymph nodes dissected. Those patients randomized to the chemotherapy arm were required to start treatment within 90 days of surgery. The study was unique in allowing a range of chemotherapy regimens including a more intense deliver of cytotoxic drug with DD-MVAC. The accrual target was 660 patients but this trial also closed prematurely in June 2008 due to slow accrual after accruing 278 patients.

A further meta-analysis incorporating individual patient data from the Italian multicentric, Spanish Urologic Oncology Group and EORTC-30994 trials was prospectively planned and will proceed once data from each trial becomes mature.

e) Data from Larger Cohort Studies

A recent collaborative effort between 11 major centers has yielded an international cohort analysis of off trial adjuvant chemotherapy [19]. Patients were grouped into quintiles based on risk characteristics for relapse and death and chemotherapy impact assessed across the cohort as a whole but also within each risk segment. The cohort consisted of 3947 patients undergoing cystectomy and lymph node dissection between 1979 and 2008, 932 (23.6%) of whom received adjuvant chemotherapy; the largest analysis of an adjuvant chemotherapy cohort to date. Adjuvant chemotherapy was independently associated with improved survival (hazard ratio, 0.83; 95% CI 0.72-0.97, P=0.017). Significantly, risk group predicated the survival impact of chemotherapy on outcome. Increasing benefit from adjuvant chemotherapy was seen across higher-risk subgroups (P<0.001), especially in those with extravesical extension or nodal involvement. There was a significant improvement in survival between the treated and non-treated patients in the highest-risk quintile (hazard ratio, 0.75; 95% CI 0.62-0.90; P=0.002). This group was characterized by an estimated 32.8% 5-year probability of cancer-specific survival, with 86.6% of patients having both stage T3 or greater and nodal involvement. These data may be useful in stratifying and selecting patients for future studies.

Analysis from the same group of investigators suggests that 2- and 3-year disease-free survival after cystectomy is a strong surrogate for 5-year overall survival [35]. This surrogate needs to be tested in prospective cohorts treated with adjuvant chemotherapy but may be key in planning studies with an initial phase II accrual in the adjuvant setting before expanding to a larger phase III cohort of disease-free survival and toxicity endpoints are met.

f) Biomarkers and Other Indicators of Potential Adjuvant Chemotherapy Benefit

The literature is beset with multiple analyses of individual markers of outcome after cystectomy, p53 aberration, cycle cell gene dysregulation, and presence of lymphovascular invasion identify patients with low risk (<pT2) disease who are at heightened risk of relapse (36-38). Recent attempts have been made to link these markers with systemic therapy interventions. In the p53 M-VAC trial, patients were screened for p53 abrogation and randomized to either 3 cycles of M-VAC or observation [39]. The trial was closed due to futility contingent upon slow accrual and low event rate. The final analysis did not demonstrate an advantage for M-VAC chemotherapy in patients whose tumors contained abnormal p53, in fact those patients had a non-significant trend to a higher relapse and death rate with chemotherapy. This result proved disappointing and once again highlighted the difficulty of running trials at the adjuvant interface in bladder cancer. Current biomarker efforts led by the International Bladder Cancer Consortium are directed at large scale tissue microarray construction and analysis for putative markers of chemotherapy response such as ERCC1 (platinum drugs) [40-43], ribonucleotide reductase (gemcitabine) [44, 45], topoisomerase II (doxorubicin, epirubicin) [46, 47], and beta-tubulin (taxanes) [45, 48, 49]. Hopefully, these studies will delineate relationships between markers and therapies as well as defining magnitude of effect to help power those studies. Targeted monoclonal and small molecule agents remain of interest in urothelial cancer and a focus of studies that will attempt to treat patients that have the target present in their tumor and therefore are more likely to respond.

SUMMARY

The body of evidence supports the use of perioperative chemotherapy, however, the best evidence is for neoadjuvant rather than adjuvant therapy. Several studies have suggested a 5-15% absolute advantage for chemotherapy in the postoperative setting. Given the small incremental benefit to adjuvant chemotherapy, the demonstration of a survival advantage may take a trial with several thousand patients unless patients accrued can be stratified for risk: benefit by clinical or pathological parameters and/or biomarkers predictive of relapse risk and/or chemotherapy benefit. The optimal timing and intensity of chemotherapy in the adjuvant setting remains to be determined. Accrual to trials of adjuvant therapy in urothelial cancer represents a major challenge.
**RECOMMENDATIONS**

Adjuvant cisplatin-based chemotherapy is supported by a recent large cohort analysis (LE: 2A), several relatively small randomized clinical trials (LE: 1B), and the results of a meta-analysis and composite analysis or randomized trials (LE: 1A). However, the consensus in the writing group is that the trials used in meta-analyses were flawed so as to make definitive conclusions difficult. On that basis, the group provides a Grade B level of recommendation for adjuvant cisplatin-based chemotherapy in the patient with pT3/4 and/or lymph node positive cancer at cystectomy, who has not had neoadjuvant chemotherapy and is medically fit.

Adjuvant regimens not containing cisplatin (including those containing carboplatin) should not be routinely used outside of clinical trials because of a lack of evidence for their benefit in that setting. We therefore offer GR against use of non-cisplatin containing regimens. Patients who cannot tolerate cisplatin-based combination therapy should be observed unless a clinical trial is available.

Until the current equipoise is resolved for adjuvant chemotherapy in this setting, clinical trial remains the best choice for patients with locally advanced bladder cancer.

**REFERENCES**


V. PERIOPERATIVE RADIOTHERAPY

Adjuvant and neoadjuvant radiotherapy for muscle-invasive and locally advanced bladder cancer were performed in the 1970s and 1980s of the last century without many convincing results [1]. However, use of modern radiotherapy in combination with surgery resulted in prospective randomized clinical trials or case-control studies which improved the local control rate, frequency of distal metastases, and overall survival in patients with locally advanced bladder cancer [1] (level of evidence: 2b, grade of recommendation: B).
1. BACKGROUND
Radical cystectomy with urinary diversion represents the treatment of choice for muscle-invasive bladder cancer according to the most recent guidelines. However, especially for patients with locally advanced disease, the survival rates are dismal at 19-59% and 9-49% for patients with pT3 and pT4 disease, respectively [2, 3]. Although the causes of failure are mainly distant metastases, local recurrences are described in 23-51% of the cases. In one series, rates of local recurrences were 6%, 18%, and 51% in patients with stage pT1, pT2, and pT3 disease, respectively [4]. In another series 11%, 23%, and 31% of the patients developed local recurrences within 5 years after radical cystectomy [5]. The considerably high rate of local failures in the various stages of bladder cancer suggests the presence of residual micrometastasis in the pelvis, either in the remaining pelvic lymph nodes or at the site of the tumor bed. The median time to local recurrence was 7-12 months whereas the median time to the development of distant metastases was 16-20 months suggesting that local recurrences might precede distant metastases [4-7]. It has been demonstrated in some studies that local failures besides pT stage and nodal metastases represent an independent predictor of distant metastasis. Furthermore, it has been shown that the presence of local recurrences is associated with a poor outcome and a median survival of 5-8 months [4-7]. Based on these data, it seems reasonable to sterilize microscopic metastasis or residues either by preoperative or postoperative radiation therapy.

2. PREOPERATIVE RADIOTHERAPY
Preoperative radiation therapy was used in the 1970s. However, conflicting results have been produced over the years so that the concept of preoperative radiotherapy to prevent intraoperative tumor cell seeding and to eradicate microscopic metastasis in the perivesical fat was not introduced in daily routine.

a) Retrospective Studies
Cole et al [8] and Pollack et al [8] published the largest retrospective series on preoperative radiotherapy and cystectomy versus cystectomy alone in muscle-invasive bladder cancer comprising 560 patients of whom 338 and 232 patients received the combination treatment of surgery alone, respectively. A mean total dose of 49.3 Gy at 2 Gy per fraction was delivered 4 to 6 weeks prior to cystectomy. The median follow-up was 91 months and 54 months in the radiation and the cystectomy alone groups, respectively. The 5-year local control rate in patients with stage T3b was significantly improved in the radiation group with 91% as compared to the cystectomy group with 72% (p=0.03). Patients with T3b disease also demonstrated a better 5-year outcome with regard to freedom from distant metastasis (67% vs. 54%), disease freedom (59% vs. 47%), and overall survival (52% vs. 40%) although these differences did not reach statistical significance. It has to be considered that 65% of the T3b patients in the cystectomy only group received systemic chemotherapy so that the results might be better than expected. In a further analysis of the patient’s data, Pollack et al [8] identified pretreatment hemoglobin, blood urea nitrogen, and preoperative radiotherapy as the only independent predictors of local control. Similar results were reported by Pollack et al [8] in an additional analysis of the patient cohort who identified pathological response (p<0.0001), clinical stage (p<0.01), hemoglobin level (p<0.02), pathologic complete response (p<0.05) and BUN concentration (p<0.05) to be significantly associated with the pelvic control rate. Restricting the analysis to pretreatment parameters only, clinical stage, hemoglobin, BUN level, and sex were predictive factors of pelvic control. Pathologic response and tumor size were independent predictive factors associated with overall survival and pretreatment hemoglobin and tumor size were the only factors associated with a long-term disease-free status.

In another retrospective study, Granfors et al [9] compared the outcome of 90 and 97 patients with muscle-invasive bladder cancer who received or did not receive neoadjuvant radiation therapy, respectively. Neoadjuvant radiotherapy resulted in a significant downstaging effect so that 7% and 57% of patients without and with radiotherapy demonstrated pT0 disease in the radical cystectomy specimen. Among cT3 tumors, 0% and 56% of the patients without and with radiotherapy achieved pT0 disease. The progression-free survival was significantly longer for patients who underwent neoadjuvant radiotherapy (p<0.001); the disease-specific survival time of patients with cT3 disease was significantly higher after neoadjuvant radiotherapy as compared to cystectomy alone (p = 0.007).

b) Prospective Studies
So far only 6 prospective randomized clinical trials have been published with only one trial demonstrating a statistically significant difference in the 2-year disease-free survival [10-14].

In one of the first trials, Slack et al [11] analyzed the outcome of 234 patients with muscle-invasive bladder who underwent preoperative radiotherapy with 45 Gy and who underwent radical cystectomy 30 days after radiotherapy. The 5-year survival after preoperative radiotherapy was 55% as compared to only 32% in the cystectomy-only group. In another prospective trial, Awwad et al [12] compared the outcome of 36 and 17 patients with cT3 carcinoma in bilharzial bladders who underwent preoperative radiotherapy with 40-41 Gy followed by radical
cystectomy as compared to radical cystectomy. The authors identified a significant 2-year survival benefit of 53% in the radiotherapy group versus 19% in the cystectomy group. However, the trial has several drawbacks: (1) only patients with T3 disease were included, (2) the patient numbers were small with only 53 recruited patients, and (3) patient numbers per arm were not equally distributed, and (4) squamous cell carcinoma of the bladder might have another clinical course than urothelial cancer. Anderstrom et al [13] evaluated the prognosis of a group of 44 patients with cT1-3a urothelial bladder cancer of whom 22 received preoperative radiotherapy with 32 to 54 Gy. The 3- and 5-year survival rates were 81% and 61% in patients without radiotherapy and they were 81% and 75% in patients with radiotherapy. Patients with a complete response after radiotherapy (pT0) had the best prognosis. Ghoneim et al [14] prospectively randomized 93 patients with cT1-T4 bilharzial bladder cancer to receive preoperative radiotherapy with 20 Gy followed by radical cystectomy versus cystectomy alone. After a minimum follow-up of 5 years, there was no statistically significant difference between both groups with survival rates of 39% and 32%. In the most recent study, Smith et al [15] randomized a group of 140 patients with invasive bladder cancer or rapidly recurring superficial high grade tumors to receive 20 Gy of pelvic radiation followed by cystectomy within 1 week or cystectomy alone. The 5-year survival rate was 53% in the combination group versus 43% in the cystectomy group (p=0.23).

A recent meta-analysis pooled the data from 5 randomized trials to compare 3- and 5-year survival rates between patients who received preoperative radiation therapy followed by cystectomy versus patients who were treated by radical cystectomy alone [16]. The corrected odds ratio was 0.94 (95% CI 0.57-1.55) indicating a non-statistically significant result. The clinical trial data achieved with this meta-analysis do not support a significant role of preoperative radiotherapy in patients with muscle-invasive bladder cancer, which was confirmed in another recent systematic review in the role of radiotherapy in bladder cancer [17]. However, it is questionable if the data achieved in these trials can be transferred into modern management of bladder cancer in the 2000s for several reasons. All of the randomized trials have been performed in 1970s and the 1980s and none of the trials could consider modern high-precision techniques such as intensity modulated radiotherapy or image-guided radiotherapy. Therefore, there might be space for new prospective randomized clinical trials in patients with muscle-invasive bladder cancer without evidence of distant metastases.

d) Postoperative Radiotherapy

Postoperative radiotherapy has the benefit that the group of patients who might benefit from radiotherapy can be better identified as compared to preoperative radiotherapy. Postoperative radiotherapy, however, bears the significant problem that 2 dose-limiting tissues are present in the pelvis: the intestinal epithelium on one hand, including intact loops of bowel and also those of an orthotopic neobladder, and the late responding connective tissues around the anastomosis of the ureter, the urethra, and the pelvis. In some reports, the frequency of radiation-induced obstruction of the small bowel was as high as 37% with 25% and 10% of the patients who required surgery or died, respectively [19]. There are no prospective randomized clinical trials of postoperative radiation therapy in patients with muscle-invasive urothelial cancer of the bladder available. The only prospective randomized clinical trial has been performed in patients with muscle-invasive carcinomas in bilharzial bladders [20]. In this trial, 236 patients with locally advanced cT3a to cT4 bladder cancer were included and they received either postoperative radiotherapy multiple daily fractionation (MDF), using 3 daily fractions of 1.25 Gy each, with 3 hours between fractions, up to a total dose of 37.5 Gy in 12 days (75 patients); or postoperative radiotherapy conventional fractionation (CF), for a total dose of 50 Gy/5 weeks (78 patients). Postoperative radiotherapy demonstrated a significant improvement with regard to 5-year disease-free survival which was 49% and 44% for hyperfractionated and conventional postoperative radiotherapy as compared to 25% for cystectomy alone. The therapeutic benefit of postoperative irradiation was consistent for all tumor types, histological grades, and pathological stages for both the disease-free survival and local control in patients with negative lymph nodes. Patients with nodal metastases demonstrated lower recurrence rates in the postoperative radiotherapy groups, but this was not associated with improved disease-free survival.

The only retrospective study on adjuvant radiation
therapy in patients with urothelial bladder cancer was published by Cozzarini et al [22], who analyzed the oncological outcome of 150 patients. All men received a total dose of 50 Gy to the pelvis and achieved a disease-free survival rate and local control rate of 44.6% and 88.4%, respectively. There are, however, 3 updated reports from nonrandomized postoperative radiotherapy studies in patients with squamous cell and adenocarcinoma of the urinary bladder [23-25]. The latest update comprised 216 patients who were treated with radical cystectomy and pelvic lymphadenectomy with (82 patients) or without (134) postoperative radiotherapy. Postoperative radiotherapy was given to the whole pelvis in a dose of 50 Gy/25 fractions over 5 weeks, and started 4-10 weeks after surgery. Postoperative radiotherapy improved the disease-free survival significantly from 33 +/- 6% for cystectomy alone to 58 +/- 6% for patients receiving postoperative radiotherapy (P=0.002). The independent prognostic factors for disease-free survival were the pathological stage, histological subtypes, nodal involvement, and the addition of postoperative radiotherapy.

RECOMMENDATIONS FOR PREOPERATIVE RADIOTHERAPY

- Preoperative radiation therapy prior to radical cystectomy results in a significant downstaging effect on muscle-invasive bladder cancer (LE: 3, GR: C)
- Preoperative radiation therapy results in a significantly increased rate of pT0 tumors, which is associated with a significantly improved local control rate (LE 2b; GR: C)
- Preoperative radiation therapy should be delivered with total dose of 49.3 Gy at 2 Gy per fraction 4 to 6 weeks prior to cystectomy (LE: 2b, GR 2)
- Preoperative radiation therapy does not result in a significant survival benefit as compared to radical cystectomy alone (LE: B, GR: ?)
- Preoperative radiation therapy might be associated with an increased risk of postoperative intestinal complications and patients should be informed accordingly (LE: 3, GR:C).

RECOMMENDATIONS FOR POSTOPERATIVE RADIOTHERAPY

- Postoperative radiotherapy cannot be recommended in patients with urothelial cancer of the bladder (LE: 3, GR: C)
- Postoperative radiotherapy with a total dose of 50Gy to the whole pelvis improves disease-free survival and local control in patients with locally advanced, lymph node negative adenocarcinoma of the bladder (LE: 2a, GR: B)

REFERENCES

VI. BLADDER-SPARING TREATMENTS FOR LOCALIZED DISEASE

1. TRANSCUTANEOUS MONOTHERAPY FOR THE TREATMENT OF MUSCLE-INVASIVE BLADDER CANCER

a) Level of Evidence Reviewed

To date, no randomized studies have been performed comparing transurethral resection (TUR) of invasive (TNM stages T2-T4, No MX) bladder cancer as monotherapy to other standard of care modalities such as radical cystectomy or combined modality therapy. The literature on this subject consists of a few carefully performed clinical trials that are observational in nature; these studies are generally comparative, non-randomized, and uncontrolled clinical experiences and are consistent at best with level of evidence 2b, grade B.

b) Background

TUR monotherapy of invasive bladder cancers has been discussed in the urologic literature since the 1940s[1]. Multiple groups evaluated the utility of this approach either in isolation or in combination with systemically administered poly chemotherapy. [2-4] Comparing TUR to other standards of the day including radical cystectomy, radiation monotherapy, and combination therapy, Henry et al observed that the 5-year survival rate for patients with T2 tumors treated by TUR only was 63%. [5] In 1998, Solsona and coworkers reported the results of a comparative, non-randomized study of 133 patients with T2-3 bladder cancer treated by TUR. The clinical course of these patients was compared to a concurrent group of patients treated by radical cystectomy in the same center.[6] These investigators reported that for patients with negative TUR bed biopsies following initial TUR, disease-specific survival was equivalent to that observed in the cystectomy group. Furthermore, patients in the TUR group with negative muscle biopsies but with carcinoma in situ were found to respond favorably to intravesical therapy. Herr et al. reported on a similar experience in 155 patients treated at a single institution with 10-year follow-up. [7] Investigators from MD Anderson Cancer Center reported that while TUR as monotherapy was effective in appropriately selected individuals with invasive bladder tumors, this approach was only applicable to approximately 11% of the patients at their center presenting with invasive bladder cancers. [8] Recently, the Valencia group has updated its experience with 15-year follow-up data. This most recent report supports the authors’ contention that in their hands at least, TUR monotherapy produces high rates of disease-specific survival across all age groups treated.[9]

c) Indications

TUR monotherapy is appropriate, based on the literature cited above, for the treatment of patients with T2-T3 N0Mx bladder cancer in whom local endoscopic resection is likely to produce complete removal of the tumor exclusive of concomitant non-invasive disease (i.e., CIS). Patients with locoregional extension of disease as evidenced by hydronephrosis or lymphadenopathy on axial imaging are not considered good candidates for this approach.

d) Surgical Technique

Successful TUR of invasive bladder cancer is confirmed by negative biopsies of the base and periphery of the resection bed. In work cited above, negative confirmatory biopsies correlated with long-term survival in those treated with TUR only.
d) Oncologic Outcome

TUR monotherapy should produce oncologic outcomes equivalent to radical cystectomy in appropriately selected patients according to long-term, single institution experiences reported by Solsona and Herr (see bibliography). Bladder preservation rates are also high in individuals with small tumors completely resected with negative follow-up biopsies.

RECOMMENDATIONS

1. TUR monotherapy is an alternative to radical cystectomy in appropriately selected (see 2. below) and counseled patients with T2-T3a N0Mx bladder cancer (LE 2b, GR: B)

2. Patients most appropriate for this approach have tumors that:
   a. Are small
   b. Are completely resectable
   c. Have negative tumor bed and periphery biopsies
   d. Are not associated with upper tract compromise (i.e., hydronephrosis)
   e. Are not associated with radiographic evidence of locoregional extension of disease (T3b, N+) at the time of first treatment

3. Should be discussed as part of the informed consent process to patients contemplating management options for invasive bladder tumors (TNM Stages T2-3a, N0Mx; LE: 3, GR: C)

REFERENCES


2. PARTIAL CYSTECTOMY

a) The Role of Partial Cystectomy

Partial cystectomy is an alternative form of therapy for muscle-invasive disease that may be used in a highly selected cohort of patients [1]. There is only level 3 or 4 evidence regarding the appropriate use of partial cystectomy for urothelial disease and it is the treatment of choice for urachal adenocarcinoma, which is not the subject of these guidelines. There are no prospective phase II studies of partial cystectomy nor are there prospective comparisons or randomized trials assessing the relative efficacy of partial versus radical cystectomy or radical transurethral resection for invasive urothelial cancer.

A very small subset of patients (<5%) presenting with muscle-invasive urothelial cancer will be eligible for partial cystectomy when applying strict criteria. The principal limiting factor is tumor location which should be high on the dome or anterior wall away from the bladder neck. Tumors on the posterior or lateral walls may also be treated with partial cystectomy if anatomically accessible [2, 3]. Tumors should be primary rather than recurrent, and there should be no CIS on bladder biopsies. A 2 cm circumferential margin of normal mucosa is recommended and tumors should be 3 cm or less in diameter.

Partial cystectomy may also used in patients with a tumor in a diverticulum in sites other than the dome and may require ureteral re-implantation in select patients [4]. A recent series studied 39 patients treated in a variety of ways, including partial cystectomy, for tumor in a diverticulum [5]. Thirteen patients demonstrated T2 or greater disease and had a 45% 5-year survival rate. Those patients with Ta and T1 disease had better long-term survival (83% and 72%, respectively). A few small case series also report the technical aspects and safety of laparoscopic/robotic partial cystectomy for urothelial cancer and the use of cystoscopy for tumor localization and initial identification of resection margins (LE 4C, GR C) [6, 7].

Several recent studies suggest that partial cystectomy is over-utilized, particularly in non-academic settings. In a population-based study in Quebec, 30% of patients with invasive bladder cancer underwent partial cystectomy over a 22-year period [8]. Equally concerning is that only 23% of patients had a pelvic lymphadenectomy and 24% of patients required a salvage radical cystectomy. Hollenbeck et al queried the SEER and National Inpatient Sample databases from 1988-2000 and
found that in 2000, partial cystectomy was still performed in 13-17% of patients and more commonly in rural, non-teaching, low volume hospitals [9]. More recently, Fedeli and colleagues reviewed the US National Cancer Database from 2003-2007 and found a lower utilization that decreased over time from 10% to 7% [10]. Capitanio et al reviewed the SEER-9 database from 1988-2004 which included 7243 patients with stages pT1-4 N1-2 M0 disease treated with partial (22%) or radical cystectomy [11]. They performed a matched analysis utilizing pT and pN stage, grade, race, age, and year of surgery and suggested that the use of partial cystectomy did not undermine long-term cancer control. These data should be interpreted with caution as within this same database, 24% of patients did not appear to have any node dissection and an additional 18% had only 1-5 nodes removed, suggesting that surgical quality was less than optimal regardless of the use of partial or radical cystectomy.

Two recent papers describe the contemporary experiences from Memorial Sloan Kettering Cancer Center and MD Anderson Cancer Center [2, 4]. The former series described 58 patients with primary non-urachal bladder cancer treated from 1995-2001 [4]. This represented 6.2% of patients presenting for surgical therapy. All but 5 patients had a unilateral or bilateral pelvic lymphadenectomy and 9 patients had node metastases. A total of 7 patients had tumor in a diverticulum. Of 5 patients with a final positive margin, 3 had negative intra-operative frozen sections of the margins presumably due to sampling error. On univariate analysis, CIS and multifocality were associated with non-muscle-invasive recurrence and lymph node metastases, and positive surgical margins were associated with advanced recurrence. CIS and node metastases were independent predictors of advanced recurrence. Median follow-up was 31 months and 69% were alive and disease-free while 22% died of disease.

In the MD Anderson series, 37 patients underwent partial cystectomy for curative intent between 1982 and 2003 [2]. All patients had pT2 or pT3 disease and 14% had node metastases. Long-term cancer control was achieved in 65% with an intact bladder with a median follow-up of 53 months. Non-muscle-invasive recurrences occurred in 9 (24%) patients and all were treated successfully. On multivariate analysis, only pathologic tumor stage was associated with recurrence-free survival.

Smaldone et al reported a single surgeon series of 25 patients operated on over a 10-year period [3]. Their protocol included 25 Gy of preoperative radiotherapy delivered to the abdominal wall in 5 fractionated doses, intraoperative intravesical Thiotepa, and postoperative 6 weeks of intravesical BCG. Preoperative radiotherapy and/or intra-operative intravesical chemotherapy have been reported in many series in an effort to minimize the risk of wound implantation, but there is no evidence to support their routine use (LE 4C, GR C). Despite strict criteria of cT1 or cT2 disease, 36% were upstaged to pT3 and 12% had node metastases, though only two-thirds of patients underwent a pelvic lymphadenectomy. Five-year recurrence-free and disease-specific survival probabilities were 62% and 84%, respectively, and tumor size was the only variable associated with recurrence. These data support a highly selective use of partial cystectomy in patients with muscle-invasive bladder cancer (LE 3, GR B).

b) Partial Cystectomy after Neoadjuvant Chemotherapy

Partial cystectomy has been incorporated into bladder-sparing protocols after initial neoadjuvant multi-agent chemotherapy in highly selected patients with localized tumors. Sternberg et al reported on 13 patients among 104 treated with a bladder sparing approach in mind who had partial cystectomy [12]. The 5-year survival for this select cohort was 69%. In a separate report from MSKCC, 115 achieved cT0 status after neoadjuvant chemotherapy and 28 underwent TUR alone and 15 underwent partial cystectomy as definitive surgical management with similar long-term survival of 74% for the combined group with a median follow-up of 10 years [13]. There may be a role for partial cystectomy as an alternative to radical cystectomy following chemoradiation therapy [14].

RECOMMENDATIONS

Highly selected patients with focal invasive cancers and cT0 or minimal residual disease after neoadjuvant chemotherapy may be candidates for bladder sparing with either TUR or partial cystectomy (LE: 3, GR: C).

REFERENCES

6. Nerli RB, Reddy M, Koura AC, Prabha V, Ravish IR.


3. RADIATION-BASED BLADDER-PRESERVING STRATEGIES: RADIATION ALONE OR COMBINED WITH OTHER MODALITIES

a) Introduction

The treatment options for muscularis propria-invasive bladder tumors can broadly be divided into those that involve removal of the bladder and those that spare it. There is a big difference among countries in the path of care that they most often use to treat these patients. For instance, in the United States only a minority of the patients are offered radiation therapy. However, in the United Kingdom, 60% of eligible patients receive radical radiation therapy, with surgery reserved for failures. The treatment of many other cancers in North America, Europe, and around the world, include organ-preserving therapy as the, or one of the, current standards of care for malignancies of the breast, larynx, anus, head and neck, soft tissues (sarcoma), and prostate. In each case, radical surgical extirpation can often be avoided without compromising patient survival. Improved radiotherapy techniques combined with an enhanced understanding of the optimal chemotherapeutic regimens have promoted multi-modality therapy in selected patients with muscle-invasive bladder cancer as a viable alternative to radical surgery alone. Cystectomy is effective in achieving local tumor control and patients are often cured by contemporary cystectomy with major series reporting 5-year pelvic control rates of 80-90% and 5-year overall survival rates from 40% to 60% [1-5]. It is this standard that treatment with bladder-preserving strategies must meet.

Contemporary radiation-based bladder-sparing therapy algorithms consist of: (1) maximal transurethral resection of the tumor (TURBT), (2) induction external beam radiation therapy with concurrent chemotherapy, (3) cystoscopic assessment of treatment response with prompt cystectomy for non-responders, and (4) active cystoscopic surveillance with a cystectomy at the first sign of invasive recurrence. These algorithms were developed as a result of the lack of adequate local control of muscle-invasive urothelial carcinoma treated by TURBT, by chemotherapy, or by radiotherapy when used alone.

b) External Beam Radiation Alone with Salvage Cystectomy Reserved for Tumor Recurrence

From the 1960s through the 1980s, the most common type of bladder-sparing treatment was external beam radiation therapy alone. Since the 1980s in the United States radiation treatment has generally been reserved for patients judged too unfit for cystectomy on the basis of comorbid conditions or due to disease extent. These negative selection criteria may have contributed to the relatively poor results achieved with radiation therapy alone compared to cystectomy (see Table 5). Approximately 10-15% of patients are excluded from treatment by radical cystectomy at the time of operation because previously unrecognized unresectable tumor spread is found. Thus in cystectomy series, but not radiation series, some of the patients with advanced local spread tumor are excluded so this may be another selection bias favoring cystectomy.

In the 1960s, the Cooperative Surgical Adjuvant Bladder Cancer Study group randomized 475 patients with Stage T2-T4a bladder cancer to preoperative radiation therapy (45 Gy) followed by open surgery or surgery alone [13]. The study was large but compromised by incomplete data collection and follow-up. Of the 138 patients who completed preoperative radiation therapy and surgery on protocol, 34% had a complete pathologic response of their bladder tumor (stage pT0). Furthermore, those with a complete pathologic response at radical cystectomy had a survival advantage of 55% versus 32% compared to those who had residual tumor at the time of cystectomy. This led in the 1970s to 4 randomized trials comparing external beam radiation therapy alone (60 Gy) with radical cystectomy reserved for local recurrence to the standard group receiving preoperative radiation therapy (40-50 Gy) with immediate radical cystectomy [6,10,14].
(Table 6). Three of these trials showed equivalent overall survival with either approach. These studies give Level 1b evidence that a bladder-preserving approach with radiation therapy alone and salvage radical cystectomy for local recurrence was not significantly different in overall survival in this “pre-neobladder” era.

Alternative radiation therapy fractionation schemes, including the use of twice-daily radiation with the potential advantage of improved biological effect to better control of rapidly proliferating tumors, and with the practical advantage of a more rapid completion of radiation therapy and thus a shorter interval to salvage cystectomy for the non-responders were studied. The randomized trial from the United Kingdom studied accelerated (twice-daily) radiation monotherapy in 229 patients with muscle-invasive urothelial carcinoma treated with radiation therapy alone [15]. There was no advantage with the twice-daily schedule over the conventional once-daily radiation schedule, and acute bowel and bladder toxicities were higher. The biological rationale underlying accelerated fractionation radiation therapy in bladder cancer therefore remains unproven. Thus, off protocol, the once–daily radiation treatments remain entirely reasonable.

### Table 5. (Section 5.3) Results of radical radiation therapy alone (Monotherapy): Muscle-Invading Bladder Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Number</th>
<th>T2</th>
<th>T3(±T4a)</th>
<th>All Stages</th>
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<td>M.D. Anderson Cancer Center [6]</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>National Bladder Cacer Group *</td>
<td>35</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eudinburgh [7]</td>
<td>889</td>
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<td>26%</td>
<td>36%</td>
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<td>London Hospital [8]</td>
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<td>39%</td>
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<td>Danish National Study [10]</td>
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<td>24%</td>
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<td>UK Cooperative Group [12]</td>
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<td>28%</td>
</tr>
</tbody>
</table>

* SD Cutler, National Cancer Institute, Unpublished observations, 1983.

### Table 6. (Section 5.3) Five year survival data from four randomized trials comparing preoperative radiation therapy (40-50 Gy) with immediate cystectomy to radiation therapy alone (60 Gy) with salvage cystectomy recurrence.

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>5-year Survival with Pre-op RT and cystectomy (%)</th>
<th>5-year Survival with RT and Salvage cystectomy (%)</th>
<th>Statistical Significance</th>
<th>Notes</th>
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<tr>
<td>Urologie Cooperative Group, UK [14]</td>
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<td>Danish National Cancer Group [10]</td>
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<td>National Bladder Cancer Group (a)</td>
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<td>MD Anderson Cancer Center [6]</td>
<td>67</td>
<td>45</td>
<td>22</td>
<td>significant</td>
<td>Large T3 tumors included</td>
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</tbody>
</table>

RT = radiation therapy
(a) SD Cutler, National Cancer Institute, unpublished observations, 1983
c) External Beam Radiation Therapy Combined with Other Modalities and with Salvage Cystectomy for Recurrence

By the late 1980s, single institutions reported the combination of a visibly complete TURBT followed by radiation therapy lead to improved local control [16, 17]. By 1994, the group from the University of Erlangen referred to the visibly complete TURBT, when followed by a tumor bed negative biopsy, as an R0 resection [17]. The importance of the visibly complete TURBT was also seen in many subsequent cooperative group trials using radiation concurrent with chemotherapy such as in RTOG 89-03 [18].

Combining external beam radiation beam therapy with brachytherapy (for the delivery of precision partial bladder radiation therapy) has been used by some groups in Holland, Belgium, and in France. Brachytherapy is done by an open cystotomy with an implant using iridium-192 as low dose rate irradiation to doses of 40 Gy combined with external beam radiation doses of 30 Gy. The majority of the reported series include patients who first underwent maximal tumor resection by either partial cystectomy or an open TURBT. The approach is reserved for patients with solitary bladder tumors less than 5 cm in diameter. The 5-year survival rates reported are from 62-84% with a disease-specific survival rate approaching 80% [19-21].

1. EXTERNAL BEAM RADIATION COMBINED WITH CONCURRENT RADIOSENSITIZING CHEMOTHERAPY

Encouraging results were obtained when cisplatin was first made available by the NCI to the National Bladder Cancer Group in the early 1980s for patients with muscle-invasive bladder cancer who were unsuitable for radical cystectomy. In a protocol combining the use of concurrent cisplatin with conventional doses of radiation was carried out from 1981 to 1986 in 68 patients with muscle-invasive bladder cancer, 64% of patients with clinical stage T2 tumors and 22% of those with clinical stage T3-T4a disease had long-term survival rates [22]. These promising findings of combining cisplatin with radiation led to a randomized trial of radiation therapy with or without concurrent cisplatin [23] in 99 patients with clinical stage T3 muscle-invasive bladder cancer conducted by the National Cancer Institute of Canada. This trial showed a significant improvement in pelvic tumor local control at 5 years in patients treated with cisplatin and radiation therapy (68%) versus radiation therapy alone (47%). Similarly, early prospective studies at the MSKCC that combined chemotherapy and TURBT resulted in T0 tumor response rates nearly twice that of chemotherapy alone, but these rates were less than 50% [24,25]. The results of combining TURBT with chemotherapy but without radiation have not been as successful in organ-preservation as the combination of chemotherapy and radiation therapy combined with TURBT. A study of 104 patients treated with TURBT and M-VAC showed a T0 tumor response rate of 49% and in these 52 patients the 5-year survival rate was 67% [26]. However, 66% of the 104 patients required radical cystectomy, suggesting a relatively low local bladder tumor control with chemotherapy and TURBT alone. As described below, modern trimodality therapy combining radiation and chemotherapy with TURBT has led to substantially higher T0 tumor response rates (64-87%) and lesser need for salvage cystectomy. This has tempered further interest in the treatment with only chemotherapy and TURBT.

A second randomized trial comparing radiation alone to radiation plus concurrent chemotherapy with 5-fluorouracil (5-FU) and mitomycin C (MMC) has been reported by a multi-center group led from Birmingham, England, involving 360 patients. The results showed no measurable differences in toxicities. There was a significant increase in pelvic disease-free rates at 2 years (67% free of recurrence compared to 54% with radiation alone, P=0.02) and at 5 years (62% and 51% respectively) [28]. The five-year overall survival rate was increased from 35% to 51%. Seventy-five percent of the patients treated with 5-FU and MMC concurrent with radiation therapy reported no late side effects. Of the 25% who did report side effects, fewer then 5% reported them as serious. Patients on this protocol underwent urologic evaluation of their bladder capacity before and after treatment. There was a median reduction in bladder capacity of 10%, which was the same in both groups.

Cooperative group and single institution trials with concurrent chemotherapy and radiation combined with TURBT. Over the last 25 years, single institutions in North America and Europe and multi-institutional cooperative groups including the Radiation Therapy Oncology Group (RTOG) and the Southwestern Oncology Group (SWOG) have enrolled over 1000 patients with muscle-invasive bladder cancer in bladder-preserving protocols. Several variables have been tested including evaluating more than cisplatin alone as the radiation-sensitizing chemotherapy and evaluating alternative radiation schemes. Beginning in the late 1980s some single institutions and the RTOG were studying neoadjuvant chemotherapy in addition to trimodality therapy for the operable patients with muscle-invasive bladder cancer (Table 7). Encouraging results led to the opening of RTOG 8903, a Phase III trial comparing neoadjuvant MCV chemotherapy, or not, prior to concurrent cisplatin and radiation. This study was closed prematurely after accrual of 123 of the planned 174 patients because there was an unexpectedly high rate of leukopenia in the MCV arm [18]. With a median follow-up of 5 years, the overall survival rate was 48%, and was 49% in patients who were
randomized to the neoadjuvant MCV arm. Likewise, there was no statistically significant difference in the T0 tumor response rate, distant metastasis, or the 5-year survival with an intact bladder. Two European phase III trials have studied the role of neoadjuvant chemotherapy before radiation alone. The Danish Group [36] treated patients with muscle-invasive bladder cancer with neoadjuvant chemotherapy before radiation and showed an insignificant 5% decrease in 5-year survival compared to patients treated with radiation alone (19% v. 24%). The other phase III trial led in the United Kingdom by the MRC Group studied neoadjuvant MCV before radical radiation or radical cystectomy (34-35). In the radical radiation sub-group of 415 patients, there was an insignificant trend to better survival in those treated with neoadjuvant MCV than those treated with radiation alone. A meta-analysis of those 2 trials showed no significant difference in survival (30.4% vs. 28.1%, P=0.334) with the addition of the neoadjuvant chemotherapy [37].

The Massachusetts General Hospital experience with 348 patients with muscle-invasive bladder cancer who were entered on the successive prospective trimodality protocols from 1986-2002 have recently been updated [33]. Bladder-sparing trimodality therapy was reserved for those patients who had a complete clinical response at the mid-point of concurrent chemoradiation after radiation dosage of 40 (Gy). These patients then received consolidation with additional chemotherapy and radiation for the total dose of 64-65 Gy. Incomplete responders were advised to undergo a radical cystectomy as were patients whose invasive tumors recurred after the full 64-65 Gy treatment. All patients were treated with an aggressive TURBT, which was visibly complete in 66% of patients. All patients were treated with cisplatin concurrently with radiation therapy. With the median follow-up for all surviving patients of 7.7 years, the 5-year, 10-year, and 15-year disease-specific survivals was 64%, 59%, and 57% (stage T2, 74%, 67%, and 63%; stage T3-T4a, 53%, 49%, and 49%). The disease-specific survival rates stratified by clinical stage are shown in Figure 4, which demonstrates that there were very few late recurrences at least up to 15 years. These results are similar to those in contemporary cystectomy series. In this series, the 5-year, 10-year, and 15-year disease-specific survival for the
TURBT

Induction radiation and concurrent chemotherapy

Repeat cystocopy with transurethral biopsy

*Complete Response* | *Incomplete Response*

Consolidation chemotherapy and radiation # adjuvant chemotherapy AND long-term cystoscopic surveillance

Radical cystectomy # adjuvant chemotherapy

Recurrent tumor

*Figure 3. Current Schema for Trimodality Treatment of Muscle-invasive Bladder Cancer With Selective Bladder Preservation.*

*Figure 4. Long-term Disease-specific Survival with Selective Bladder Preservation from the Massachusetts General Hospital Experience (33).*
102 patients undergoing cystectomy were 55%, 44%, and 44%, respectively. This indicates the very important contribution of prompt cystectomy for disease control in patients whose tumors recur. A recent evaluation of patients undergoing salvage cystectomy at the Massachusetts General Hospital over these years indicates quite acceptable surgical morbidity or mortality compared to major primary cystectomy series. (Eswara & Heney, submitted 2010).

d) Comparison of Survival Outcomes Following Curative Therapy in Contemporary Series by Cystectomy or by Bladder-preserving Trimodality Therapy with Cystectomy Reserved for Recurrence

Comparing results of bladder-preserving therapy to those of contemporary radical cystectomy series is confounded by the discordance between clinical staging (TURBT) and pathologic (cystectomy) staging. Clinical staging is more likely to underestimate the extent of disease with regard to penetration into the muscularis propria or beyond than is pathologic (cystectomy) staging [38]. Thus if any favorable outcome bias exists among these selected, it is in favor of the pathologically-reported cystectomy series. For patients with muscle-invasive bladder cancer, the overall survival outcomes following either contemporary radical cystectomy at major single institutions or by trimodality therapy are shown in Table 8. The University of Southern California reported on 633 patients undergoing radical cystectomy with pathologic stages T2-T4a with an overall survival rate at 5 years of 48%, and at 10 years of 32% [1]. The Memorial Sloan Kettering Cancer Center (MSKCC) contemporary radical cystectomy series showed that in 184 patients with tumors pathologic stage pT2-pT4, the 5-year overall survival rate was 36%[2]. The actuarial survival rate of all 269 patients with pathologic stages ranging from pT0 to pT4 in this series was 45%. These results are similar to the Massachusetts General Hospital Series [33] as well as those from University of Erlangen (17,31) and RTOG [18]. The similarity in survival is likely in part to the prompt use of cystectomy when necessary for recurrence in the bladder-preservation series.

e) Quality of Life After Radiation-based Bladder-preserving Therapy for Muscle-invasive Bladder Cancer

The instruments to assess quality of life have been well established for prostate cancers and gynecologic cancers, but not for bladder cancer. The instruments that are currently used for bladder cancer patients are adaptations and thus their validity is somewhat uncertain. These studies are also limited by incomplete sampling of all potential participants which leaves unclear whether or not the non-participants are those who have had a worse outcome or who are the most satisfied. Despite these limitations, some general principles can be derived from this literature.

Minimal late pelvic toxicity is certainly required for successful implementation of a selective bladder-preserving protocol. Long-term bowel and bladder toxicity after chemoradiotherapy was investigated in patients enrolled in prospective sequential RTOG trials (8903, 9506, 9706, and 9906). One study reported on 157 patients who underwent combined modality therapy and who survived at least 2 years from the start of treatment with their bladders intact. The median follow-up was 5.4 years [39]. Seven

Table 8. (Section 5.3) Muscle-Invasive Bladder Cancer: Survival Outcomes Following Curative Therapy in Contemporary Series

<table>
<thead>
<tr>
<th>Series</th>
<th>Stages</th>
<th>Number</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>5 year</td>
</tr>
<tr>
<td>Cystectomy:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SWOF/ECOG/CALGB* # 2002 [3]</td>
<td>cT2-cT4a</td>
<td>317</td>
<td>49%</td>
</tr>
<tr>
<td>Selective Bladder Preservation:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>U. Erlangen* 2002 [17,31]</td>
<td>cT2-cT4a</td>
<td>326</td>
<td>45%</td>
</tr>
<tr>
<td>M.G.H.* 2009 [33]</td>
<td>cT2-cT4a</td>
<td>348</td>
<td>52%</td>
</tr>
<tr>
<td>R.T.O.G. 1998 [18]</td>
<td>cT2-cT4a</td>
<td>123</td>
<td>49%</td>
</tr>
</tbody>
</table>

* These series include all patients by their intention-to-treat.
# 50% of patients were randomly assigned to receive 3 cycles of neoadjuvant M-VAC.
percent of the patients experienced late grade 3 or 4 pelvic toxicity (5.7% GU and 1.9% GI). In only 1 of 9 patients, did a grade 3-4 GU toxicity persist. This indicates that rates of late pelvic toxicity for patients who undergo selective bladder preservation and retain their native bladder are low.

Zeitman and colleagues reported a study on patients receiving TURBT, chemotherapy, and radiation in the treatment of the bladder cancers at the Massachusetts General Hospital (MGH) [40]. Of 221 patients with clinical stage T2-T4a cancer of the bladder treated at the MGH from 1986-2000, 71 were alive with their native bladders and disease-free in 2001. These patients were asked to undergo a urodynamic study (UDS) and to complete a quality of life questionnaire. Sixty-nine percent participated in some component of the study with a median time from the trimodality therapy of 6.3 years. This long follow-up is sufficient to capture the majority of the late radiation side effects. Seventy-five percent of patients have normal functioning bladders by UDS. Reduced bladder compliance, a recognized complication of radiation, was seen in 22% of patients. However, distressing bladder symptoms were seen only in one-third of these patients. Two women showed bladder hypersensitivity, involuntary contractions, and incontinence. The questionnaires showed that bladder symptoms were uncommon overall in both sexes. However, 19% of women reported problems with bladder control, and 11% of them wore pads. The distress from urinary symptoms was only half as common as symptom prevalence. Bowel symptoms occurred in 22% of patients and caused distress in 14%. The majority of men retained sexual function with or without use of sildenafil. Global health-related quality of life was high. The majority of the patients treated by trimodality therapy therefore retained good bladder function. It was concluded that there is a small but detectable level of lasting bowel dysfunction and distress and that this might be judged as the additional price that these patients have to pay to retain their bladders.

Two cross-sectional questionnaire studies, one from Sweden and one from Italy, have compared the outcome following radiation with the outcome following cystectomy [41-42]. The questionnaire results for urinary function following radiation are very similar to those recorded in the MGH study. Over 74% of the patients recorded good urinary function. Both studies compared bowel function in irradiated patients with that seen in patients undergoing cystectomy. In both, the bowel symptoms were greater for those receiving radiation than for those receiving cystectomy (10% vs. 3% and 32% vs. 24% respectively), but in neither was this statistically significant. In contrast to men who had been irradiated for prostate cancer, the majority of the male bladder-sparing patients reported adequate erectile function (full or sufficient for intercourse) and only 8% reported dissatisfaction with their sexual lives. In the Swedish and Italian series 38% and 25% of the men retained functional erections as compared to 15% and 8% of cystectomy controls. Use of sildenafil by patients in the MGH series may have been the major reason for better retained erectile function.

**J) Translational Research: Prognostic or Predictive Molecular Tumor Markers as Predictors of Response to Radiation Treatment**

Tumor suppressor genes such as p53 and pRB have been studied in detail in bladder cancer, but both markers have led to contradictory data in the assessment of risk for disease-progression and survival [43]. Cell-cycle regulatory proteins p27 and Ki-67 might predict recurrence and disease progression but are not ready for routine clinical use [44-46].

The bladder tumors pre-treatment apoptotic index or altered expression of the RB1 or the BCL2 genes might alter tumor response to radiation therapy [47-49]. RTOG investigated the outcome of 73 patients treated in 4 RTOG bladder-preserving protocols and noted that among patients treated with transurethral surgery and chemotherapy concurrent with radiation-altered expression of p53, CDKN2A, and pRB had no prognostic significance but overexpression of Her-2 (ERBB2) correlated significantly with a reduced complete response rate (50% vs. 81%, p=0.026). The aim of targeted therapies is to interfere with molecular events related to tumor proliferation [50]. Examples of these therapies are cetuximab, an anti-EGFR monoclonal antibody; gefitinib and erlotinib, EGFR-specific inhibitors; trastuzumab, an anti-human EGFR Type 2 (Her-2)-related monoclonal antibody; and bevacizumab, a VEGF monoclonal antibody [51]. Both EGFR and HER-2 are targets identified on cancer cells, whereas VEGF is a target that acts on the tumor microenvironment. Studies have shown reduced complete response rates when HER-2 is over expressed [51-53]. These results have led to an ongoing RTOG protocol (RTOG-0524) for patients with muscle-invasive bladder cancer who are not fit for a cystectomy. This phase I / II trial investigates paclitaxel and daily radiation therapy with trastuzumab given to patients whose tumors over express HER-2. This study is one of the first examples of a molecular targeted therapy being added to treatment for patients with localized muscle-invasive bladder cancer. To date 55 patients have been enrolled with the results still pending. Recently the group in Leeds and in Oxford in the United Kingdom, in collaboration with the Ontario Cancer Institute in Toronto, have evaluated MRE 11 expression in patients with muscle-invasive bladder cancer treated with radical radiation or with cystectomy [55]. MRE 11 is one of a panel of DNA
damage signaling proteins active in the process of DNA double strand break repair. DNA double stand breaks are the most lethal form of injury produced by ionizing radiation and by some chemotherapy agents. MRE 11 had been singled out as one possible predictor of radiation treatment outcome. The cohorts of patients treated with radical radiation and a separate cohort of patients also treated in Leeds by radical cystectomy have documented that high MRE 11 protein expression by the tumor predicts improved outcome with radiation therapy but not in the cystectomy cohorts. Comparing the high MRE 11 patients by treatment showed that the patients treated with radiation have a significantly higher disease-specific survival than those treated with immediate cystectomy (P=0.02) while those with low MRE 11 protein expression do insignificantly better with surgery than with radiation. These results tentatively identify MRE 11 overexpression as a predictive molecular marker of improved cause-specific survival following radiation therapy for muscle-invasive bladder cancer.

**g) Levels of Evidence (LE) and Grades of Recommendation (GR) for Radiation-based Bladder-preserving Strategies for Muscle-invasive Bladder Cancer**

1. Radiation therapy followed by salvage cystectomy for tumor recurrence has comparable survival to preoperative radiation therapy and cystectomy. (LE 1b, GR A).

2. Radiation therapy and chemotherapy result in a higher rate of pT0 status than does radiation therapy alone (LE 1b, GR A).

3. Combined radiation and chemotherapy allow good preservation of bladder function in the great majority of patients. (LE 2a, GR B).

4. There is no clinical trial basis to indicate that neoadjuvant chemotherapy prior to radiation therapy improves survival. (LE 1a, GR A).

5. Complete TURBT, when possible, is associated with higher rates of local tumor control and higher cure rates than does incomplete initial tumor resection for selected patients in trimodality radiation/chemotherapy trials. (LE 2a, GR B).

6. Limited data suggests that high expression of the molecular marker MRE 11 may be a putative predictor for cause-specific survival following radical radiation therapy for muscle-invasive bladder cancer. (LE 3, GR B).

7. Tramodality therapy consisting of TURBT plus concurrent radio sensitizing chemotherapy and radiation is judged safely possible, and, when combined with early salvage cystectomy for recurrence, this bladder-preserving treatment approach offers a chance for long-term cure and survival in selected patients comparable to radical cystectomy, and affords a 70% chance of maintaining a well-functioning native bladder (see Table 8). Quality of life studies have demonstrated that the retained native bladder functions well and long-term toxicity of chemoradiation to pelvic organs is low. These reports support the acceptance of modern bladder-sparing trimodality therapy for selected patients as a proven alternative to cystectomy (LE 3, GR C).

**See Table 9** for a summary of these recommendations.

**CONCLUSION**

In selected patients with muscle-invasive bladder cancer, bladder-preserving therapy with cystectomy reserved for tumor recurrence represents a safe and effective alternative to an immediate radical cystectomy. Cumulative published data of more than 1000 patients in single institution and multi-institution cooperative group trials demonstrate that trimodality therapy results in excellent local control in 70% of patients with muscle-invasive bladder cancer while preserving a native functional bladder without compromising long-term survival. The 10-year overall survival and disease-specific survival rates in the bladder-sparing protocols are comparable to the overall results reported with contemporary radical cystectomy. Moreover, the 15-year results indicate a plateau in disease-specific survival, suggesting no evidence of increased rates of recurrence with longer follow-up times. Life-long bladder surveillance is essential. Prompt cystectomy for tumor recurrence is necessary to prevent tumor dissemination. Thus, bladder-preserving therapy is a bona fide option and valid alternative to radical cystectomy in selected patients. This approach should be discussed along with all of the other treatment options during overall initial treatment planning. This approach contributes significantly to the quality of life of the patients so treated and represents a unique opportunity for urologic surgeons, radiation oncologists, and medical oncologists to work hand-in-hand in a joint effort to provide patients with the best treatment option for this disease.
Table 9. Summary of Recommendations

<table>
<thead>
<tr>
<th>Treatment/Comparison</th>
<th>Evidence</th>
<th>Level of Evidence</th>
<th>Grade of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT alone vs 40Gy+Cystectomy</td>
<td>3 of 4 RCTs report similar survival</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>ChemoRT vs RT alone</td>
<td>2 RCTs report significant improvement in bladder tumor eradication</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>Neoadjuvant CT with RT or ChemoRT</td>
<td>3 RCTs and 1 meta-analysis report no benefit</td>
<td>1a</td>
<td>A</td>
</tr>
<tr>
<td>ChemoRT preserves good bladder function</td>
<td>3 QOL studies and RTOG protocols report good tolerance</td>
<td>2a</td>
<td>B</td>
</tr>
<tr>
<td>Complete TURB with ChemoRT</td>
<td>3 reports (1 phase III, 2 phase II) show benefit</td>
<td>2a</td>
<td>B</td>
</tr>
<tr>
<td>Predictive Biomarkers of outcome after RT</td>
<td>MRE 11 expression predicts improved CSS (1 study)</td>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>Trimodality therapy vs immediate cystectomy</td>
<td>Comparison of 3 contemporary series of each report similar 5- and 10-yr survival</td>
<td>3</td>
<td>C</td>
</tr>
</tbody>
</table>


VII. TREATMENT OF MIXED HISTOLOGY UROTHELIAL CARCINOMA

Urothelial carcinoma of the bladder represents by far the most common histology of bladder cancer. However, cancers classified as “urothelial” contain non-urothelial components in 5-40% of cases.[1,2] In general, the higher the grade of the urothelial component and more invasive the cancer, the more likely that non-urothelial components will be found. Whether this is because such cancers are less differentiated and more easily develop aberrant histologic features or because the mixed urothelial cancers are generally very aggressive and are often not diagnosed until they are far advanced is unknown.

In general, however, molecular and genetic markers of urothelial cancer are present in non-urothelial as well as urothelial components, implying a clonal origin.[3,4] Most of these cancers are fairly rare and most information about them comes from case series. However, for the two most common mixed histologies, urothelial carcinoma with squamous and/or carcinomas elements, some data from randomized prospective studies exist.[5] Although collected retrospectively. These will be reviewed. This section is not meant to be encyclopedic, but instead will focus on 6 urothelial carcinoma variants that all urologists and pathologists will see and need to be familiar with: nested variant urothelial cancer, micro papillary urothelial cancer, carcinogenesis (sarcoma urothelial cancer), and urothelial cancer with small cell, squamous, and carcinomas components. While not all aspects of management of each variant will be discussed, we will highlight recent information which in most has significantly affected management.

1. NESTED VARIANT UROTHELIAL CANCER

It was originally identified as an aggressive entity by Talbert and Young[5] who characterized the tumor as one with a deceptively benign histologic appearance. Small nests and tubules of urothelial cells infiltrate through the lamina propria and usually the muscularis. Its appearance can be mistaken for a proliferative variant of von Brunn’s nests, a finding present in many individuals. This entity can appear as an isolated tumor or along with more classic urothelial cancer—a most invariably high grade, in other portions of the bladder or adjacent to the nested variant portion. It has been estimated to represent 0.3% of all urothelial cancers.[6] Little is known about its response to non-surgical treatments. This malignant variant has even a higher male predominance than standard urothelial cancer (3:1 males to females in the United States–SEER[7]). Perhaps its most important clinical feature is mistakes it for either a benign condition or a bland non-muscle-invasive urothelial cancer. Because these cancers cannot be diagnosed without at least lamina propria invasion, the standard treatment should be radical cystectomy in the absence of distant metastases and because the vast majority are more invasive than this in the absence of distant metastases. Whether neoadjuvant or adjuvant chemotherapy for urothelial cancer is beneficial is unknown. Although adjuvant radiation or chemotherapy have not been shown to be beneficial, it is likely that the rarity of this disease and the advanced nature of the cases treated in such ways would leave this issue up for further study.[8]

2. UROTHELIAL CARCINOMA WITH MICROPAPILLARY DIFFERENTIATION

It is another variant often considered to have bland histology, was first described as part of the urothelial carcinoma complex by Amin et al in 1994 [9]. It is now considered to represent between 1 and 2% of all urothelial cancers and has a strong male predominance.[1,10,11] The histologic appearance resembles micropapillary tumors arising in the ovary, lung, breast, and other anatomic locations.[12] The immunohistologic phenotype of these tumors has been elegantly outlined.[12] All 13 of the cases tested in that report[12] were positive for MUC1, MUC2, CK7, PTEN, p53, and ki67. CK20 and 3BVE12 were negative in half the cases and Her/neu was negative in 9 of the 13. In general, except for p53 staining, at least 50% of cells were positive for
the 6 markers present in every specimen. All of the patients in this series and several of the others[10] had at least muscle invading cancer and most had disease beyond the bladder. In a recent review of cases from MD Anderson Cancer Center, Kamat et al[11] found that these cancers may be detectable prior to muscle invasion and that cystectomy still is recommended. The response to BCG was extremely poor, with 18 of 27 patients experiencing progression to stage T2 or greater at a median 8 months follow-up, one-third of whom had progressed to metastatic disease. At 30 months median follow-up, only 5 of 29 patients were free of disease with an intact bladder. [11] Neoadjuvant chemotherapy did not appear superior to immediate cystectomy. The authors recommended against such an approach unless there was surgically unresectable (cN1 or cT4b) disease. Following immediate cystectomy, 71% of 32 cT4a or lower stage patients were alive at 5 years. In contrast, only 32% of 23 similar patients treated with neoadjuvant chemotherapy followed by cystectomy were alive at 5 years.

3. SARCOMATOID CARCINOMA AND CARCINOSARCOMA OF THE URINARY BLADDER

They consist of high grade cancers with malignant epithelial and mesenchymal elements. While pathologists debate if there is a distinction between the two, classically sarcomatoid carcinomas consist of urothelial cancer with a spindle cell (mesenchymal) component which retains expression of epithelial molecular markers, while carcinosarcoma contains recognizably more differentiated sarcomatous elements such as osteosarcoma.[13,14,15] As opposed to nested variant or micropapillary urothelial cancers, the aggressive nature of this tumor is not overlooked because of bland histology. Extremely rarely, this condition can be confused with other benign conditions such as pseudosarcomatous, myofibroblastic proliferations—most commonly postoperative spindle cell nodules and pseudotumors.[1] The presence of outright urothelial carcinoma, however, usually makes the distinction quite obvious. Molecular analyses including those for p53 indicate a common clonal origin for both carcinomatous and sarcomatoid components.[16,17]

A review of data from the SEER cancer registry[18] reported that between 1973 and 2004, this entity represented 0.6% of all primary bladder cancers. Nearly 75% of cases had regional or distant disease at the time of diagnosis. Two-thirds of the patients were male, actually a slightly lower percentage than pure urothelial cancers and far lower than micropapillary or nested variant cancers. In general the treatment recommended is cystectomy even for non-muscle-invasive carcinomas, almost all of which invade at least the lamina propria.[18] The role of chemotherapy or radiation remains at best anecdotal for this extremely aggressive malignancy; even with disease confined to the bladder, 5- and 10-year survival rates in the 25-35% range have been reported.[18] However, since nearly 75% of patients have more advanced disease at diagnosis,[18] surgery alone is often not curative. Anecdotally good responses of advanced cancers with combined surgical treatment and chemotherapy have been reported,[19] but they remain the rarity. It should be remembered that over 40% of these cancers have multiple sites within the bladder[18] so that careful bladder mapping in the rare circumstances where partial cystectomy would seem feasible is mandatory.

While the role of neoadjuvant chemotherapy is unclear, Black et al[13] reported downstaging to pT0 in 5 of 11 (45%) patients with clinical stage T2-T3 tumors using urothelial cancer-like regimens.

4. SMALL CELL CARCINOMA

It can exist in a pure form, but, in the urinary tract over 50% have an epithelial component. Occasionally, the epithelial component can be of non-urothelial type such as squamous cell or adenocarcinoma, but the vast majority of mixed tumors are with urothelial cancers.[1]

As opposed to other urothelial cancers with mixed histologies which are generally treated as urothelial cancers, it has been recognized by the World Health Organization that any amount of small cell histology should be regarded as a small cell carcinoma.[20] This is presumably because this small cell component determines the patient’s prognosis.

As with small cell carcinomas elsewhere, the majority are positive for chromogranin A and synaptophysin, and over 90% present with muscle invasion.[1] As with carcinosarcoma, molecular analyses have indicated similar genetic changes in the small cell and coexistent urothelial carcinomatous components.[1,21]

In general, mixed histology small cell carcinoma is recognized as a systemic disease[1,3] and probably should receive systemic chemotherapy aimed at small cell carcinoma (e.g., cisplatin and etoposide based therapy) along with extensive local treatment. [1] In an MD Anderson series, the pT0 rate in patients with cT2-4a mixed urothelial and small cell cancers treated with neoadjuvant neuroendocrine regimens was 10/12 (83%), compared with 3/9 (33%) with a urothelial regimen.[13] Moreover, the disease-specific survival at 5 years for these 21 patients treated with neoadjuvant chemotherapy was 78%, compared to 36% in 25 patients who underwent immediate cystectomy.[22]
Bladder sparing approaches have also been reported. Bex et al have published results for chemoradiation that approach those for chemotherapy and cystectomy,[23] although primarily only patients with limited disease were reported.

5. THE MOST COMMON OF THE MIXED UROTHELIAL CANCERS ARE THOSE WITH SQUAMOUS AND/OR ADENOCARCINOMATOUS ELEMENTS

They account for as many as 30% of patients undergoing cystectomy for what has been termed muscle-invasive urothelial cancer. In general, these patients fare less well than those with pure urothelial carcinoma even when stratified by stage.[2] While no randomized prospective studies have specifically addressed these cancers or any of the other mixed variant urothelial cancers, because of their high proportion, they have been included in randomized prospective phase III trials of treatments for invasive urothelial cancer and, at least in one of the mature long-term studies of neoadjuvant chemotherapy with cystectomy, results have been analyzed.[24] In SWOG 8710, 59 (19.2%) of 307 patients with cT2-4a cN0 cM0 urothelial cancer had squamous (N=37), adenocarcinomatous (N=20), or squamous and adenocarcinomatous (N=2) elements. Patients were randomized to receive 3 cycles of M-VAC chemotherapy before cystectomy or undergo immediate cystectomy. There was evidence of a survival benefit for patients with mixed histology cancers who received M-VAC compared to those who went directly to cystectomy (HR = 0.46, 96% CI 0.25-0.87) (p=0.02). This was so for both clinical T2 and cT3-4a tumors (5-year survival 0.73 [M-VAC + cystectomy] vs. 0.54 [cystectomy alone] for cT2; or 0.58% [M-VAC + cystectomy] vs. 0.34 [cystectomy only] for cT3, 4a) and was far better than the benefit of M-VAC for pure urothelial cancers (HR=0.90, p=0.48). Not surprisingly M-VAC also improved downstaging to pT0 compared to cystectomy for mixed histology tumors (34% vs. 4%, p=0.004). The strengths of this study were its randomized prospective design and the presence of central histology review. The weaknesses were the relatively small number of mixed histology cases (N=59) and lack of quantification of the non-urothelial cancer component. Despite these shortcomings, until more information becomes available, patients with cT2-T4a urothelial cancers with squamous or adenocarcinoma elements should receive cisplatin-based combination chemotherapy before cystectomy to optimize their chances of survival.

IN SUMMARY

Mixed urothelial cancers with variant histologies are generally found with only high grade urothelial cancer and behave at least as aggressively as high grade urothelial cancer and often even more so.

Nested variant and micropapillary urothelial cancers have deceivingly bland histologies and at times may be confused for benign lesions. Even when detected in non-muscle-invasive stages, these should be treated with aggressive local extirpative therapy. Endoscopic and intravesical management should be discouraged.

Carcinosarcomas and urothelial cancers with small cell elements usually are diagnosed correctly, but again are extremely aggressive malignancies. Carcinomas should be treated with local extirpative surgery. The role of additional systemic chemotherapy is being explored and has received some favorable reports.[19] Urothelial cancer with small cell components should be treated as small cell carcinoma with neoadjuvant cisplatin/etoposide followed by aggressive local treatments—either surgery or chemoradiation. Muscle-invasive urothelial cancers with squamous or adenocarcinomatous elements have responded particularly well to multi-drug cisplatin-based urothelial cancer regimens, especially M-VAC, and it would appear that neoadjuvant chemotherapy should be used for them before definitive surgery. Awareness of these features of these common mixed urothelial cancers by urologists and pathologists should assist in their management.

RECOMMENDATIONS

- Nested variant and micropapillary urothelial cancers, regardless of whether they are detected in non-muscle-invasive or muscle-invasive stages, should be treated with aggressive local extirpative therapy (LE: 3, GR: B)
- Carcinomas should be treated if possible with local extirpative surgery (LE: 3, GR: B)
- Urothelial cancer with small cell components should be treated with neoadjuvant chemotherapy including neoadjuvant cisplatin and etoposide followed by aggressive local treatment (LE: 3, GR: B)
- Muscle-invasive urothelial cancers with squamous or adenocarcinomatous elements should be treated with neoadjuvant multi-drug cisplatin-based urothelial cancer regimens before definitive surgery (LE: 3, GR: C)

REFERENCES


VIII. FOLLOW-UP

1. DISTANT RECURRENCES

Recently the long-term oncological outcome of radical cystectomy was analyzed in a contemporary series of 2287 patients who underwent radical cystectomy between 1998 and 2008 [1], LE 3. The mean and median follow-up was 35 and 29 months, respectively. The 5-year overall, recurrence-free, and cancer-specific survival rates were 57%, 48%, and 67%, respectively, with distant and local recurrence rates of 37% and 6%, respectively. In another series, Canter et al [2] reported on a 5-year recurrence-free survival and cancer-specific survival of 56.5% and 59.5%, respectively, among 212 patients with a mean follow-up time of 28 months, LE 3. Again, the majority of patients developed distant metastases. Contemporary cystectomy series have demonstrated a 5-15% probability of pelvic recurrence. Most recurrences manifest during the first 24 months, often within 6-18 months after surgery. However, late recurrences have occurred up to 5 years after cystectomy.

The goal of all follow-up strategies is to detect systemic metastases as early as possible to allow adequate systemic treatment with or without removal of metastatic lesions with a benefit in terms of progression-free and cancer-specific survival. To achieve the goal of an individualized follow-up scheme, natural timing of recurrence, probability of recurrences, functional deteriorations at particular sites, and possible treatment options of a recurrence should be considered [3].

Recently, a nomogram based on 728 patients who underwent cystectomy was presented. Standard predictors were pathological stage of the primary tumor (pTN) and nodal status (pN), LE 2b. The prediction of recurrent disease increased by 3.2% when the nomogram included: age, lymphovascular invasion, CIS, neoadjuvant chemotherapy, adjuvant chemotherapy, and adjuvant radiotherapy [4]. This nomogram can be used to predict the individual risk of systemic relapse and to develop a risk-adapted follow-up protocol.
a) Distant Recurrences

Distant recurrences are seen in up to 50% of patients treated with cystectomy. Most recurrences are seen in the first 24 months, although progression has been observed after more than 10 years [5-8]. The most likely sites for distant recurrences are the lungs, liver, and bones [9]. Treatment of metastatic disease with cisplatin-based combination chemotherapy with either M-VAC or cisplatin and gemcitabine results in a mean survival time of around 14 months.

Helical CT represents the standard imaging technique of choice to detect lung metastases [9, 10]. Use of a 5-mm contiguous reconstruction allows detection of a minimum-sized lesion of 10 mm (LE 2b). For the detection of liver metastases, CT should be performed with native images as well as after using nonionic, iodine-containing water-soluble contrast agents; multidetector helical CT is today's standard [11, 12]. For helical CT, 5 mm reconstructions should be used, allowing a minimum-sized lesion of 10 mm to be detected.

The majority of lymph node metastases originating from urogenital cancer are located in the retroperitoneum so CT scans of the abdomen and pelvis are the imaging procedures of choice [13, 14]. On these cross-sectional modalities, nodal metastases are usually suspected according to location and size criteria, i.e., a maximum short axis diameter ≥ 1 cm is considered malignant [13]. However, CT scans of the abdomen and pelvis might give false-negative results in up to 30% of cases due to difficulties in the interpretation of lymph nodes based on morphology and size alone [14]. Magnetic resonance tomography (MRT) scans of the abdomen and pelvis do not provide additional information and should be restricted to patients with contraindications to CT [10] (LE 2b). To date, PET has not been shown to improve sensitivity in patients with metastatic urogenital cancer overstaging by doing CT scanning alone [15, 16], (LE 3). Bone scintigraphy (BS), conventional radiographic techniques, computed tomography, (18) F–FDG PET/CT and whole body MRI represent potential imaging studies to diagnose and to monitor skeletal metastases [17-20].

However, based on 2 recent retrospective clinical studies it appears questionable if early detection of recurrences is associated with a survival benefit when compared to recurrences that are detected due to symptoms [6, 7], (LE 2b). In the first study, 479 patients who underwent radical cystectomy with adjuvant therapy and who were followed according to a standardized follow-up protocol were evaluated to determine whether diagnosis of asymptomatic recurrence after radical cystectomy by routine follow-up investigations conferred a survival benefit versus symptomatic recurrence. After a median follow-up of 4.3 years, 174 recurrences were detected, of which 87 were symptomatic and 87 were asymptomatic. The 5-year cancer-specific and overall survival rate was significantly higher in the group of patients with asymptomatic metastasis so that the authors recommend routine cross-sectional imaging of the chest and the abdomen. On the other hand, Volkmer et al [7] identified 444 out of 1270 patients with recurrences after radical cystectomy, of which 154 and 290 were asymptomatic and symptomatic, respectively. The overall survival rates at 1, 2, and 5 years were not significantly different between both groups. The authors draw the conclusion that symptom-guided follow-up might provide similar results to a strict follow-up protocol at lower costs.

RECOMMENDATIONS

- Postoperative follow-up after radical cystectomy should be performed in a risk-adapted approach using currently available nomograms (LE: 3, GR: C)
- Symptom-oriented follow-up might result in the same long-term outcome as standardized follow-up protocols but at a lower cost (LE: 3; GR: C)
- Helical CT represents the imaging modality of choice to identify lung, lymph node, and liver metastasis (LE 2b; GR: B)

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2. FOLLOW-UP AND TREATMENT OF SECONDARY URETERAL AND URETHRAL TUMORS

a) Acquisition of Evidence

The recommendations given on follow-up and treatment of secondary ureteral and urethral tumors after radical cystectomy are based on an extensive Medline search. Regarding surgical treatment of invasive bladder cancer, there is only limited prospective, randomized data. Evidence obtained from publications on this topic is mainly based on retrospective multicenter series. Articles were selected according to the following criteria: quality of study evaluation, topic relevance, and presence of intermediate and long-term outcome. Older studies were only included if data were scarce in recent publications. Generally, follow-up regimens for ureteral and urethral recurrences should be adapted according to the natural timing and probability of recurrence, possible functional deterioration at recurrence-specific sites, as well as the availability of an efficient treatment option. The level of evidence and grade of recommendation given are based as outlined by the Oxford Centre for Evidence-based Medicine [1].

b) Secondary Ureteral Tumors

1. INCIDENCE AND TIME TO URETERAL RECURRENT

According to recent series, secondary urothelial tumors account for approximately up to 20% of all recurrences after radical cystectomy for invasive bladder cancer [2]. As opposed to local and distant recurrences, metachronous upper urinary tract recurrences after invasive bladder cancer are considered late oncological events. Most ureteral recurrences have been reported to occur after a median time of 24-41 months after radical cystectomy [3-7]. As a result of improved survival rates in invasive bladder cancer, an increasing number of patients will achieve long-term survival and will therefore remain at risk for tumor recurrence in the upper urinary tract. In numerous studies, the 5-year rate of ureteral recurrences after radical cystectomy is reported to range from 2-9% [2, 4, 6, 8-15]. In a longitudinal study using landmark time analysis of a total of 1329 patients treated with radical cystectomy, it was shown that the risk of upper urinary tract recurrence does not decrease over time with 3- and 5-year cumulative incidences of 4% (95% CI 3-6%) and 7% (95% CI 5-8%) [15]. Furthermore, ureteral recurrences have been reported to occur even 9 years after curative surgery, which highlights the importance of long-term surveillance of the upper tracts after radical cystectomy.
2. **Rationale of a Risk-adapted Strategy for Follow-up**

Several clinical and pathological parameters have been identified as risk factors for metachronous upper urinary tract recurrence and should be taken into consideration when addressing the patient’s individual risk of recurrence. The rationale of a risk-adapted strategy is supported by a recently performed large retrospective analysis evaluating the long-term risk of upper tract recurrence in 1420 patients who had undergone cystectomy [16]. In this study, a number of risk factors were shown to potentiate the risk of upper tract recurrence. Multivariate analysis revealed that patients with no risk factors (history of carcinoma in situ (CIS) and recurrent bladder cancer, high-grade pTa-T1 bladder cancer, and distal ureteral malignancy at radical cystectomy) had only a 0.8% risk of developing ureteral recurrence 15 years after surgery whereas it increased to 13.5% in patients with 3-4 existing risk factors [16]. Furthermore, a recent large retrospective single center series on 174 patients with recurrence after radical cystectomy showed that the rate of concomitant distant recurrences in patients with secondary urothelial carcinoma was only 11% [2].

Approximately 75% of upper tract recurrences are detected when patients present with symptoms, such as gross hematuria or flank pain. These symptoms are often associated with locally advanced disease and, consequently, are associated with poor outcomes after radical nephroureterectomy [6]. Thus, new strategies for earlier detection of upper tract recurrences while they are still localized are necessary for effective treatment by radical nephroureterectomy [6] given the opportunity of local curative treatment [6]. Assessment of risk factors for upper tract recurrence might help to identify high-risk patients and tailor surveillance regimes according to a risk-adapted strategy, thereby reducing the need of unnecessary follow-up examinations and surveillance costs in low-risk patients.

3. **Risk Factors for Upper Urinary Tract Recurrence**

- **Ureteral Margin and Frozen Section Analysis**

Ureteral tumor involvement at final pathological analysis of radical cystectomy specimens was found in 4.8-13.0% of the patients and in 3.6-8.3% of the examined ureters [4, 10, 11, 15, 17]. It has been shown in various studies that tumor involvement of the distal ureter at cystectomy is an independent risk factor for upper tract recurrence [15, 16] with an approximately 2.6-fold increase in the relative risk [16]. While there is substantial evidence that suggests that intraoperative frozen section analysis is a reliable tool to detect malignant ureteral margins at radical cystectomy, its role is controversial [4, 5, 10, 11, 17]. In two recent studies, the sensitivity and specificity of frozen section analysis for the detection of malignant ureteral margins was reported to range between 74-75% and 98-99%, respectively, with a positive predictive value of 94%, resulting in an overall accuracy of 98% [4, 10]. On the other hand, heterogeneous data exist on whether a sequential resection of malignant ureteral margins can unequivocally be advocated to reduce the risk of a malignant anastomotic margin at cystectomy [4, 5, 10]. In two recent studies, the rates of converting initially positive ureteral margins into negatives with a sequential resection strategy were as high as 39-41%, [4, 10] whereas in another study a conversion rate of up to 82% was reported [5]. In this study, those with initially positive but finally negative margins still had a 4.4-fold increased risk as compared to those patients with initially negative margins [5]. However, their risk decreased after conversion to a finally negative ureteral margin since those patients with positive anastomotic margins had an even higher 7.4-fold risk of recurrence [5].

Since the incidence of malignant ureters at cystectomy is highest in the distal ureters [18], some authors have suggested resecting the ureters more proximally at the crossing with the iliac vessels [11]. A retrospective series among 755 patients undergoing cystectomy reported CIS in the most proximally resected ureters in only 1.2% of the patients [11]. In this study, a considerable number of 17% of patients with CIS on frozen section analysis had upper tract recurrence and 80% of the patients with CIS at the ureteral margin had also CIS of the bladder. The authors suggested performing frozen section analysis only in patients with known CIS of the bladder. This may minimize the risk of ureteral strictures due to ischemia of the distal part of the ureter and also be beneficial for patients after prior pelvic irradiation therapy, but makes the use of an afferent tubular ileal segment for ureteral reconstruction necessary [11].

- **Carcinoma in situ of the Bladder**

In patients with non-muscle-invasive bladder cancer (pTa, pTis, pT1), the presence of CIS of the bladder was found to be a risk factor for metachronous upper tract carcinoma [10]. Conversely, in patients with muscle-invasive disease, concomitant CIS was not found to be independently associated with upper tract recurrence [4, 6, 8, 14, 19], whereas in patients with CIS-only disease at cystectomy, a significantly higher rate of upper tract recurrences was reported [20]. This finding may be artificially skewed towards the patient cohort with low-stage disease at cystectomy since a confounding effect of survival differences between different tumor stages has to be assumed.
• **Tumor Stage and Multifocality**

In several studies, tumor stage was investigated as a possible risk factor of upper tract recurrence. Approximately 65-100% of upper tract recurrences occur in patients with organ-confined bladder cancer (pT2bpN0M0 or lower stage disease) [8, 9, 14, 19, 21]. In one study, patients with pTa-T1 bladder cancer were reported to have a 1.8-3.8 fold higher risk of upper tract recurrence as compared to patients with muscle-invasive disease [3]. Similar to the outcome of patients with CIS-only disease at cystectomy, tumor stage was not an independent risk factor for upper tract recurrence, but was a rather strong predictor of prolonged survival after radical cystectomy. These data may be biased by the fact that patients with high-stage disease were at considerably higher risk for early local or systemic recurrence as compared to patients with non-muscle-invasive disease [2, 22].

In a recent study, multifocality of the initial bladder tumor was found to independently contribute to a higher risk of ureteral involvement at radical cystectomy and subsequent upper tract recurrence, [4] which supports the results of a prior study [23]. Limited data exist as to whether or not urethral tumor involvement predicts a higher likelihood for upper tract recurrence [6, 14]. Urethral tumor involvement in female patients has been significantly associated with a higher risk for upper tract recurrence. Likewise, in male patients, urothelial carcinoma of the prostatic ducts invading the lamina propria was associated with a higher risk for secondary ureteral tumors but not for patients with a continuous expansion of urothelial carcinoma into the prostate (classified as pT4a stage) [6, 14]. Most presumably, this observation may also be biased due to impaired survival rates in patients with pT4a urothelial carcinoma of the bladder.

4. **Survival After Upper Urinary Tract Recurrence**

The 3-year survival rate for patients with upper tract recurrence lies between 0 and 25%, but long-term survival of more than 9 years has also been reported in some series [6, 19, 24]. Survival after secondary ureteral recurrence is mainly predicted by tumor stage and lymph node tumor involvement. In a single-center series it was demonstrated that in patients with pT3 or greater secondary upper tract carcinoma, the median survival was only 1.3 years, compared to 3.4 years in patients with pTa-T1 cancers [6]. Similar results were seen in another series of 85 female patients who had an upper tract recurrence rate of 2.4%. All recurrences were muscle-invasive at nephroureterectomy [21].

Some data suggest that tumor location also affects survival in patients with upper tract recurrence [25]. In some series, recurrence at the ureteroileal anastomosis was found in up to 40-60% of the patients with upper tract recurrence [4, 25]. Importantly, patients with anastomotic tumor recurrence tended to develop early progression to distant metastatic disease, whereas patients with more proximal upper tract recurrences showed improved recurrence-free survival after radical cystectomy [25].

5. **Diagnosis of Upper Tract Recurrence**

• **Radiological Imaging**

According to current studies, patients diagnosed with asymptomatic upper tract recurrence during routine follow-up have a significantly higher survival advantage than those with symptomatic recurrences [6]. This stresses the importance of an early detection of metachronous ureteral malignancy for a timely initiation of a curative treatment.

In a recent analysis, the accuracy of a total of 1064 intravenous pyelography (IVP) studies of 322 patients, who underwent routine follow-up of the upper tract at 1, 2, 3, 5, 7, and 10 years after radical cystectomy, was investigated. Of these patients, upper tract recurrence was detected in only 15 (4.7%), but only 8 of them had suspicious findings on IVP. Patients with positive final ureteral margins were at highest risk for recurrence. Therefore, the authors concluded that routine excretory urography should be limited to patients at high risk for upper tract recurrence. Likewise, Slaton et al developed a stage-specific surveillance protocol in patients after radical cystectomy and suggested the use of upper tract imaging every 1-2 years after radical cystectomy for all tumor stages [26], but specific risk factors were not taken into consideration in this study.

Although former studies reported similar sensitivity rates of IVP and multidetector computed tomography (MD-CT) urography for the detection of upper tract recurrence ranging from 0-55%, [8, 9, 14, 19, 21, 26] some current studies have adopted MD-CT urography as the preferred diagnostic option compared to conventional IVP for the detection of upper tract tumors [27]. Contemporary series reporting on the value of MD-CT derive mainly from series in which patients had either primary upper tract tumors or underwent upper tract imaging for a history of microscopic or gross hematuria and are also limited by a relatively small number of included patients. To provide some recent aspects and developments in this diagnostic field the results of the most current studies will be outlined in the following.

In patients with primary upper tract tumors, MD-CT urography shows a significantly higher sensitivity, specificity, and test accuracy of 96%, 100%, and 99% as compared to IVP at 75%, 86%, and 85%, respectively [27]. For MD-CT urography, the location of the primary tumor seems to have a direct impact on the detection accuracy. The sensitivity for the detection of tumors in the renal pelvis was found to range from 78-94% but decreased to 19-54% for
tumor lesions in the ureter [28]. In a retrospective series of 188 patients with a history of urothelial carcinoma (using diagnostic ureterorenoscopy as the diagnostic reference standard), MD-CT urography showed a positive predictive value (PPV) of 63-67% for the identification of a tumor lesion in the upper tract [29, 30]. In both of these studies, characteristic findings on MD-CT urography suspicious of an upper tract tumor were filling defects and urothelial wall thickening. Interestingly, when stratified by location, urothelial wall thickening was more predictive of tumors in the pelvicalyceal system (PPV 88%) than in the ureter (PPV 33%). Conversely, filling defects were more predictive in the ureter (PPV 88%) than in the pelvicalyceal system (PPV 50%) [29]. MD-CT was able to correctly predict the pTNM staging in 58-88% of the patients with upper tract malignancies [28, 31]. However, even in contemporary series, the main drawback of MD-CT urography is the low positive predictive value for small tumors or urothelial wall thickening (0-46%) [32].

The use of a split-bolus technique among 200 patients presented initially with hematuria was prospectively assessed in a recent series [33]. Split-bolus techniques provide improved imaging by simultaneous nephrographic and excretory CT-phase acquisition. The corresponding sensitivity, specificity, and PPV rates were 100%, 99%, and 99%, respectively [33]. Alternatively, in one study, the use of MRI urography images was investigated in 17 patients with a total of 23 upper tract lesions. A sensitivity of 74% for the detection of small urothelial carcinomas (2 cm or less) was reported [34]. Possible further technical improvements include the acquisition of diffusion-weighted MRI images in patients with upper tract obstruction due to upper tract tumor lesions [35], but, still, these techniques have failed to detect flat urothelial lesions [36].

For local staging of the primary tumor lesion and regional lymph nodes, magnetic resonance imaging (MRI) has not proven diagnostic superiority to MD-CT but is indicated in patients with contraindications to MD-CT (iodine allergy, renal insufficiency) [34]. MRI remains contraindicated in patients with pacemakers. Gadolinium infusion must be omitted in patients with severe renal insufficiency (creatinine clearance less than 30 mL/min) to avoid the risk of subsequent nephrogenic systemic fibrosis. [37].

- **Urinary Cytology and Molecular-based Urinary Markers**

Some authors have used urinary cytology at least annually in patients after radical cystectomy [2, 13]. However, despite its high specificity (80-100%) the sensitivity of voided urine cytology for the detection of upper tract tumors is low (36-60%) [38, 39]. After urinary diversion, the detection of malignant cells in voided urine samples is significantly hampered because of the difficulty in distinguishing urothelial cancer from intestinal epithelial cells [40]. Most importantly, the additional use of urinary cytology in established follow-up regimens (with radiological and clinical examinations) does not significantly lead to an earlier detection of upper tract recurrences [40]. Selective ureteral urinary cytology results in an improved positive predictive value of greater than 85% for high-grade muscle-invasive upper urinary tract urothelial carcinomas, [41] but, for screening purposes, invasiveness and additional costs have to be considered.

Alternatively, urine-based markers have recently become a popular tool to overcome the limitations of conventional urinary cytology. Evidence in literature derives mainly from patients with primary upper tract tumors with relatively small numbers of included patients. In a comparative analysis of 30 patients with urothelial carcinoma of the upper tract, fluorescence in situ hybridization (FISH) showed significantly higher sensitivity rates as compared to urinary cytology (77% vs. 36%) but not for specificity (95% vs. 100%), and this has been confirmed in other studies [39, 42]. Moreover, FISH analysis, which uses gene-labeled probes for the chromosomes 3, 7, 9, and 17, is less interference-prone than urinary cytology [38]. For immunocytology, a prior small study in 16 patients with upper tract carcinoma reported a sensitivity rate of 100% for the detection of low grade (G1-2) tumors [43]. Altogether, due to their non-interference probe analysis, FISH is a promising tool to contribute to a more non-invasive diagnosis of high-grade upper tract carcinomas. Nevertheless, taken together, there is not enough evidence to support the routine use of urinary cytology and urine-based markers alone for the follow-up of the upper tracts [44].

- **Ureterorenoscopy**

Ureterorenoscopy with biopsy using semirigid or flexible instruments is the method of choice for the histological diagnosis of an upper tract carcinoma [45]. Access to the upper tract after urinary diversion can be particularly challenging and may require the use of combined retrograde and antegrade techniques [46]. For evaluating the local T stage, upper tract biopsies are less reliable because of the limited capability of biopsy instruments to retrieve adequate tissue specimens sufficient for the evaluation of the complete pelvicalyceal or ureteral wall [6]. This fact is supported by a prior study that demonstrated that even when lamina propria was present within the specimens, almost 50% of the tumors were initially misdiagnosed as superficial and were found to be invasive in the final nephroureterectomy specimens [47].

6. Treatment of Upper Urinary Tract Recurrence

- **Radical Nephroureterectomy**

Radical nephroureterectomy is the standard treat-
ment for patients with invasive upper tract recurrence [6, 13, 21]. Eligibility of patients (in terms of performance status and tumor extent) to undergo open radical nephroureterectomy is a predictive factor for improved survival. A prior study demonstrated that while the overall median survival of patients with upper tract recurrence was only 10 months, those who were eligible for radical nephroureterectomy had a median overall survival of 26 months [8].

Increasing experience with laparoscopic radical nephroureterectomy suggests that it is oncologically equivalent to open surgery for tumors of equal grade, stage, and lymph node status. These data derive mainly from patients with primary upper tract carcinoma. A recent study comparing retrospectively the outcomes of patients treated with open (N=704 patients) and laparoscopic radical nephroureterectomy (N=70 patients) for primary upper tract urothelial carcinoma found no significant differences in 5-year cancer-specific survival between both the open and laparoscopic groups [48]. One limitation of this analysis is that patients treated with laparoscopic radical nephroureterectomy had significantly less likelihood for lymph node tumor involvement at the time of surgery compared to patients treated with open surgery, which might have biased the final survival analysis. Nonetheless, given the lack of data and the challenging postoperative anatomy in the retroperitoneum and pelvis after radical cystectomy and urinary diversion, with the need to enter and reconstitute the ureteroileal anastomosis, laparoscopic radical nephroureterectomy in secondary upper tract recurrence still to be regarded as an investigational treatment option.

- **Lymphadenectomy**

The role and extent of regional lymphadenectomy at radical nephroureterectomy in patients with upper tract recurrence has not been well-defined and remains controversial. Open radical nephroureterectomy was accompanied by regional lymphadenectomy only in a few retrospective series [6, 8, 14]. In these series, the rate of locally advanced disease (pT3-T4) ranged from 54-66% with lymph-node positive disease found in 32-83% of the patients.

Similar to the increasing evidence for a therapeutic benefit of extended lymphadenectomy for invasive bladder cancer [49, 50] there is recent evidence that also suggests that extended lymphadenectomy in invasive upper tract carcinoma is a strong predictor for improved disease-free and cancer-specific survival [51]. A retrospective series on 132 patients with primary muscle-invasive upper tract urothelial carcinoma showed that pathological tumor stage and lymph node tumor involvement were independent risk factors for disease-free survival [52]. Moreover, the number of removed lymph nodes and the extent of lymphadenectomy was an independent risk factor for recurrence-free and cancer-specific survival. Interestingly, in this study, patients who did not receive any lymphadenectomy at the time of surgery had comparable survival rates to those with pathologically confirmed node-positive disease at radical nephroureterectomy. By contrast to patients with upper tract recurrence, the rate of lymph-node positive disease in primary upper tract carcinoma was only 25% [52, 53]. Moreover, the ideal anatomic template of regional lymphadenectomy according to the primary site of recurrence has not been established, which is mainly due to the inconsistent lymphatic drainage in the retroperitoneum in urologic malignancies [54]. Altogether, given the lack of evidence for a therapeutic benefit of regional lymphadenectomy, its role in patients with upper tract recurrence remains unclear and therefore currently is considered as a diagnostic procedure.

- **Adjuvant Chemotherapy**

The role of adjuvant chemotherapy in node-positive upper tract recurrence has only been addressed in a few studies [13]. In locally advanced upper tract carcinoma, the results of adjuvant chemotherapy remain poor as only 5% or fewer of the patients will achieve long-term survival [13]. The low incidence of upper tract recurrences makes it unlikely that randomized prospective studies on the role of adjuvant therapy can be performed. Controlled observational and registration type multi-institutional studies with pooling of data are encouraged.

- **Conservative Treatment for Upper Tract Recurrence**

Conservative treatment options for patients with upper tract recurrence after invasive bladder cancer include endoscopic and percutaneous resections. Indications for performing renal-sparing treatment in patients with upper tract recurrence are bilateral tumors, solitary kidney, or severe renal insufficiency, and tumor features of small size, low grade, and low stage. Studies reporting on outcomes after endoscopic treatment of upper tract carcinomas derive almost exclusively from patients with primary carcinomas who have a significantly improved prognosis as compared to patients with metachronous tumors. Approximately 50-75% of the patients with upper tract recurrence present initially with high-stage, high-grade disease compared to only about 30% of the patients with de novo urothelial carcinoma of the upper tract [6, 8, 9, 19, 21, 24, 55, 56]. Moreover, in patient series performing radical nephroureterectomy and regional lymphadenectomy, lymph node tumor involvement has been reported in 32-83% [6, 8, 14]. These data indicate that upper tract recurrences are more aggressive malignancies than primary urothelial cancers. Optimal indications for conservative nephron-sparing treatment of secondary upper tract tumor recurrences remain to be defined.
RECOMMENDATIONS FOR FOLLOW-UP AND TREATMENT OF SECONDARY URETERAL TUMORS

- Surveillance regimens should be based on a risk-adapted strategy (LE: 3, GR: B).
- The number of risk factors potentiates the risk of recurrence. Risk factors include: (a) positive ureteral margin, (b) carcinoma in situ of the bladder and ureter, (c) tumor multifocality, (d) urethral tumor involvement, and (e) male gender (LE: 3, GR: B).
- Patients with final positive ureteral margins in the definitive pathology report at surgery are at increased risk of ureteral recurrence. Frozen section analysis for this finding has a high sensitivity and specificity for the detection of malignant ureteral margins (LE: 3, GR B).
- Ureterorenoscopy with biopsy is the diagnostic procedure of choice for the diagnosis of a metachronous upper tract recurrence after radical cystectomy (LE: 3, GR: C).
- Cytology and urine-based markers such as fluorescence in situ hybridization and immunocytology are indicative of upper tract recurrence, but their sole use cannot be recommended for exclusive follow-up of the upper tracts (LE: 3, GR: B).
- From an oncologic standpoint, routine upper tract imaging is only indicated in patients with high risk or clinical symptoms suspicious of a metachronous upper tract recurrence and the optimal interval for follow-up imaging is unclear (LE: 3, GR: C).
- Nephroureterectomy is the treatment of choice for invasive upper tract recurrence, providing prolonged survival (LE 3, GR: B).

Based on scarce data, regional lymphadenectomy in patients undergoing radical nephroureterectomy is of limited diagnostic value, and its therapeutic role is undetermined. (LE: 3, GR: C).

c) Secondary urethral tumors

1. INCIDENCE OF URETHRAL RECURRENTS AFTER RADICAL CYSTECTOMY

According to contemporary series, the risk of urethral recurrence is low, occurring after a median time of 14-24 months in 3.7-8.1% of male patients undergoing radical cystectomy for bladder cancer, [57-62] with a resulting 5-year urethral recurrence-free probability after radical cystectomy of approximately 95% [57, 60]. Most urethral recurrences are detected by evaluation of symptoms (57-61%), whereas 31-39% are detected by abnormal urethral cytology [58, 63]. Patients with symptomatic urethral recurrences have no significantly different median time to diagnosis as compared to patients diagnosed by cytological abnormalities [58]. Urethral recurrences in superficial tumor stages (pTa, pTis) are diagnosed in many cases by abnormal cytology (59-100%) as opposed to invasive tumors (pT1-T4), which are often detected after patients have developed local symptoms (~79%) such as gross hematuria, bloody urethral discharge, palpable mass, change in voiding habits, or local pain [58, 64].

2. RISK FACTORS IN MALE PATIENTS

In a large, retrospective single-center series of 729 male patients treated with radical cystectomy with a median follow-up of 38 months, independent risk factors for urethral recurrence were found to be a history of non-muscle-invasive bladder cancer, prostatic urethral involvement, and NMIBC (pTa, pTis, pT1) at radical cystectomy. In this study, superficial prostatic involvement (pTa, pTis) was a stronger predictor for urethral recurrence compared to invasive prostatic involvement [58]. Similar findings were found in another large, retrospective, single-center series of 768 male patients with a longer median follow-up of 13 years in which prostatic urethral involvement, but not tumor multifocality or bladder CIS, was an independent risk factor for urethral recurrence. By contrast to the prior report [58], patients with invasive prostatic involvement had a higher risk for urethral recurrence compared to patients with superficial prostatic urethral tumors [57].

3. URINARY DIVERSION AND URETHRAL RECURRENT

Some series suggest that patients with orthotopic diversion have a decreased risk for urethral recurrence as compared to patients with supranational diversions [57, 61, 65]. However, other comparable series did not find orthotopic diversion to be a significant independent risk factor compared to cutaneous diversions [58]. Prior studies have hypothesized that the continued exposure of the remnant urothelium to urine in orthotopic diversions may have a protective effect against the development of a urethral recurrence [66]. These conflicting results may also be due to a patient selection bias since patients with lower tumor stages might rather be treated with orthotopic diversion than patients with locally advanced disease [58].

4. PREOPERATIVE PROSTATIC BIOPSY AND FROZEN SECTION ANALYSIS

In one study, preoperative prostatic urethral biopsies showed a high negative predictive value of 99% compared to final urethral margin status whereas a positive finding correlated in only 68% of the cases with a positive final urethral margin status [67]. Confirmatory results of the relatively low positive
predictive value of transurethral loop biopsies at the level of the verumontanum as to the final results of cystoprostatectomy specimens were reported in 246 patients. The sensitivity and specificity was only 53% and 77%, resulting in a positive and negative predictive value of 45% and 77%, respectively [68]. By contrast, in this study, sensitivity and specificity of frozen section analysis was 100% [67]. A recent retrospective study of 294 patients confirmed that a positive urethral margin status is the strongest independent risk factor for urethral recurrence as compared to prostatic urethral and stomal invasion [60]. This strengthens the importance of achieving a tumor-free urethral margin at radical cystectomy.

5. Risk Factors in Female Patients

In female patients undergoing radical cystectomy, the rate of urethral recurrence was reported to range between 0.8-4.3% [21, 69-71]. By contrast to the low rate of concomitant urethral malignancy in females with primary bladder cancer (~2%), [72] a higher rate of urethral malignancy at radical cystectomy of 12% has been reported [73]. A history of multifocal or recurrent bladder cancer was found to contribute to an increased risk for urethral recurrence [21]. Furthermore, the risk of tumor involvement of the distal urethra at radical cystectomy is significantly higher in patients with bladder neck or vaginal involvement and preoperatively enlarged inguinal lymph nodes [74-76]. A pathological reevaluation of 67 female cystectomy specimens showed that concomitant urethral tumors were exclusively located in the proximal or mid portion of the urethra. Moreover, women with urethral tumors often showed localization of the primary tumor at the bladder neck. These tumors were of higher grade and stage and harbored a higher risk of node-positive disease [75]. Stein et al prospectively evaluated 71 female cystectomy specimens and reported that tumor localization at the bladder neck and urethra was present in 19% and 7%, respectively. The presence of a bladder neck tumor significantly correlated with the highest risk of concomitant urethral malignancy. Conversely, approximately 60% of the patients with malignancy at the bladder neck had no evidence of tumor involvement of the proximal urethra. In this study, frozen section analysis of the distal urethral margin showed a 100% sensitivity and specificity for detection of a positive urethral margin as compared with the final pathological analysis [74]. Another study on 85 female patients confirmed the usefulness of frozen section analysis with a sensitivity of 100% for the detection of a malignant urethral margin [21]. Nonetheless, one must remember that urethral recurrence may occur even in patients with negative final urethral margins possibly due to a submucosal extension of the primary bladder tumor into the urethra with unaffected urothelial layer at frozen section analysis [76]. This highlights the importance of an adequate full-thickness biopsy of the urethral margin for frozen section analysis [73]. Altogether, the present data underscore the value of the intraoperative frozen section analysis for the detection of urethral malignancy at radical cystectomy. Furthermore, they add to the growing body of evidence that patients with invasive bladder cancer at the bladder neck should not be excluded from an orthotopic approach in advance unless the intraoperative frozen section analysis reveals evidence of malignancy at the distal urethral margin [73].

6. Survival after Urethral Recurrence

The 5-year disease-specific and overall survival after urethral recurrence is reported to be only 35% and 52%, with a median overall survival after diagnosis of 28-54 months [58, 60, 63]. There are heterogeneous results in the current literature whether bladder or urethral recurrence pathology is the most important factor for overall survival after urethral recurrence. While Huguenot et al found no differences in survival [58], Lin et al reported in 24 patients with urethral recurrence that bladder pathology determined predominantly their survival [77]. Conversely, Clark et al found among 47 patients with urethral recurrence that stage of urethral recurrence but not bladder cancer pathology was more predictive for overall survival [63]. Possible explanations for these contradictory observations may be different patient selection criteria and the different use of prophylactic urethrectomies at radical cystectomy which may have biased the survival analyses of both studies. Second, the number of patients with pT0 disease after urethrectomy differs considerably in the 2 studies. Lin et al included 9 patients (37%) with pT0 disease [77], whereas Clark et al excluded all pT0 patients from final survival analysis [63]. In their analysis, Huguet et al found none of the patients to have pT0 stage at urethrectomy [58], and, most importantly, 26% of their patients with urethral recurrence had upper tract recurrence, [58] which tends to be high stage and high-grade disease at initial diagnosis [6]. Third, survival in patients with urethral recurrence and concomitant distant metastases is mainly determined by the presence of metastatic disease [2]. In conclusion, it remains still a matter of debate whether urethral or bladder cancer pathology is more predictive for overall survival after urethral recurrence.

7. Diagnosis and Staging of Urethral Recurrence

Given the low rate of urethral recurrence, there is little data or agreement on the optimal follow-up of the asymptomatic patient with a retained urethra after radical cystectomy. All patients with urethral bleeding, pain, or mass should be evaluated promptly. The follow-up regimens described in current literature derive mainly from different high-volume centers and are based on urinary cytology,
urethral washings, urethroscopy, and different imaging modalities [57, 59, 61, 62, 77, 78]. In terms of frequency of follow-up, some authors suggest the routine use of urinary cytology, urethral washings, and urethroscopy on a quarterly basis for the first 2 years continued semiannually afterwards, [61] whereas others only conduct clinical follow-up [58]. It seems therefore reasonable to tailor surveillance regimens according to the patient’s individual risk profile. Urinary cytology is certainly a useful and noninvasive diagnostic tool to detect urethral recurrence but its sensitivity is considerably reduced in patients after urinary diversion [40]. Controversial data exist to the question whether the routine use of urethral washings in patients with a retained urethra after cystoprostatectomy is of prognostic advantage. Among 24 patients with a median follow-up of 28 months after urethrectomy, a significant impact on disease-free survival was not observed between those who routinely received urethral washings and those who did not [77]. Urethroscopy with biopsy is certainly the method of choice for the histological diagnosis of urethral recurrence but the use of urethroscopy on a regular basis has not appear to provide any survival benefit [9, 57, 59, 60, 62]. For local staging after detection of a urethral malignancy, there is increasing evidence that magnetic resonance imaging is superior to MD-CT in patients with urethral malignancy in terms of staging accuracy [78].

8. Management of Urethral Recurrence

- Non-invasive Urothelial Tumors (pTa-pTis)

In patients with a non-invasive urethral recurrence, a urethra-preserving strategy can be attempted using transurethral resection of the tumor lesion [64]. However, in a series with high-grade pTa urothelial carcinoma of the urethra after radical cystectomy treated with TUR, only 3 of 4 patients with recurrence progressed to invasive disease. After recurrence, all were managed with salvage urethrectomy and remained disease-free after a median time of 24-44 months [64]. The authors concluded that an additional adjuvant local treatment, i.e., BCG, in high grade tumors may have reduced the risk of further recurrence [64]. In a prospective analysis of patients with carcinoma in situ in the urethra after radical cystectomy, the use of intraurethral BCG perfusion weekly for 6 weeks showed a complete remission rate of 80% but did not show any therapeutic response in patients with papillary or invasive disease [59].

- Invasive Urothelial Tumors (pT1-pT4)

Urethrectomy is the treatment option of choice in male patients with invasive urethral recurrence providing long-term survival [62]. In 2 recent studies, the use of prophylactic urethrectomies in male patients with invasive prostatic tumor involvement at radical cystectomy was not found to confer any survival benefit compared to patients treated with urethrectomy at the time of urethral recurrence [58, 61]. Similar results were obtained from a recent analysis of the SEER database investigating the timing of urethrectomy as a possible predictor for improved survival among 2401 male patients who underwent radical cystoprostatectomy for bladder cancer. A total of 195 men (8.1%) developed urethral recurrence and were treated with either concurrent or salvage urethrectomy. The use of concurrent urethrectomy at radical cystoprostatectomy versus salvage urethrectomy was not found to confer any significant independent survival benefit (HR = 0.775, 95% CI 0.592-1.014, p=0.0632). Interestingly, by contrast to patients treated at urban non-teaching hospitals, patients treated at teaching hospitals were more likely to undergo salvage urethrectomy for recurrence versus immediate urethrectomy. In this study, tumor stage at radical cystectomy was the only independent variable that predicted performance of concurrent urethrectomy [62]. Furthermore, complication rates and intraoperative blood loss are not significantly different in patients treated with delayed or immediate urethrectomy [79]. In female patients, given the overall low rate of urethral recurrence, the use of prophylactic urethrectomies without evidence of invasive malignancy at the urethral margin does not have a significant impact on the oncological long-term outcome after radical cystectomy [72, 80, 81]. As for upper tract recurrence, adjuvant treatment modalities for urethral recurrence have yet to be addressed sufficiently in the literature and should be performed only within prospective randomized trials.

RECOMMENDATIONS FOR FOLLOW-UP AND TREATMENT OF SECONDARY URETHRAL TUMORS

- Risk factors for urethral recurrence in male patients are prostatic tumor involvement (either superficial or invasive) and bladder neck involvement in female patients (LE: 3, GR: B).

- Intraoperative frozen section analysis has a high sensitivity and specificity for the detection of a malignant urethral margin for both male and female patients (LE: 2b, GR: B).

- Patients with positive urethral margins in the final pathology report are at increased risk of urethral recurrence (LE: 3, GR: B).

- The use of routine surveillance urinary cytology, urethral washings, and diagnostic urethroscopy in asymptomatic patients has not shown a survival benefit (LE: 3, GR: B).

- Urethrectomy is the preferred treatment in patients with invasive carcinoma at the urethral margin at radical cystectomy or at a later recurrence (LE 3, GR B)
• Local conservative treatment is an option in patients with non-invasive tumor(s) or carcinoma in situ of the urethra (LE: 3, GR: C).

• In patients with urethral recurrence and concomitant distant recurrence outside the urinary tract, systemic chemotherapy is indicated (LE: 3, GR: C).

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Committee 7

Urinary Diversion

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## IV. RECOMMENDATIONS
I. INTRODUCTION

Radical cystectomy and urinary diversion have been assessed the highest relative value in terms of difficulty of the surgery for any procedure in urology. They are also the most difficult laparoscopic or robotic procedures and more so if the diversion is performed totally intracorporeally. The risk of cystectomy and urinary diversion is based not only on the technical challenges of the procedure but also on the nature of the patient's need. The incidence of bladder cancer increases continually with advancing age; thus, the responsibility of providing optimal surgical treatment for elderly and possibly frail patients is common among urologists. Improvement in patient rehabilitation is noteworthy through continent cutaneous diversions and neobladders and better enterostomal therapy support. In this context, there must remain continued emphasis on refining the surgical technique of radical cystectomy and urinary diversion to provide utmost safety for the patient.

The International Consultation on Urological Diseases (ICUD) has looked at published evidence and produced recommendations at various levels. For proper assignment to levels of evidence, one has to consider study design (prospective, retrospective), number of patients enrolled, if the study cohort consists of all patients available or not, type of assessment tool and its psychometric properties (validity/reliability), and response rate. Unfortunately, not a single randomized controlled study within the field of urinary diversion exists. Consequently, almost all studies used in this report are of Level 3 evidence – good quality retrospective studies or case series – or Level 4 evidence including expert opinion based on “first principles” research. Therefore, the grades of recommendations given are again of Grade C only [1]. Grade C recommendation is given when expert opinion is delivered without a formal analytical process. In order to check the power of the “expert opinion” and the validity of the consensus reached by the diversion group, each committee member disclosed the experience, surgical volume, and types of diversions used at his or her home institution. The results are presented in Table 1.

Our expert opinion is based on almost 16,000 diversions and radical cystectomies performed in 3 continents (Africa, USA, Europe). This committee represents a well-balanced combination of pioneering institutions of any type of diversion, high volume centers and surgeons, as well as data from low volume institutions, plus a leading pediatric urology institution and the Swedish registry for bladder cancer, which reports any case from Sweden, including treatment, that has been observed in the respective period.

Some conclusions from Table 1 are:

- Only 3/11 institutions have experience with any type of diversion.
- Anal diversions play no role in the US, but are of value in pediatric patients and in the third world.
- Continent cutaneous diversions play a secondary role; even former pioneering institutions (LA) use it with decreasing frequency.
- Conduit (42.2%) and neobladder (38%) are the standard diversions at large centers.
- Truly population-based data from the USA [2] and from the Swedish Bladder Cancer Registry (S. Jahnson, Linköping, Sweden) show a neobladder rate in the range of 15%; with increasing hospital volume the neobladder/continent diversion rate
approaches 75%, addressing the impact of hospital volume on the use of continent reconstruction and the question of continent diversion being a new parameter for measurement of quality of care. Our group considers these data a further argument for the centralization of radical cystectomy and urinary diversion.

- A detailed analysis of Table 1 brings us to the key question for criteria used to define the limits for low, intermediate, and high annual hospital and surgical case load. In most publications, one single radical cystectomy per year was defined as low annual surgical case load, 2 radical cystectomies per year are intermediate, and 3 or more radical cystectomies per year as high. Even though 2 cases per year represent 100% more than one radical cystectomy per year, from a practical point of view, these surgeons have a very low case load. On the other end, a surgeon who performs 3 or 4 radical cystectomies is already defined as a high volume surgeon. So, the limits appear to be chosen totally arbitrarily. The same applies to the annual hospital case load. We need realistic criteria! Our committee considers a minimum annual case load of 25 radical cystectomies done by not more than two surgeons, to be the basis of a high volume center.

- Another major difficulty the committee had to master was the lack of standardized reporting in the urological literature. Recently Donat emphasized the need for standardized reporting of outcomes and complications, especially in urological oncology, because of the mostly elderly population and the associated comorbidities [3]. Radical cystectomy and urinary diversion are 2 steps of one operation. However, the literature uniformly reports the complications of radical cystectomy while ignoring that the majority complications are diversion-related. While this may seem semantic, it is not [4].

Until recently, significant disparity in the quality of surgical complication reporting as well as the lack of universally accepted reporting guidelines, definitions,

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and grading systems have made it impossible to compare the surgical morbidity and outcomes in patients who have undergone cystectomy. There is a clear case for reporting of complications in a standardized way. The Clavien system provides such a straightforward and validated instrument, and it has already been successfully adopted by several urological centers [4, 5].

This article discusses the reconstructive options after radical cystectomy due to bladder cancer or other conditions, the criteria for selection of the most appropriate procedure, and the outcomes and complications associated with the available diversion options.

II. GENERAL ASPECTS OF URINARY DIVERSION

1. URINARY DIVERSION AND RENAL FUNCTION

a) Preoperatively

Renal function has an important bearing on outcome following urinary reconstruction as there is an increase in acid load as a result of absorption of urinary constituents through the bowel mucosa. The larger the surface area of bowel and the greater the contact time with urine, the greater the acid load will be. Thus, continent reconstruction poses a greater potential problem than conduit urinary diversion. In the presence of normal renal function, most patients with a continent reservoir are able to compensate, provided the reservoir is emptied to completion at regular intervals. In the presence of renal impairment, the ability to cope with the increase in acid load is reduced, which may result in a metabolic acidosis.

There is no exact renal function cutoff below which continent urinary reconstruction should not be performed, but, as a general guide, in the presence of a serum creatinine >150 μmol/l or glomerular filtration rate (GFR) < 50 mL/min, one should avoid a continent diversion [6].

One proviso is in the presence of obstructive renal impairment, drainage may be performed to allow renal function to recover before a final decision is made. Continent urinary diversion has also been performed as a staged procedure in preparation for renal transplantation in patients with end-stage renal disease [7].

b) Postoperatively

There are many potential reasons for deterioration in renal function following urinary diversion including: transmission of high pressure to the upper urinary tract secondary to obstruction, physical or functional, at any site—n particular ureteroileal and stomal stenosis; stone formation; and reflux of infected urine.

The pathological changes seen with varying etiologies are the same, and thus the cause at the time of detection may not be obvious. As well a natural age-related decline, estimated to be 1 mL/ min each year over the age of 50 [8], may occur, and there may be many non-urologic causes for declining renal function including hypertension, diabetes, and drugs.

Many studies that report on renal function after urinary diversion are small with limited follow-up and report retrospectively on serum creatinine with or without ultrasound or intravenous urography (IVU) appearance. This is unfortunate as the serum creatinine remains within normal limits until there has been approximately a 50% reduction in GFR and the presence of upper tract dilation does not necessarily equate to a reduction in renal function.

Ideally, for an accurate assessment of function we should rely on serial isotopic GFR. 51 Cr-EDTA is used frequently as it is freely filtered through glomeruli and minimally reabsorbed from intestinal segments. Measurement of pre- and postoperative renal function using radioisotope studies would provide the best information on the safety of lower urinary tract reconstruction with regard to the upper tracts.

Kristiansson et al reported 10-year follow-up using 51 Cr-EDTA isotopic GFR on patients who were randomized to an ileal (n= 18) or colonic (n=20) conduit as well as a refluxing or non-refluxing ureteroileal anastomosis [9]. Thirty-four percent of patients had a drop in GFR of more than 25%, 40% in the colonic group and 28% in the ileal group. There was no difference in GFR reduction between refluxing and non-refluxing ureteroileal anastomoses, although renal scarring and bacteriuria were more common with a refluxing anastomosis. Ureteroileal strictures developed up to 14 years postoperatively. In these patients, ureteric reimplantation improved renal function in 6 of 7 renal units, and balloon dilation improved renal function in 1 of 5 renal units.

More recently, Samuel and colleagues using serial isotope GFR have reported follow up of more than 4 years in 178 patients who had an ileal conduit with freely refluxing ureteroileal anastomoses [10]. Fifty-two (29%) demonstrated a worsening GFR of more than 5% (mean 31%) at a mean of 8.2 years. In 33 (18%), there was no identifiable obstruction as a cause for deteriorating GFR.

In a single center non-randomized retrospective comparison of 275 patients with minimum follow-up of 12 months (mean 52) who underwent ileal conduits or orthotopic bladder substitution, Song et al reported hydronephrosis in 1.4%, 8.3%, and 6.3% following
ileal conduit (n=78), orthotopic bladder substitution with refluxing anastomoses (n=86), and orthotopic bladder substitution with anti-refluxing anastomoses (n=11), respectively [11]. Chronic renal failure (defined as creatinine above 3.0 mg/dL) occurred in 7.7% of those in the conduit group compared with 3.5% of those with a refluxing anastomosis and 2.7% of those without in the orthotopic bladder substitution groups. The mean preoperative serum creatinine was significantly higher in the conduit group and all of those in the conduit group who progressed to chronic renal failure were thought to have renal deterioration unrelated to the urinary diversion. Pyelonephritis was significantly more common in the orthotopic bladder substitution groups.

c) Continent Cutaneous Diversion

Following continent cutaneous diversion, Kristjansson and colleagues, using 51 Cr-EDTA isotopic GFR, reported a decrease in renal function of more than 25% total GFR in 28% of 18 patients 11 years after a cecal reservoir [9].

In another paper, Jonsson reported follow-up on 126 patients up to 25 years (median 9.5) post Kock pouch [12]. They recorded a reduction in 51-Cr-EDTA GFR from 6 years onwards, but this was equivalent to that expected in relation to aging. It was concluded that renal function was not affected by the diversion as long as obstruction was recognized early and managed appropriately.

Fontaine et al reported over 10 year follow-up of a heterogeneous group of 53 patients with bladder exstrophy – 37 continent cutaneous diversions and 16 with the urethra as the continence mechanism [13]. Using 51 Cr-EDTA clearance, they found no deterioration in renal function in 43 of the 53. In the remaining 10 (19%), which consisted of 8 with a Mitrofanoff combined with either ileal or sigmoid augmentation or pouch, 1 with a Kock pouch, and 1 with an ileocelecal patch and reconstruction onto the native urethra, GFR fell by 20% or more.

d) Orthotopic Bladder Substitution

As with other types of reconstruction, there are few long-term reports of GFR following orthotopic reconstruction. Thoeny and colleagues reported a prospective analysis in 76 patients with a median follow-up of 84 months (range 60-155) after a low pressure ileal afferent limb bladder substitute [14].

Preoperative mean serum creatinine +/- 1 SD was 98 +/- 19 µmol/L and at 10 years thereafter was 83 +/- 27 µmol/L. Twelve (16%) of 76 patients had increased serum creatinine, 5 of whom had preoperative dilation or obstruction. In this prospective study, renal deterioration was seen only in the presence of pre-existing renal pathology or postoperative obstruction; however, more precise assessment of GFR is not available.

They concluded that ureteroileal obstruction was the leading cause of renal deterioration following orthotopic bladder substitution and that it is less prevalent with refluxing anastomoses to a low pressure afferent limb detubularized ileal reservoir.

e) Ureterocolonic Diversion

As a result of significant complications, the popularity of ureterosigmoidostomy declined once conduit urinary diversion became established. Deterioration in renal function as a result of high pressure reflux of infected urine was one of the main concerns. Modifications in technique have made colonic diversion a much safer procedure; however, its popularity remains modest.

Conclusions

Urinary diversion into bowel segments is not inherently damaging to the kidneys. In general, renal function after diversion into continent detubularized reservoirs compares favorably with ileal conduit diversion. However, the literature is insufficient to recommend one form of diversion over another. There remains a long-term risk of renal deterioration, which is often asymptomatic, and thus close follow-up is necessary for all patients who have undergone urinary diversion in order to identify correctable causes early.

Those with renal pathology prior to surgery seem to be at greatest risk of postoperative renal deterioration. Serum creatinine is an imprecise measure of renal function. Isotopic GFR measurement will detect renal function deterioration most accurately and at an early stage. The latter, however, is not available to all patients. In these situations, follow-up with serum creatinine and ultrasound should be followed by diuresis renography if upper tract dilation is seen. Early intervention for physical obstruction often results in a sustained improvement in renal function.

2. SECONDARY TUMORS AFTER URINARY DIVERSION

a) Urinary Diversion in Isolated Bowel Segments

Our review included the patient data presented by Austen and Käble in their paper published in the Journal of Urology [15] and in their reply to a letter to the editor of that journal [16]. Those data had been obtained through a MEDLINE search up to October 2004. We used the same headings as Austen and Käble (i.e., urinary diversion and carcinoma), and, similar to those investigators, we analyzed the data on latency period, histological findings, tumor location (ureterointestinal anastomosis vs. distance to the anastomosis), initial diagnosis leading to urinary diversion (malignant vs. benign), and treatment of...
the secondary tumors. We also included 4 patients from Lund and Oslo.

Table 2 shows the total number of tumors found in isolated bowel up to August 2010, including the cases reported by Austen and Källble [15, 16] and 2 cases from Lund. During the period 2004 to August 2010, 15 carcinomas after ureterosigmoidostomy were described.

Until recently, all risk calculations were severely hampered by the absence of easily accessible hard data on the total number of procedures performed. As a courtesy, Källble et al. provided some information of the first multicenter study that allows us to relate the number of secondary tumors with the number of various types of urinary diversions done [18].

They analyzed the operative records of 44 German hospitals for urinary diversions performed from 1970-2007 and registered all reported tumors till 2009. In 17,758 urinary diversions, 32 secondary tumors occurred (Table 3). The tumor risk in ureterosigmoidostomy (2.58%) and cystoplasty (1.58%) was significantly higher than in other continent forms or urinary diversion (p<0.0001). The risk in orthotopic (ileo)colonic neobladders (0.97%) was significantly higher (p=0.0001) than in ileal neobladders (0.05%). The difference between ileocecal pouches (0.18%) and ileal neobladders was not significant (p=0.46), and the tumor risk with ileal conduits was minimal (0.02%), (Table 4).

b) Ureterosigmoidostomy

Since 2004, there have been reports of 15 adenocarcinomas and 8 adenomas after ureterosigmoidostomy (a reference list can be obtained from the present authors), and descriptions of more than 200 cases had already been published 20 years ago [19]. All 15 adenocarcinomas appeared in patients who had undergone surgery due to bladder extrophy. Median latency was 37 years (range 13-56 years). In 3 patients, conversion to other forms of diversion had been performed after 8 months, 14 years, and 18 years, respectively, but it was not reported whether the ureterocolic anastomoses were removed in those cases.

It is likely that the etiology of tumor development after ureterointestinal diversion is multifactorial. There is evidence of the involvement of increased levels of N-nitrosamine and/or free oxygen radicals in response to infection and chronic inflammation.

Conclusions

Patients who have undergone conduit diversion, continent cutaneous diversion, or orthotopic bladder substitution do not seem to be at increased risk of secondary malignancy. By comparison, the risk is slightly higher after cystoplasty, albeit not increased enough to support endoscopic surveillance. However, the present knowledge regarding gastric cystoplasty is insufficient, and hence patients should be followed after such surgery. Furthermore, yearly colonoscopy is recommended in cases involving ureterosigmoidostomy, beginning 10 years after the procedure.

3. COMPLICATIONS

Any critical analysis and comparison of urinary diversion technique centers around the questions: Is there a perfect solution? or: Which diversion technique is the best? or: Which one has the lowest complication rate? At this point our committee must disappoint the readers of this report and rather explain why it is absolutely inappropriate to ask these questions.

Table 2. Secondary tumors after diversion using isolated gut segments

<table>
<thead>
<tr>
<th></th>
<th>Ileum</th>
<th>Colon</th>
<th>Ileoceleal</th>
<th>Stomach</th>
<th>Total no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conduit</td>
<td>15+1*</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>22</td>
</tr>
<tr>
<td>Continent cutaneous</td>
<td>0</td>
<td>14**</td>
<td>0</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>Neobladder</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Rectal bladder</td>
<td>-</td>
<td>5</td>
<td>-</td>
<td>-</td>
<td>5</td>
</tr>
<tr>
<td>Cystoplasty</td>
<td>41</td>
<td>15</td>
<td>2</td>
<td>10</td>
<td>68</td>
</tr>
<tr>
<td>Total</td>
<td>60</td>
<td>42</td>
<td>2</td>
<td>10</td>
<td>114</td>
</tr>
</tbody>
</table>

From publications by Austen and Källble (15,16), since 2004, and 4 Lund cases.

* This case was transferred from continent cutaneous diversion using colonic segment.

**Includes 2 Lund cases (described in this paper) but excludes a case (17) from Austen and Källble, that is now transferred to the ileal conduit group.
### Table 3. Numbers of Secondary Tumors in 17,758 Urinary Diversions

<table>
<thead>
<tr>
<th>no. secondary tumors</th>
<th>no. divsions</th>
<th>% median latency period (years)</th>
<th>mean time operation to analysis (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neobladder ileal</td>
<td>2</td>
<td>4190</td>
<td>(0.05 %) 3.0</td>
</tr>
<tr>
<td>Neobladder ileocecal</td>
<td>3</td>
<td>239</td>
<td>(1.26 %) 4.0</td>
</tr>
<tr>
<td>Neobladder Colonic</td>
<td>1</td>
<td>70</td>
<td>(1.43 %) 6.0</td>
</tr>
<tr>
<td>Pouch ileocelecal</td>
<td>3</td>
<td>2181</td>
<td>(0.18 %) 12.0</td>
</tr>
<tr>
<td>Ileocystoplasty</td>
<td>4</td>
<td>233</td>
<td>(1.71 %) 21.5</td>
</tr>
<tr>
<td>Colocystoplasty</td>
<td>0</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Conduit ileal</td>
<td>2</td>
<td>8637</td>
<td>(0.02 %) 11.0</td>
</tr>
<tr>
<td>Conduit Colon</td>
<td>1</td>
<td>430</td>
<td>(0.23 %) 40.0</td>
</tr>
<tr>
<td>Ureterocutaneostomy</td>
<td>0</td>
<td>1138</td>
<td></td>
</tr>
<tr>
<td>Ureterosigmoidostomy</td>
<td>16</td>
<td>620</td>
<td>(2.58 %) 26.0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>32</td>
<td>17,758</td>
<td></td>
</tr>
</tbody>
</table>

Table 4. Tumor Risk in Continent and Incontinent Urinary Diversion

<table>
<thead>
<tr>
<th></th>
<th>Ileum</th>
<th>(ileo-)colon</th>
<th>total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Conduit</strong></td>
<td>0.02%</td>
<td>0.23%</td>
<td>0.03%</td>
</tr>
<tr>
<td></td>
<td><em>p</em>= 0.84</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pouch/Neobladder</strong></td>
<td>0.05%</td>
<td>0.28%</td>
<td>0.13%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>0.03%</td>
<td><em>p</em>= 0.00001</td>
<td>0.27%</td>
</tr>
</tbody>
</table>

*p<0.0001

<table>
<thead>
<tr>
<th>Cystoplasty</th>
<th>1.71%</th>
<th>0.00%</th>
<th>1.58%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ureterosigmoidostomy</strong></td>
<td></td>
<td></td>
<td>2.58%</td>
</tr>
</tbody>
</table>

*p=0.46

Käible 2011
• Muscle-invasive bladder cancer occurs in a comorbid population with a mean age of 65-69 years in contemporary radical cystectomy series. The incidence of “early complications,” defined as occurring either during the hospital stay or within 90 days of surgery, has been reported in the range of 20-67% [5]. Therefore, accounting for the impact of surgical morbidity on patient outcome is essential for treatment planning, for clinical trial design, and for assessing new surgical techniques.

A recent evaluation of the urologic oncology literature revealed that the majority of series that reported on radical cystectomy morbidity had not employed a formal complication reporting system, had not utilized grading systems other than categorizing them into “major” versus “minor,” had not accounted for comorbidities, or had not defined complications. This makes it impossible to compare data and most certainly leads to an underestimation of morbidity for the procedure. In addition, the incidence of perioperative complications have often been utilized as surrogate measures of surgical competency, institutional quality of care, success of new surgical techniques, and have even been suggested as benchmarks for financial reimbursement [5].

• The difficulty in comparing complications across series is manifold. The lack of standardization is hampering the progress of reducing morbidity and complications associated with radical cystectomy. Radical cystectomy and urinary diversion are two steps of one operation. However, the literature notoriously reports on complications of radical cystectomy, ignoring that the vast majority of complications are diversion-related. This may seem semantic, but it is not [4]. This is of particular importance for this consensus report.

• Until recently, any publication on cystectomy and urinary diversion complication rates has reported the rates by simply dividing the absolute number of events by the total number of patients treated, irrespective of the time to the complication onset. Early complications occur in a short and well-defined interval of 90 days postoperatively. Stratification of complication rates to the first, second, or third month postoperatively is not meaningful. In contrast, long-term complications may occur decades later. Since most complications develop time-dependently, they should be reported using the Kaplan-Meier method for time-dependent events in analogy to reporting tumor recurrence. This can easily be explained by the example “incisional hernias.” We observed 41 hernias in 923 patients (4.4%). In contrast, the Kaplan-Meier method revealed a rate of 6.4% at 10 years—45% higher rate than that published usually. Standardization of reporting long-term complications does not only impact on definitions but also an statistical analysis. Only data on long-term complications that consider their time-dependency will be comparable. Otherwise, complications that occur early are overrepresented, while those occurring late might be underrepresented, since the number of patients will decrease over time [20].

An ideal methodology for reporting adverse events related to surgical therapy should include 10 established basic reporting criteria [5]: (1) a clear description of the method of data acquisition, (2) an indication of the duration of follow-up, (3) an indication of whether or not outpatient complication data are included, (4) definitions/inclusion criteria of at least one complication, (5) an indication of the mortality rate and cause of death, (6) an indication of the morbidity rate (number of patients and the total number of complications recorded), (7) an indication of procedure-specific complications, (8) the utilization of a grading system to clarify severity of complications, (9) an indication of the median or mean length of stay, and (10) an indication of the methodology utilized to assess patient risk stratification (e.g., Charlson-Romano index, ASA scoring).

Recently, efforts have been made to standardize the reporting of early complications. The Clavien system in the Memorial Sloan-Kettering Cancer Center modification has proven to be a useful tool to classify these complications according to domains (e.g., genitourinary, gastrointestinal, infectious) and grades [5]. Unfortunately, this system is less suitable for reporting long-term complications [20].

The recent literature on urinary diversion shows a trend to the increasing use of standardized reporting of complications in urologic oncology, in particular of complications of urinary diversion (4, 5, 20). Table 5 presents a representative example of adequate reporting: It is the summary of neobladder-specific early (≤ 90 days) complications in 1013 patients with neobladders. Table 6 presents an attempt to compare diversion-related complications in a realistic way [20, 21, 22].

Conclusions

Surgical morbidity following urinary diversion is significant and, when strict reporting guidelines are incorporated, higher than previously published. Accurate reporting of postoperative complications after radical cystectomy is essential for counseling patients, combined modality treatment planning, clinical trial design, and assessment of surgical success. Specific diversion related complications, i.e., neobladder-vaginal fistula or hypercontinence following orthotopic bladder substitution in women are reported in the respective sections.
Table 5. Neobladder specific complications within 90 days of surgery by category in 1013 patients with neobladders

<table>
<thead>
<tr>
<th>category</th>
<th>no complication</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>infection</td>
<td>777 (76.7%)</td>
<td>38</td>
<td>146</td>
<td>35</td>
<td>5</td>
<td>12</td>
<td>236 (23.3%)</td>
</tr>
<tr>
<td>abscess</td>
<td>988</td>
<td>2</td>
<td>20</td>
<td>3</td>
<td></td>
<td></td>
<td>25</td>
</tr>
<tr>
<td>UTI</td>
<td>837</td>
<td>38</td>
<td>138</td>
<td></td>
<td></td>
<td></td>
<td>176</td>
</tr>
<tr>
<td>sepsis</td>
<td>978</td>
<td>6</td>
<td>15</td>
<td>2</td>
<td>12</td>
<td></td>
<td>35</td>
</tr>
<tr>
<td>genitourinary complications</td>
<td>843 (83.2%)</td>
<td>100</td>
<td>6</td>
<td>64</td>
<td>0</td>
<td>0</td>
<td>170 (16.8%)</td>
</tr>
<tr>
<td>renal failure</td>
<td>995</td>
<td>11</td>
<td>3</td>
<td>4</td>
<td></td>
<td></td>
<td>18</td>
</tr>
<tr>
<td>ureteral obstruction</td>
<td>965</td>
<td>16</td>
<td>1</td>
<td>31</td>
<td></td>
<td></td>
<td>48</td>
</tr>
<tr>
<td>urinary leak</td>
<td>948</td>
<td>44</td>
<td></td>
<td>21</td>
<td></td>
<td></td>
<td>65</td>
</tr>
<tr>
<td>urinary fistula</td>
<td>1002</td>
<td>6</td>
<td></td>
<td>5</td>
<td></td>
<td></td>
<td>11</td>
</tr>
<tr>
<td>urinary retention</td>
<td>985</td>
<td>23</td>
<td>2</td>
<td>3</td>
<td></td>
<td></td>
<td>28</td>
</tr>
<tr>
<td>miscellaneous</td>
<td>918 (90.6%)</td>
<td>0</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>95 (9.4%)</td>
</tr>
<tr>
<td>metabolic acidosis despite treatment</td>
<td>1007</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>surgical</td>
<td>985 (97.2%)</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>28 (2.8%)</td>
</tr>
<tr>
<td>incisional hernia</td>
<td>1010</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3</td>
</tr>
</tbody>
</table>

Grade 1: oral medications
Grade 2: intravenous medications
Grade 3: interventional radiology or operation
Grade 4: lasting disability or organ resection
Grade 5: death

Table 6. Diversion-specific (not cystectomy) long term complications * using non-standardized reporting

<table>
<thead>
<tr>
<th>f.u. median (years):</th>
<th>Conduit</th>
<th>Neobladder</th>
</tr>
</thead>
<tbody>
<tr>
<td>patients (n=):</td>
<td>Bern</td>
<td>Mayo</td>
</tr>
<tr>
<td>complications (n=):</td>
<td>192</td>
<td>1453</td>
</tr>
<tr>
<td>patients with (n=):</td>
<td>87/131</td>
<td>643/1057</td>
</tr>
<tr>
<td>patients with (%):</td>
<td>66.0</td>
<td>61.0</td>
</tr>
<tr>
<td>within years:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5:</td>
<td>45</td>
<td>50</td>
</tr>
<tr>
<td>10:</td>
<td>50</td>
<td>68</td>
</tr>
<tr>
<td>15:</td>
<td>54</td>
<td>70</td>
</tr>
<tr>
<td>20:</td>
<td>94</td>
<td>80</td>
</tr>
<tr>
<td>Reoperation rate (%):</td>
<td>40</td>
<td>6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Complications (pts/%)</th>
<th>Conduit</th>
<th>Neobladder</th>
</tr>
</thead>
<tbody>
<tr>
<td>bowel</td>
<td>32</td>
<td>215 (20.3%)</td>
</tr>
<tr>
<td>UTI</td>
<td>30</td>
<td>174 (16.5%)</td>
</tr>
<tr>
<td>stoma</td>
<td>32</td>
<td>163 (15.2%)</td>
</tr>
<tr>
<td>anastomosis</td>
<td>18</td>
<td>122 (11.5%)</td>
</tr>
<tr>
<td>urolithiasis</td>
<td>12</td>
<td>162 (15.3%)</td>
</tr>
<tr>
<td>renal function</td>
<td>35</td>
<td>213 (20.2%)</td>
</tr>
</tbody>
</table>

* Bern: > complications 3 months; > 5 years follow-up
Mayo: > 30 days of surgery
Ulm: > 3 months of surgery

Madersbacher J Urol, 2003
Shimko J Urol, 2011
Hautmann J Urol, 2011

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4. URINARY DIVERSION AFTER PELVIC IRRADIATION

Tumor recurrence of a urologic, gynecologic or gastrointestinal tumor or a defunctionalized bladder in patients who had received definitive radiation therapy may be followed by salvage radical cystectomy. Historically, these patients have been considered to have a risk of significant postoperative morbidity and unsatisfactory functional results. Complications have been attributed to radiation damage to the ureter and bowel, resulting in increased rates of anastomotic problems, upper urinary tract obstruction, and infection. Therefore, most centers use supravesical urinary diversion with a transverse colonic segment (23-29) or cutaneous ureterostomy.

In a series of patients with urinary diversion after pelvic irradiation [30], 58.5% of these patients experienced one or more complications occurring within a 90 day period from the date of surgery. Seventy-seven percent of the patients with neobladders versus 52.2% of the patients without neobladders had complications. The rate of grade 3-5 (major) complications, according to the modified Clavien system of the Memorial Sloan-Kettering Cancer Center, was 28% in patients with neobladders and 31.9% in patients without neobladders. The majority of these complications were classified as genitourinary or infection-related. In-hospital mortality was 0% for patients with neobladders and 11.6% for patients without neobladders. In 10 of 25 patients with orthotopic reconstruction, serious and highly unusual late complications were observed, e.g., spontaneous ileal perforation, ileal stenosis, stenosis of the descending colon, spontaneous neobladder perforation, and neobladder-vaginal fistula.

This series confirms the high morbidity of radical cystectomy in a comorbid population with experienced surgeons in a high volume institution. Salvage treatment after failure of the initial therapy for localized cancer is always more difficult. These patients are an adversely selected group because the first attempt of curative treatment had failed. Judgment is required to decide who should have a surgical resection after previous radiation therapy, and then technical expertise is needed to do the operation with acceptable success. This series adds to the evidence that salvage surgery for bladder and prostate cancer, as well as gastrointestinal and gynecologic cancers, can be done safely. Overall complication rates are higher than those noted in patients without previous radiation therapy [30]. In the future, the problems with salvage are likely to increase. Dose escalation for prostate cancer radiation therapy is a potential reason. Currently, the dose to the prostate with conformal radiation therapy is 74-78 Gy. Implant radiation, either by itself or combined with external radiation therapy, is another method to increase or boost the dose to the prostate. While such dose escalation may improve local control of the prostate cancer, any salvage surgery may become that much more difficult. Earlier detection of treatment failure using PSA may increase the pool of patients potentially suitable for salvage surgery, but it is uncertain if earlier and more aggressive surgery will translate into better results with acceptable morbidity. Bladder preservation strategies will also provide a greater challenge for salvage surgery. Fortunately, the dose of external radiation therapy to the pelvis for bladder cancer is less than that delivered for prostate cancer (≤ 60 Gy).

During pelvic radiotherapy for cancer, the cecal pole as well as parts of the ascending colon, appendix, and ileum are exposed to considerable doses of radiation. Since these segments of bowel are used for reservoir and afferent segment construction, it is plausible that the high complication rate that was observed was secondary to radiation damage of the intestinal segments.

Limited data are available on the outcome of continent urinary diversion in patients with previous pelvic irradiation [23, 24, 26, 31]. Bochner et al [32] reported the outcome of orthotopic ileal urinary diversion during salvage cystoprostatectomy after failed radiation for bladder and prostate cancers. They noted a total of 6 complications (33%) in 18 patients, including prolonged urinary leakage in 2, and afferent nipple stenosis, ureteral stenosis, enteropouch fistula, and urinary retention in 1 each. The reoperation rate during the mean 28 month follow-up was 17%. Of the patients, 33% were incontinent during the day and 44% were incontinent at night. Gheiler et al [33] reported a similar experience. Brand [34] described cecal rupture after Indiana ileocecal continent diversion as a postoperative complication, underlining the vulnerability of the irradiated cecal region. Other than this report, all published studies of the results of continent cutaneous and orthotopic urinary diversion in irradiated patients have an average follow-up of only 1-2 years. Nevertheless, alarmingly high open reoperation rates of up to 25% have been reported during this limited follow-up. Comparing results in early publications [35, 36] with subsequent data published many years later by the same groups clearly demonstrates that conclusions based on small series with limited follow-up may be misleading.

Since radiation damage is historically known to increase with time, these aspects are especially important when evaluating complications of surgical procedures in irradiated patients. Proper patient selection for salvage surgery has also contributed to the improvements in long-term outcome [37]. Selection of appropriate surgical candidates for
salvage therapy depends on several factors: recurrent prostate or bladder cancer versus gastrointestinal or gynecologic cancer, extent of recurrent disease, and existence of fistula formation. It is believed that patients with more advanced local disease, refractory voiding symptoms related to a fibrosed non-functional bladder, or severe symptoms related to other complications associated with the prior irradiation will be better served with cystectomy and lower urinary tract reconstruction. Based on the published long-term experience, salvage surgery (cystoprostatectomy, anterior exenteration) with orthotopic lower urinary tract reconstruction is a safe, effective procedure that can provide a potential curative intervention and a functional lower urinary tract for properly selected patients in whom previous definitive radiation therapy has failed, with results only marginally worse as compared to non-irradiated patients, at least in high volume centers [38].

5. PREGNANCY AND URINARY DIVERSION
Fertility-sparing cystectomy is restricted to children or premenopausal women with benign diseases. Once the problems associated with urinary incontinence have been solved and the patients have reached puberty, sexuality and fertility become more significant. At this time the medical responsibility shifts from the pediatrician and pediatric urologist to the gynecologist and general practitioner. However, these colleagues rarely have major experience with the psychological aspects of sexuality, fertility, and pregnancy in these patients. Meanwhile, all functions of female sexuality can be preserved, if a fertility-sparing cystectomy and urinary diversion—including a neobladder—is performed. Consequently, the patient’s desire for a normal sexual life has to be respected.

a) Childbirth
In all patients with urinary diversion, the form of delivery must be planned considering many relevant aspects: potential damages to the urinary diversion by the Cesarean section, potential damages to the pelvic floor by vaginal delivery, special anatomic problems of the mother, and, last but not least, the health of the child. Vaginal delivery should be performed with caution in:
• patients with ureterosigmoidostomy
• patients with malpresentation
• patients with cervical prolapse

b) Cesarean section:
Hensle et al consider the elective scheduling of a Cesarean delivery before the onset of labor the preferred method in patients with urinary diversion, in particular in those with orthotopic continent urinary diversion [39]. There are no contraindications against a Cesarean section.

Cesarean section should be performed very cautiously in:
• patients with intraperitoneal hydrocephalus shunts
• patients with pouches, enterocystoplasties, or neobladders

c) Special Aspects
1. WHICH FORM OF URINARY DIVERSION SHOULD BE RECOMMENDED IN YOUNG PATIENTS WHO PLAN TO HAVE CHILDREN?
Our review of the literature shows a successful course of pregnancy is possible with all types of urinary diversion. We therefore strongly recommend that the choice of the type of urinary diversion should consider first the individual situation and needs of the patient, but with secondary respect to a potential pregnancy.

2. IS SIMULTANEOUS STERILIZATION AN OPTION?
In the twentieth century, the majority of patients with urinary diversion had simultaneous sterilization. The first patient who became pregnant following urinary diversion did so despite previous sterilization. Nowadays, sterilization of patients undergoing urinary diversion is not performed routinely, since pregnancy is not considered contraindicated in patients with urinary diversion.

3. ARE THERE MEDICAL INDICATIONS FOR AN INTERRUPTION?
In 1972, Olesen recommended a therapeutic abortion if the renal function was abnormal when pregnancy was diagnosed [40]. Since the difficulties of saving the renal function during pregnancy have been ameliorated, we think that this general recommendation should be obsolete in 2011.

4. WHAT EXAMINATIONS ARE RECOMMENDED BEFORE, DURING AND FOLLOWING PREGNANCY?
Richmond et al suggest that whenever possible, counseling of patients with myelomeningocele should be done before conception, when radiological pelvimetry and renal function assessment could be carried out without risk to the fetus in utero [41].

All pregnant women with any type of urinary diversion should be assessed (ideally antepartum) by an multidisciplinary team of experts, involving the obstetrician (perinatologist), urologist, obstetric anesthesiologist, general surgeon, neonatologist, and nursing staff who work together to develop (tailor) the optimal peripartum plan on a case-by-case basis [42].
Kennedy et al recommend an initial screening maternal ultrasound examination at 20 weeks of gestation to look for maternal hydronephrosis. Follow-up maternal renal ultrasound examinations should be performed if hydronephrosis is noted initially or for recurrent episodes of pyelonephritis [43].

In Germany, the patient is seen by the obstetrician every 4 weeks during the first 4 months of gestation, every 3 weeks during the next 3 months, every 2 weeks during the next 2 months, and then in weekly intervals until delivery. We strongly recommend that the patient be seen by a urologist at the same intervals until delivery. The urologist should perform urinalysis, microbiologic controls of the urine, renal ultrasound (including estimation of the resistive index, when hydronephrosis is present), and controls of the storage function and emptying of the urinary diversion.

5. WHAT INFORMATION ON RECONSTRUCTIVE UROLOGY DOES AN OBSTETRICIAN NEED?

The obstetrician needs complete information on the anatomic situation of the patient with urinary diversion. The knowledge of all reports on surgical procedures performed in the particular patient in the past is compulsory. Precise information on the fixation points of the urinary diversion and of the course of the ureters is necessary. Urological input at the time of surgery helps identification of the lower urinary tract anatomy, prompt recognition of any inadvertent urinary tract injury, and assistance in the repair of any damage.

6. IS LONG-TERM ANTIBIOTIC PROPHYLAXIS REQUIRED DURING PREGNANCY WITH A URINARY DIVERSION?

Symptomatic urinary tract infection is a problem encountered in a large proportion of patients with urinary diversion. Contributing factors to urinary tract infections are urinary stasis, difficulty with clean intermittent catheterization, and ureteric compression.

Twenty-one percent of the patients reviewed had premature labor, presumably related to the high incidence of lower urinary tract infections and acute episodes of pyelonephritis. The authors advocated aggressive antibiotic therapy for all urinary tract infections in this group of patients [44]. Therefore, Hensle et al considered it advisable to keep all these women on antibiotic prophylaxis through pregnancy [39].

We think that a low-dose antibiotic prophylaxis is at least advisable in the following patients:
- patients with a history of febrile UTI during pregnancy,
- patients with hydronephrosis,
- patients with ureteral reflux,
- patients with impaired renal function,
- patients requiring catheterization, and patients with uretersigmoidostomy.

7. PREGNANCY FOLLOWING URINARY DIVERSION AND RENAL TRANSPLANTATION

The first successful pregnancy after renal transplantation ended in 1958 with the delivery of a healthy child [45]. Since that time, a growing number of reports on successful pregnancies have been published. Problems like immunosuppression, impaired renal function, and obstructive uropathy may lead to a much less favorable prognosis as for pregnancy in patients with urinary diversion alone. Until today, only 3 pregnancies in women with a kidney transplanted to an ileal conduit were reported. In 2 cases, pregnancy had to be terminated in the tenth and twenty-second weeks, respectively, because of progressing renal failure from compression of the ileal loop [46]. The only successful pregnancy was published by Hein et al [47]. Their patient had a neurogenic bladder caused by an occult spina bifida. At the age of 14, an ileal conduit was created. Nine years later, the patient suffered from progressive renal failure caused by chronic pyelonephritis. She underwent bilateral nephrectomy. At the age of 26 years, a living donor kidney transplantation was performed. Four months later, the patient became pregnant. In the thirty-fifth week, an intermittent obstruction of the left ureter was noted, leading to the decision of terminating the pregnancy. Delivery of a healthy male was accomplished by a low segment Cesarean section because of a narrow pelvic cavity. The postoperative course was uneventful.

8. PREGNANCY TESTS IN PATIENTS WITH URINARY DIVERSIONS

In a recent study, Nethercliffe and coworkers analyzed urine of patients with urinary diversion using the Clearview pregnancy test (Unipath Ltd, Bedford, England) [48]. Although all of these patients were not pregnant, positive pregnancy tests were found in 8 women and 5 men (false-positive rate: 57%). The authors suggest that the mucus produced in enterocystoplasties may interfere with the pregnancy test. Patients and doctors have to be aware of this [49].

III. TYPES OF URINARY DIVERSION

1. ORTHOTOPIC BLADDER SUBSTITUTION IN MEN

a) Indications and Tumor Stage

The indication for cystectomy is almost always bladder cancer. The extent of pelvic disease has little
b) Age and Motivation

Although there is no age cut-off for orthotopic bladder substitution, in practice many patients over the age of 70 years will opt for a simpler conduit urinary diversion as the postoperative course is less arduous and urinary incontinence is less likely. The motivation of the patient is probably the most important factor when considering their suitability for an orthotopic bladder substitute, although it is difficult to assess this objectively. Patients must be prepared to commit to the long-term follow-up program necessary. There is no point in the surgeon being enthusiastic if the patient is not; this will result in poor function and the risk of complications.

c) Sphincter Function

Urinary continence after orthotopic bladder substitution depends, amongst other factors, on adequate urethral sphincter function. Caution should be exercised before offering orthotopic bladder substitution in patients with significant urethral strictures.

d) Surgical Technique

Nerve-sparing cystectomy does not just increase the chance of maintaining erectile function. In men with an orthotopic bladder substitute, who had attempted nerve-sparing, nighttime continence was better than in those who did not [54]. The rate at which nighttime continence was achieved and the final nighttime continence rate were both improved. This results from preservation of the afferent intrapelvic anatomic sensory nerve supply to the pelvic floor and external urethral sphincter [55] with preserved urethral sensation. An impaired urethral sensation is associated with poorer continence [56]. Nerve sparing also preserves the efferent autonomic innervation to the sphincteric smooth muscle, which may mediate resting pressure generation (“tonus”).

If tumor characteristics permit, then nerve sparing should be attempted. This can be bilateral if disease is not muscle-invasive, or unilateral if there is lateralized muscle-invasive disease. In men, the nerves are at particular risk dorsolateral to the seminal vesicles, in the vesicoprostatic angle, and in the region of the prostatic apex.

e) Reservoir Configuration

An orthotopic bladder substitute must be a low-pressure reservoir of adequate capacity (allowing a socially acceptable voiding interval without urinary leakage) and must empty to completion. If this is so, the upper urinary tracts will be preserved, and metabolic disturbance will be minimal. Many surgical techniques have been reported but some key factors are alike. Detubularization and a spherical shape ensure that an orthotopic bladder substitute has low pressure and maximum volume for the length of bowel used. A spherical reservoir has 4 times the capacity and a quarter of the pressure compared to a cylinder made from the same length of bowel. The use of less bowel reduces the reservoir’s surface area and therefore the chance of absorptive complications, but larger reservoirs have lower end-filling pressures [57] and better continence, particularly in the early postoperative period. This advantage is short-term, though, and the functional capacity of an orthotopic bladder substitution that is made from a shorter segment increases rapidly from 150 mL to 400-500 mL [58]. The use of excessive length of bowel may produce low-pressure floppy reservoirs that empty less effectively. Larger reservoirs have a greater chance of rupture, because when they are allowed to fill to capacity, the wall tension at a given pressure is greater. The use of 40-45 cm of ileum is sufficient for the reservoir itself. Popular techniques include an ileal afferent limb orthotopic bladder substitute using 55 cm of distal ileum, preserving the 25 cm of terminal ileum, and the W-shaped bladder substitute [59, 60].

f) Minimally-invasive Surgery

There is increasing interest in laparoscopic and robotic cystectomy, with either intracorporeal or
extracorporeal formation of ileal conduit or the orthotopic bladder substitute [61-64]. Whether reports with intermediate follow-up suggesting equivalent pathologic and oncologic outcome will be confirmed remains to be determined [65]. But there are advantages in terms of blood loss, transfusion rate, postoperative pain, and return of bowel function [64]. In most reported series, cases have been highly selected; it remains to be seen what the limitations of minimally-invasive surgery might be in terms of tumor size and bladder mobility. With regard to the reconstruction, although there are a number of reports of intracorporeal surgery, most surgeons currently prefer to perform an extracorporeal technique as this is faster. However, to do this, the ureters must be kept long and there is concern about an increased risk of ureteroileal stenosis [61]. Once a reservoir has been constructed the urethral anastomosis may be carried out by an open technique or by re-establishing a pneumoperitoneum. The technology will probably need to improve before intracorporeal reconstruction becomes standard practice.

g) Functional Aspects

1. Voiding

The mechanism of voiding for patients with an orthotopic bladder substitute is well-described [57,66] in case of an ileal reservoir (not cecal!). A passive pressure rise occurs in the reservoir during filling, and this stretches the reservoir wall, activating the intestinal stretch receptors, resulting in a sensation of filling. The patient learns this new sensation during postoperative voiding rehabilitation. For an ileal reservoir, voiding occurs by reducing outlet pressure and pelvic floor and sphincter relaxation, perhaps combined with slight straining. If straining occurs, the upper urinary tracts and the reservoir are equally subjected to the resulting abdominal pressure rise, and so no pressure gradient is created from the reservoir towards the upper tracts. In the early postoperative period, men should sit to void, to help them to learn how to empty the reservoir. Late voiding difficulty occurs in 20% of men [67] within the first 10 postoperative years for a variety of causes, but almost all of these men void normally after endoscopic assessment and relief of the underlying bladder outlet obstruction.

2. Continence

Continence is achieved when outlet pressure exceeds reservoir pressure. This requires careful preservation of the urethral sphincter and the formation of a low pressure reservoir, by doubly cross-folding detubularized ileum (see above) to achieve the desired reservoir volume of 400-500 mL. The reservoir is constructed with an initial volume of around 150 mL, and in the first postoperative weeks, the patient has to work actively to stretch the reservoir. Stretching the reservoir is done by delaying voiding when the patient feels that the urge to void is irresistible and that leakage may occur. A rapid increase in reservoir capacity following surgery allows daytime continence to be achieved. Nighttime continence is established less quickly. During sleep, a detrusor-sphincter reflex normally increases outlet pressure as the bladder wall stretches during filling; this reflex is lost after cystectomy. As the reservoir fills at night, therefore, additional outlet contraction is not recruited, and when the rise in reservoir pressure exceeds outlet pressure, leakage occurs. This tendency to leak is normally compounded because vasopressin is secreted at night, and urine is therefore concentrated. However, the intestinal wall of the bladder substitute will secrete water into the reservoir, to try to render its contents iso-osmolar, and so overnight urine output is greater after orthotopic bladder substitution than before cystectomy [68].

Men achieve self-assessed continence by day and by night in 92% and 76% of cases, respectively. Attempted nerve-sparing improves daytime continence, and increasing age worsens it [54]. Men with type II diabetes gained daytime continence more slowly than controls and were less likely to achieve nighttime continence. Urinary tract infection also worsens continence [69], and an unexpected deterioration in continence should prompt exclusion of infection and residual urine. Urine infection should be uncommon.

3. Upper Urinary Tract Preservation

Voiding with an orthotopic bladder substitute cannot produce reflux; this has been confirmed scintigraphically [70]. Long-term upper tract outcomes are excellent: as few as 2.7% of patients should develop ureteroileal stricture, if a direct end-to-side ureteroileal anastomosis is used [71, 72]. The use of stents in ureteroileal anastomosis after orthotopic bladder substitution has been shown to improve outcomes [73]. Up to half of patients who develop a short ureteroileal stricture can be successfully managed endourologically [72].

These data are consistent with the outcome of a randomized surgical trial done to determine the effect of different afferent mechanisms with an orthotopic bladder substitute. This showed clearly that the use of an antireflux nipple valve was associated with a worse outcome than a dynamic isoperistaltic afferent tubular ileal segment [74]. This was confirmed in another randomized study recently [75]. In the long-term, the upper tracts are well preserved, and upper tract calculi are rare [76].

Table 7 presents specific long-term complications when standardized reporting is used [20].

4. Postoperative Management

Of paramount importance is the active postoperative
management and regular long-term follow-up of patients with an orthotopic bladder substitute. The key issues [77] are achieving a capacity of 400-500 mL, residual free voiding of sterile urine, and the treatment of any outlet obstruction.

2. ORTHOTOPIC DIVERSION IN FEMALES

a) Patient Selection: Patient-related Factors

There are both patient-related and cancer-related factors influencing the appropriateness of continent orthotopic diversion in women (Table 8). The patient-related factors are generally based on the recommendations of surgeons performing these diversions rather than on evidence-based studies.

A number of the contraindications to continent diversion are identical for men and women. These include the basic requirements of adequate renal function, available healthy bowel, and a functional urethral sphincter. Preexisting incontinence is a relative contraindication for women considering a neobladder. Some bladder cancer patients experience urge incontinence due to the tumor itself, which may be expected to improve after the cystectomy. A woman with stress urinary incontinence may be willing to continue to wear pads rather than deal with a stoma, or may be considered for a sling or Burch procedure at the time of diversion with planned self-catheterization.

Age alone is not a criterion for offering continent diversion [78, 79]. The impact of age on outcomes with orthotopic diversion has not been fully examined in females. In our experience, women over age 75 are at higher risk of incontinence but some of them will have excellent neobladder function (unpublished data). Medical comorbidities, cardiac and pulmonary function, and cognitive function are all important factors that should be considered, along with the patient’s social support and patient preference.

b) Patient Selection: Oncologic Factors

Prior to the wide adoption of orthotopic diversion for females, it was necessary to show that it was safe to preserve the urethra during the cystectomy. De Paepe et al initially reviewed 22 female cystectomy specimens and found urethral involvement in 36% [80]. Coloby and colleagues evaluated 47 consecutive cystectomy specimens with step sectioning through the urethra, finding only 7% with urethral involvement, all of whom also had bladder neck involvement [81]. Stenzl had similar findings in a review of 356 specimens with localized invasive cancer, as did Mariani and Chen [82-84]. Finally, Stein and colleagues evaluated 67 specimens with 13% urethral involvement. Again only bladder neck involvement and anterior vaginal wall invasion predicted urethral involvement, though 50% of those with bladder neck tumor had no tumor in the urethra [85]. In most of these studies, tumor involvement of the trigone, the presence of carcinoma in situ (CIS), or multifocal primary tumors did not predict urethral recurrence.

It is now standard to require a negative frozen section of the urethral margin prior to proceeding with neobladder construction in women [78, 86, 87, 88, 89, 115]).

Table 8. Contraindications For Orthotopic Diversion In Women

<table>
<thead>
<tr>
<th>Absolute contraindications:</th>
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</thead>
<tbody>
<tr>
<td>Renal insufficiency (estimated creatinine clearance of &lt; 35-40)</td>
</tr>
<tr>
<td>Cancer invading the anterior vagina</td>
</tr>
<tr>
<td>Positive frozen section at the urethral margin</td>
</tr>
<tr>
<td>Inadequate available bowel</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Relative contraindications:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive cancer at the bladder neck on TURBT</td>
</tr>
<tr>
<td>Severe co-morbidities requiring very short operative time</td>
</tr>
<tr>
<td>Significant stress incontinence</td>
</tr>
<tr>
<td>Locally extensive disease at surgery (stage T4)</td>
</tr>
<tr>
<td>Prior pelvic radiation</td>
</tr>
</tbody>
</table>

Table 7. Diversion specific long-term complications (>3 months post-op) at 10 years in 923 patients with neobladder operated between 1986-2008 using the Kaplan-Meier method

<table>
<thead>
<tr>
<th>Complication</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ureteroileal stenosis</td>
<td>13.80%</td>
</tr>
<tr>
<td>Refluxing anastomosis (Wallace)</td>
<td>6.40%</td>
</tr>
<tr>
<td>Non-refluxing (Le Duc)</td>
<td>17.00%</td>
</tr>
<tr>
<td>Urinary retention (female)</td>
<td>42.20%</td>
</tr>
<tr>
<td>Subvesical obstruction in men</td>
<td>8.20%</td>
</tr>
<tr>
<td>Functional obstruction in men</td>
<td>5.10%</td>
</tr>
<tr>
<td>Clean intermittent catheterization required</td>
<td></td>
</tr>
<tr>
<td>Incisional hernia</td>
<td>6.40%</td>
</tr>
<tr>
<td>(41 in 923 patients = 4.4%)</td>
<td></td>
</tr>
</tbody>
</table>

Hautmann, J Urol 2011
In summary, it is reasonable to advise against neobladder reconstruction for a woman with invasive bladder neck involvement or suspected invasion of the vaginal wall or cervix. However, such patients may be considered for neobladder diversion if intraoperative frozen section of the urethral margin is negative. It appears that overall 60-70% of women undergoing cystectomy might be reasonable candidates for continent diversion (88).

c) Anatomic Basis of the Preservation of Continence in Women

Orthotopic neobladder was introduced as an option for women in the 1990s. Prior to that time, it was generally believed that the primary continence mechanism in women was located in the bladder neck itself [90].

However, it was ultimately recognized that the urethra alone could provide continence if the sphincter mechanism was carefully preserved [91].

Colleselli and colleagues did elegant cadaver studies showing that the primary rhabdosphincter in adult women is an “omega” shaped structure under the pubic symphysis deep to the endopelvic fascia surrounding the distal third of the urethra. The main nerves supplying this sphincter are the somatic pudendal nerves which run under the endopelvic fascia. The autonomic nerves coursing through the pelvic plexus and along the lateral vagina supply the smooth muscle of the bladder neck and urethra. The smooth muscle extends throughout the length of the urethra [92]. Similar findings had been described by others [93]. The distal urethra was found to correspond to the area providing continence on videourodynamic studies performed in women who had undergone orthotopic reconstruction after cystectomy [94]. There is consensus that preservation of the rhabdosphincter function is critical to maintaining continence in women undergoing neobladder reconstruction [79, 86, 87, 95-97]. Avoiding dissection into or below the endopelvic fascia surrounding the urethra helps ensure that this muscle and its nerve supply are not disturbed [96]. Stenzl, Studer, and others suggest that preservation of this plexus in a “nerve-sparing” approach is crucial to maintaining urethral tone and may decrease the risk of late urinary retention due to spasticity of the denervated smooth muscle of the urethra [93, 98-100]. Stenzl compared 66 patients from 3 centers who had bilateral nerve preservation to 28 who had 1 side preserved and 7 who had no nerve preservation (due to tumor infiltration or scarring). The report does not indicate how these data were collected or if there was a difference in follow-up or other variables between the groups. Self-catheterization was required in only 9% of the first group (66 patients) compared to 0% of the group with 1 nerve spared (28 patients) and 72% of the 7 patients without nerve preservation [95]. However, others have routinely dissected the presacral tissue as part of the node dissection without a clear reduction of continence [97, 101]. To date, no randomized comparison of these 2 techniques has been performed.

d) Complications

Most of the early and late complications of women undergoing radical cystectomy and neobladder are identical to those of men and are managed in a similar fashion [20, 102, 103]. Two complications are different in female patients:

1. Pouch-vaginal Fistula

This complications occurs in 1-5% of patients even in experienced hands [86, 101, 104]. Awareness of this potential complication is important at the time of surgery. When possible, the anterior vaginal wall should be left intact, taking a strip of vagina only in cases with close approximation of the tumor. Any vaginal incision should be carefully closed in a watertight manner with absorbable suture. An omental flap may be transposed to the pelvis and tacked to the pelvic floor on either side of the urethral stump [79, 97].

These fistulae rarely heal spontaneously except in the first few weeks after surgery. Therefore, a prolonged trial of catheter drainage or more proximal diversion is probably not warranted. Vaginal estrogen supplementation may help healing prior to such a repair. Repair can be attempted vaginally, with a Martius labial fat pad flap or muscle flap from the leg interposed between the layers in difficult or irradiated cases. When attempts to repair a vaginal fistula have failed, the patient may be better served by conversion to a cutaneous diversion.

2. Urinary Retention

Urinary retention is clearly more common in women than men undergoing orthotopic diversion (Table 9). Such retention may occur early, but often appears after a year or more of good neobladder function and emptying. In the Ulm series of 116 women, the rate of retention increased steadily over time to approximately 50% by 5 years [78]. The etiology has been debated, but most authors believe it is due to a mechanical kink in the urethra-pouch anastomosis as the full pouch falls posteriorly during Valsalva maneuver [79, 97, 103, 110-112]. This can often be documented on a lateral straining cystogram. However, not all patients with retention have this finding. Other suggested etiologies include autonomic denervation of the urethral stump or disordered re-innervation resulting in inability to relax the sphincter [78, 94, 113, 114].

Since the first description of this potentially undesirable late complication of orthotopic bladder substitution in women [109] in 1996, a number of authors have
suggested modifications in surgical technique to try to prevent this problem and have presented data to suggest improved outcomes [79, 95, 97, 110, 112]. However, all are consecutive series and because the complication may appear late, such reports may be biased by shorter follow-up in the “new” group. Nevertheless, some attempt to fill the posterior pelvis and re-establish anterior and superior fixation of the new bladder seems to be warranted. At the University of Southern California, a sacrocolpopexy with mesh and omental transposition laid between the bladder and vagina have been routinely performed [79]. Ali-el-Dein described anchoring the vaginal apex to the preserved round ligaments and also used an omental flap [97]. However, others believe these maneuvers are unnecessary [118], and recent results suggest that they have not prevented retention (see below). Studer has suggested that the location of the urethral opening in the pouch is an important variable [115]. A recent study from the group in Ulm suggested that patients in whom the bladder neck itself is preserved (for example those with non-urothelial tumors) have a higher risk of retention than those in whom the urethra is divided just below the bladder neck [108]. Preservation of the uterus and its supporting ligaments when possible may be an effective way to help prevent retention, though again this question has not been subjected to a prospective or randomized trial [116].

Treatment of retention is intermittent catheterization. Alpha blockers are not effective [97]. Transurethral resection of a urethral fold and open reduction of the pouch size with anterior fixation to the abdominal wall have also been described [97, 116].

It is clear that every woman undergoing neobladder reconstruction should be advised that intermittent catheterization may be required for adequate emptying and must be willing and able to learn how to perform this. Many women who are dry but require self-catheterization seem quite happy with the diversion in spite of this [117].

e) Continence (Table 9)

Continence results in the literature are difficult to compare between series because of a lack of consensus on definitions, varied follow-up periods, and varied mechanisms of data collection. Some of the larger series reporting continence results with neobladders have not separated out patients by gender [86, 110, 115]. Few studies have used the “gold standard” of a validated, anonymous questionnaire to evaluate continence. In addition, urinary retention may develop as a late event, so follow-up time is an important variable in these reports. In one of the largest series, Ali-el-Dein and associates reported on a total of 136 women who underwent a radical cystectomy and orthotopic substitution, with 100 patients evaluable at a mean follow-up of 36 months. Overall, 95% of the women were continent in the day, 86% were continent at night, 2 were completely incontinent, and 16% were in chronic retention [102].

Stein and colleagues completed a mailed questionnaire study using the validated Bladder Cancer Index with 56 women returning the questionnaire (64% of the 87 surviving women). Significant daytime incontinence was reported in 23% of the women and nighttime incontinence in 34%. Somewhat surprisingly, 61%
reported that they catheterized at least once per day and 39% always voided by self-catheterization. Only 18% of the women who catheterized reported that it was a moderate bother and 56% reported it was no bother at all [117].

f) Sexual Function and Quality of Life

Only a few studies have examined the postoperative sexual function of women undergoing radical cystectomy and urinary diversion [118-122]. Results suggest that sexual dysfunction is common and may be potentially improved by leaving the uterus intact when possible and preserving the autonomic nerves lateral to the vagina [119, 120]. Comparisons of most aspects of quality of life in both men and women between types of urinary diversion have been limited but do not show any convincing differences [122,123, 124].

Conclusion

Orthotopic neobladder reconstruction is an attractive option for selected women undergoing radical cystectomy for bladder cancer. Oncologic outcomes appear to be excellent with appropriate selection criteria. Careful attention to patient selection, surgical technique, and follow-up are all important to optimize functional results.

Additional studies are necessary to allow surgeons to minimizing incontinence and urinary retention in these patients.

3. CONTINENT CUTANEOUS URINARY DIVERSION

a) Introduction

The modern era of continent urinary diversion began 30 years ago with the introduction of continent cutaneous diversion, which at that time was represented by the Kock pouch. Since then, numerous techniques for this type of diversion have been described, but some of these appeared only once in the literature, indicating that they were associated with technical problems, high complication rates, and suboptimal functional results. Today, only a handful of methods are in use, and, in general, they are the second choice after orthotopic bladder substitution for patients undergoing radical cystectomy.

b) Indications

• In patients with bladder cancer undergoing radical cystectomy, the main indication for continent cutaneous diversion is when urethral removal is deemed necessary due to a high risk of recurrence of urothelial carcinoma. This risk can be estimated based on the pathology report from the preoperative transurethral resection biopsies of the prostate. Such biopsies should be taken from the bladder neck to the verumontanum on both sides before cystectomy. Relying on frozen sections of the urethra obtained during surgery may be dangerous because of the risk of a false negative report from the pathologist. Urothelial cell carcinoma located in the urethra or involving prostatic ducts or stroma is the main indication for urethrectomy.

• In female patients, biopsies should also be obtained from the bladder neck, and, if positive, urethrectomy should be performed. Furthermore, it is necessary to exercise caution if there is a tumor close to the bladder neck, as well as in cases involving widespread CIS. Optimal knowledge regarding the urothelial pathology of the lower urinary tract is of importance when informing and discussing with the patient preoperatively.

• Some patients may prefer continent diversion to orthotopic reconstruction because of the risk of urine leakage after the latter procedure.

c) Prerequisites

Although antirefluxing ureteric anastomosis is not necessary in orthotopic bladder substitution, it is required in continent cutaneous diversion because the efficient outlet mechanism can allow high intravesical pressure. Both ileum and the right colon can be used for construction of the pouch. Different types of inlet, pouch, and outlet have been combined. The stoma is usually in the right lower quadrant or in the umbilicus. In this review, the techniques that are most widely used today are described. The majority of these were developed in the 1980s and 1990s, although a few new methods were also reported in the last decade.

d) The Outlet

• The intussuscepted ileal nipple valve

• The Kock pouch: The Kock pouch was the first method to be accepted by the urologic community after it was described by Kock and refined by Skinner’s group in the 1980s [125, 126]. However, the initial enthusiasm about this procedure was soon dampened by increasing reports of complications, including the following: the afferent ileal nipple valve was prone to stenosis with subsequent upper tract dilatation and risk of renal impairment; the efferent counterpart was subject to erosion by mesh, pinhole fistula, sliding, and prolapse with risk of urine leakage and/or difficulties in catheterization. The risk of afferent nipple stenosis is estimated to be 30% after 5 years [127]. Because of the technical complexity of the Kock pouch and the high complication rate, this procedure is no longer used in routine clinical practice. A modified technique for constructing the efferent nipple [128] has been described, but no further information is available in the literature from the past 5 years.
• **The Mainz pouch I:** The ileal nipple valve was also used in the first Mainz pouch that was described [129] but modifications were subsequently introduced due to the above-mentioned problems. Today, the appendix is the first choice, but if it missing or unsuitable, a nipple valve is configured and fixed to the ileocecal valve and the reservoir wall with staples [130]. In terms of complexity, the Mainz pouch I with an intussuscepted nipple valve cannot be considered inferior to the Kock pouch.

• **The appendix:** Advantages of using the appendix are that it is “ready made” and a smaller portion of bowel is used. Inasmuch as the appendix is not always available or suitable, it is necessary to be familiar with other methods for continent cutaneous diversion. The main problem associated with using the appendix is the tendency towards stomal stenosis. In the Mainz study [131], 63 (32%) of 196 patients underwent a total of 107 interventions. Using a similar technique, other investigators [132] observed 28% stenosis within a mean follow-up of only 33 months. More recently, it was found that 6 of 52 patients needed early operative intervention to revise the stoma, and late stomal complications occurred in 12 of 52 [133]. This clearly offsets the excellent continence (100%) reported in several publications.

• **The tapered/stapled ileal outlet:** Several variations of the tapered/stapled ileal outlet have been described, all of which comprise a narrowed ileal segment that creates passive resistance. A true intraluminal closure mechanism is absent in most, which may have an impact on continence. The advantage of this approach is its simplicity.

• **The Indiana pouch:** In this procedure, the ascending colon patched with an ileal segment constituted the pouch, the outlet being a 10-cm plicated or stapled ileal segment. Some modifications in fashioning the outlet were also introduced, such as stapling the ileum with a gastrointestinal anastomosis (GIA) stapler and metallic staples, and using only the right colonic segment. In addition, Lambert [134] described the use of this technique in Europe [137, 138]. As correctly stated by the authors of this report, “construction of the pouch is sophisticated”. Indeed, this is the main drawback of the method and represents a serious obstacle to general acceptance.

**e) Stone Formation**

Stone formation is a common phenomenon after urinary tract reconstruction, and its etiology is multifactorial, including residual urine, chronic bacteriuria, mucus, and foreign material such as staples [139]. Although an incidence as high as 44% has been reported [140], most reports indicate rates of 5-20%. In the series of 191 Lundiana outlets, pouch stones occurred in 22 (12%) patients, and in 18 of those patients, the stones were removed endoscopically (unpublished data). the importance of regular pouch irrigation has been recognized and should be encouraged.

**f) Perforation/Rupture**

The risk of this complication is higher after continent cutaneous diversion than after orthotopic bladder substitution, because the former lacks a pop-off mechanism [141]. In the series of 191 Lundiana pouches (unpublished data), this complication was seen in 8 patients: 6 of these individuals underwent open surgery, whereas 2 were cured by antibiotics and drainage.
g) Other Important Aspects

There is virtually 100% bacterial colonization after intestinal urinary diversion, but, provided the flow of urine is not obstructed, clinical symptoms are exceedingly rare. This is discussed in another review published by Wullt and co-workers [142].

Conclusion

Continent cutaneous diversion has a place as an option for reconstruction of the urinary tract in patients who undergo cystectomy. The main indications seem to be in patients in whom urethrectomy has to be performed and in those in whom the prospect of possible urine leakage after orthotopic neobladder is repugnant. Multiple techniques have been described. However, many of them are too complicated to gain widespread acceptance. Simplicity characterizes the appendiceal outlet and the outlet of the different modifications of the Indiana pouch, and excellent functional results can be obtained. However, complications from the pouch and the outlet are not infrequent and lifelong surveillance of these patients is necessary.

4. CONDUIT URINARY DIVERSION

The conduit is still the most commonly performed urinary diversion today [2, 143]. This is also confirmed by our group (Table 1). Nevertheless, there is very little new information in the literature and a lack of hard data, including standardized reporting. Recent efforts to overcome this dilemma at least in part are the 2003 and 2011 series published by Madersbacher et al and Shimko et al.

The introduction of continent urinary diversion minimized the impact of urinary diversion on body image and allowed the patient to live a more “normal” life. Despite these potential benefits of continent urinary diversion, ileal loop conduit has remained the more commonly used form of urinary diversion, likely due to the fact that it is technically simpler to perform. Rarely conduits are formed from large bowel. Whether or not this last point regarding complications is true remains a point of debate. Large bowel surgery has a higher infectious complication rate than small bowel surgery, the mesocolon is shorter, and the vascular supply more critical, depending on the segment used. Advantages are, for example, a bigger stoma! The metabolic abnormalities associated with jejunal conduits provide a compelling reason to limit the use of jejunal conduits to patients who, for whatever reason (i.e., prior irradiated bowel or distal ureters and/or inflammatory bowel disease) cannot undergo either an ileal or colonic urinary conduit.

Urinary conduit using ileum is the most commonly performed conduit procedure [144]. Studies comparing ileal or colonic urinary conduit diversion have documented fairly similar long- and short-term complication rates [145]. It is likely that ileum is used more commonly because it is the technically simplest conduit to perform. Acknowledging this, there are still settings where it is preferable that colon, as opposed to ileum, be used. Specifically, in the setting of patients with short bowel syndrome or in patients who have had prior irradiation of the ileum or distal ureters, a colonic conduit should be considered. Another setting where a sigmoid colon conduit should be considered is in the patient who is undergoing en bloc resection of the colon or rectum, as this may eliminate the need for an additional bowel anastomosis.

Ileum or colon are the preferred intestinal segments for use in urinary conduit diversion. Jejunum is technically feasible, but should be used as a last resort, given the higher rate of metabolic abnormalities. A recent Cochrane review of the available evidence comparing ileal conduit to colonic conduit failed to show significant differences in upper urinary tract infection or ureterointestinal stenosis [147]. This review did not specifically look at rates of stomal stenosis or metabolic abnormalities, but others have noted similar rates of these long-term complications when comparing ileal to colonic conduit [145, 146]. To this end, the choice of ileum versus colon in conduit diversion should be based upon surgeon preference and patient characteristics, as discussed earlier.

a) Complications Following Conduit Diversion

The discussion of complications again is hampered by insufficient standardized reporting.

Short-term Complications

A recent review of complications in 1057 patients undergoing ileal loop diversion at the Mayo clinic documented a 3.6% incidence of abscess at the bowel anastomosis and a 2.7% incidence of enteric fistula formation, although some of these complications occurred more than 3-6 months after surgery [22]. Given that bowel leak, abscess, and/or fistula formation are potentially lethal complications, meticulous surgical technique should be employed when performing the ileoileal bowel anastomosis [147].

The other short-term complication that is highly relevant to urinary conduit diversion is urine leak at the ureteroileal anastomosis. Estimated to occur in 2-5.5% of patients [145, 148], this complication was associated with an astonishingly high rate of mortality in early ileal conduit series [149, 150]. While more recent reports do not demonstrate such high mortality rates with this complication [146], this is still a complication that should be avoided with the use of proper surgical technique and placement of ureteral stents. A recent randomized clinical trial of
54 patients undergoing either ileal loop conduit or ileal neobladder documented more frequent urine leak on postoperative day 1 in the unstented group, although no differences were noted on postoperative days 3 and 7. Importantly, stenting reduced the risk of early upper tract dilatation and was associated with improved bowel function. Stenting was not associated with an increased risk of ureteroileal stricture or upper tract infection [147]. To this end, we recommend routine ureteral stenting in all patients undergoing ileal loop conduit.

**Long-term Complications**

Ileal conduits have been used for many years. However, standardized and detailed information is only rarely available regarding the incidence of complications. Madersbacher et al, for example, reported on a cohort of 131 patients undergoing ileal conduit diversion who survived at least 5 years, where an overall complication rate of 66% was observed [21]. In fact, many patients experienced more than one complication during the first 5 years, and complications can continue to develop even beyond 15 years; 24% of patients developed stoma problems, 24% had bowel complications, 23% had symptomatic urinary tract infection (UTI), and 27% had deterioration of renal function.

In the Mayo series, 19% of patients undergoing ileal loop diversion developed new onset chronic renal insufficiency (defined as a serum creatinine greater than 2.0 mg/dL) at a median of 2.3 years after surgery [22].

There are a number of reasons why these patients experience deterioration in renal function. One common etiology is renal scarring secondary to infection. Reported long-term pyelonephritis rates following ileal loop conduit vary from 6-23% [151, 21]. In the Mayo series, 12% of patients reported a pyelonephritis episode at a median of 2.3 years after surgery. The overall infectious complication rate in this series was 16.5% [22]. There has been some debate concerning the value of nonrefluxing ureteral anastomoses in conduit surgery, but the available evidence does not support the use of nonrefluxing reimplants in the setting of urinary conduit. Given that refluxing ureters allow easier radiologic follow-up of the upper tracts, as loopograms should allow free reflux of contrast facilitating assessment of the remaining urothelium, refluxing ureteral reimplants should be routinely performed at the time of ileal conduit.

Another potential cause of long-term renal insufficiency is ureteroileal anastomotic stricture. This is thought to occur primarily due to distal ureteral ischemia and is associated with a high re-operation rate. A recent systematic review of the literature noted an 8.2% incidence of anastomotic stricture following ileal conduit [148]. The group at the Mayo clinic reported a 10% anastomotic stricture rate with a median time to stricture of 1.1 years [22]. It has been suggested that the individual end-to-side ureteroileal anastomosis technique described by Bricker may have a higher rate of stricture when compared to using a conjoined (Wallace) technique [149]. However, 2 recent retrospective series failed to document any difference in the rate of ureteral stenosis between the 2 different types of reimplant [152, 153]. The choice of ureteral reimplant, therefore, should be based on individual patient characteristics and surgeon preference.

Long-term complications associated with the urinary stoma are not infrequent occurrences following ileal loop conduit. Stomal stenosis has been reported to occur in 2-4% of patients undergoing ileal loop diversion, with a median time to diagnosis of 9.2 years in one study [22, 148]. Chechile et al noted a stomal revision rate of 5.5% in their patients undergoing ileal loop and, importantly, noted no difference in the re-operative rates between patients undergoing end versus loop type stomas [154]. The incidence of parastomal hernia following ileal loop varies from 3.7-13.9% [22, 148] and was noted to occur at a median of 2.4 years after surgery.

Table 6 presents a comparison of conduit versus neobladder. The data must be interpreted with caution. The neobladder long-term complication rate seems to be much lower (40% vs. 60%)!

The conduit complication rate seems to be endless! As expected, the UTI rate favors the neobladder (5% vs. 25%) and the ureteroileal anastomosis complication rates are identical.

**Conclusion**

*Ileal conduit diversion remains the most commonly used method for reconstructing the urinary tract in conjunction with radical cystectomy. It is probably technically easier than continent reconstruction. However, the complications, early as well as late, are legion. Several studies confirm a high incidence of upper tract complications, probably increasing with length of follow-up.*

*It is difficult to draw definitive comparisons with other diversion techniques as surgical techniques have improved markedly over the last 25 years, and few series report comparable long-term outcomes (> 20 years) in patients with neobladders.*

5. URETEROSIGMOIDOSTOMY

Regarding this type of diversion, **there is really no new information**. This corresponds to conduit diversion.

**a) Preoperative Considerations**

The success of uretersigmoidostomy depends on patient selection. Factors are anal sphincteric function, renal function, liver function, degree of
ureteral dilation, history of prior radiation therapy, primary colonic disease, and patient's compliance with long-term medications [155]. Paramount to success is an adequate anal sphincter mechanism. This should be assured both by history and preoperative testing using large volume enemas with the patient assuming normal activities. Inability of the patient to retain 400 to 500 mL in the upright position for 1 hour is a contraindication to ureterosigmoidostomy [155]. Patients with neurogenic bladder are not suitable candidates for ureterosigmoidostomy, as there may be associated anal sphincter dysfunction [156]. Preoperative evaluation of the patient selected for ureterosigmoidostomy should include studies for bowel disease that might contraindicate the operation. The presence of diverticulitis or colon polyps may be investigated by barium enema or colonoscopy [155]. Compromised renal function results in accentuation of hypercritical acidosis that results from ureterosigmoidostomy. Consequently, patients should have normal renal function to avoid this complication. Inability to handle the excess ammonia absorption has been reported to lead to hyperglycemia encephalopathy. Therefore, ureterosigmoidostomy should be avoided in patients with liver disease [157]. In the presence of ureteral dilation, creation of a nonrefluxing anastomosis may be difficult to achieve. Compliance with long-term medication, such as antibiotics and bicarbonate, is mandatory in patients with ureterosigmoidostomy [155].

b) Preoperative preparation
An adequate bowel preparation is mandatory prior to ureterosigmoidostomy to avoid infectious complications. The regimen includes a low residue diet, oral laxatives, cleansing enemas, and oral intestinal antiseptics for 3 days preoperatively [155].

c) Advantages
In 1973, Wear and Barquin enumerated the following advantages of ureterosigmoidostomy over Bricker's ileal loop: voluntary sphincteric control of urination without an external stoma and its complications, no indwelling tubes or external collecting device, shorter operating time and easier technique, ability to stage the operation, ability to perform via intraperitoneal or extraperitoneal approach, requirement of 2 rather than 5 suture lines, and better acceptance by the patient and his relatives [158, 159].

d) Early Complications
- Postoperative Anuria
The most serious immediate complication from ureterosigmoidostomy is anuria if the anastomosis is not stented. Anuria after removal of the ureteral stents indicates bilateral obstruction caused by tissue edema. In both cases, percutaneous nephrostomy tubes should be placed, especially in case of fever or flank pain [160].

- Urine Leakage
Leakage of urine occurs as an early complication of ureterosigmoidostomy with a reported incidence of 3.5% after combined technique of ureterocolic anastomosis [161]. Small leaks usually seal spontaneously. Extensive leaks, especially those associated with prolonged ileus or signs of peritonitis, are indications for immediate reoperation. Bilateral percutaneous nephrostomy tubes and defunctioning colostomy are viable conservative therapeutic options [162].

- Pelvic Abscess
This diagnosis should be considered if a patient develop otherwise unexplained fever. Ultrasonography and computed tomography with or without aspiration establish the diagnosis in most cases. Once diagnosed, open or percutaneous drainage should be carried out [162].

e) Late complications
- Reflux
Reflux is rare except after the Nesbit technique of direct mucosa-to-mucosa anastomosis [163]. The incidence is high with dilated ureters, so if one or both ureters are significantly dilated, ureterosigmoidostomy should not be considered [164]. Allen interposed an ileal nipple valve between the dilated ureters and the sigmoid colon to solve this problem [165].

- Pyelonephritis
Pyelonephritis is one of the most common and most dangerous complications of ureterosigmoidostomy, even with the combined or transcolonic techniques. Wear and Barquin reported an incidence of 81% with the older refluxing techniques of Coffey [166] and Nesbit [167], as compared with an incidence of 5.7% after the Leadbetter's [168] combined technique [164]. Williams et al reported an incidence of 45% with the Goodwin transcolonic technique [169, 170]. Zincke and Segura reported an incidence of 20% with the combined technique of ureterosigmoidostomy [171]. The combination of high bacterial counts inside rectal contents and the high rectosigmoid pressure during voiding might be responsible for the high incidence of pyelonephritis. Thus, long-term antibacterial suppressive therapy is recommended for patients with ureterosigmoidostomy [172].

- Ureterocolic anastomotic stricture
Ureteral obstruction at the ureterocolic anastomotic site may occur as a late complication in 32% of patients when the Leadbetter technique [160] is used and in 49% with other types of ureterocolic anastomosis [164]. The incidence of upper tract dilatation after
ureterosigmoidostomy with a submucosal tunnel was 12.8–45% [161, 173, 174, 175, 176].

- Incontinence

Incontinence after ureterosigmoidostomy is a drastic social problem. It can be attributed to high rectal pressure. Patients should be advised to empty on a regular basis, including once or twice during the night [166]. Imipramine hydrochloride at bedtime is indicated for those with persistent nocturnal enuresis [177]. Daytime continence rates for ureterosigmoidostomy range from 83–97% [161, 173, 174, 175, 176] and nighttime continence rates from 58-92%.

Conclusion

Although the mortality and initial morbidity following ureterosigmoidostomy have been significantly reduced, some inherent chronic complications remain problematic.

f) The sigma rectum pouch (Mainz Pouch II)

The sigma rectum pouch is another low pressure modification of ureterosigmoidostomy. The procedure was introduced by the Mainz group in 1993 [178]. The procedure entails single folding and antimesenteric splitting of the rectosigmoid colon to improve the urodynamic characteristics of the reservoir. The Goodwin technique is utilized for ureteral reimplantation [179]. In 1996, the same group reported on their experience with the sigma rectum pouch in 73 patients [180]. Stenosis at the ureteral implantation site was encountered in 5 patients (6.8%). Daytime continence was achieved in 95% of patients. Nocturnal enuresis was encountered in only 2% of patients. All patients were on prophylactic alkalization. Similar satisfactory short-term results were reported [181 - 183]. However, no long-term results were reported following this technique.

6. PALLIATIVE URINARY DIVERSION

The issue of palliation and urinary diversion centers around 2 issues: (1) management of elderly/geriatric patients with muscle-invasive bladder cancer in whom radical cystectomy/urinary diversion is associated with a considerable morbidity and mortality, and (2) patients with tumor-induced upper urinary tract dilatation and renal insufficiency in a palliative setting. A recent analysis of the SEER-database revealed a peak age incidence of bladder cancer around 85 years [184]. Due to demographic changes with a 3-fold rise in the number of octogenarians expected in the next 25 years, a substantial increase of elderly patients with bladder cancer can be expected [185].

a) Bladder sparing or radical cystectomy with urinary diversion in elderly patients?

There exists no randomized study to compare a bladder-sparing strategy versus palliative cystectomy in geriatric patients. Several reports have documented feasibility and oncological efficacy of cystectomy in the elderly.

Although perioperative mortality was substantially higher in the advanced age group (5.3% vs. 1%), postoperative morbidity was similar (34% in those <70 years, 39% in those ≥70 years) [186]. The Memorial Sloan-Kettering Cancer Center retrospectively analyzed 44 octogenarians who underwent radical cystectomy [187]. Postoperative mortality was 4.5% and 29 patients (66%) had to be hospitalized acutely after surgery, emphasizing the considerable mortality and morbidity of this procedure in octogenarians [187]. The major advantage of radical cystectomy is the avoidance of local problems caused by locally advanced disease; following radical cystectomy, the rate of local recurrences is small [188]. One has to be aware, however, that in contrast to younger patients, the oncological superiority of radical cystectomy compared to bladder-sparing approaches in elderly patients is not convincingly demonstrated [189].

b) Types of Palliative Urinary Diversion

• Cutaneous Ureterostomy

This is the most popular form of alternative non-bowel form of diversion in elderly patients or in a palliative setting [190, 191]. In a recent series of 72 patients 80 years of age or older undergoing radical cystectomy and urinary diversion, cutaneous ureterostomy was performed in 87.5% [191]. Operative time is short, and renal function is not a selection factor. Construction of a single stoma in the lateral or midline position is generally feasible and ensures easy care with minimal patient discomfort. Stenting is usually necessary to avoid stomal stenosis. Saika et al assessed health related quality of life in elderly patients (>75 years) who underwent radical cystectomy and received either an ileal conduit, cutaneous ureterostomy, or orthotopic bladder substitution [190]. After a follow-up of over 3 years, no relevant differences in any area of quality of life was seen in the 3 groups, underlining the role of cutaneous ureterostomy in frail, elderly patients [190].

• Defunctionalization of the Contralateral Renal Unit

If only 1 kidney is diverted and urine continues to flow downstream, it may be necessary to defunctionalize the latter [192]. These patients are usually poor candidates for nephrectomy. In a previously obstructed kidney, ligation of the ureter usually causes significant pain and spontaneous ureteral recanalization [192]. In these cases, renal arterial embolization should be considered.

• Palliative Treatment of Ureteral Obstruction

Common causes of malignant compression of the
ureterovesical junction and the prevesical ureter are locally advanced bladder, prostate, and cervical cancers. Malignant obstruction of the mid- and upper ureter is usually caused by metastatic lymphatic spread. Indication for treatment should be considered very carefully [192]. Septic episodes are rare in malignant ureteral obstruction if there has been no retrograde endoscopic manipulation. The insertion of a regular double J stent or percutaneous catheter will result in frequent consultations to change the catheters, even under anesthesia. Any manipulation carries the risk of infection and dislocation, and quality of life should be the main treatment goal.

- **Percutaneous Nephrostomy**
  Drainage of an obstructed upper urinary tract caused by a locally advanced or metastatic urothelial cancer leads to an ethical dilemma—s such drainage going to facilitate treatment with chemotherapy or radiotherapy, or is it perpetuating and allowing other problems to develop? Aravantinos et al concluded, based on an analysis of 270 cases, that only patients with specific cancers (e.g., prostate cancer) that progress slowly by nature may substantially benefit from the procedure [193]. Bilateral nephrostomies are generally poorly tolerated and usually only the renal unit with the better function should be diverted by nephrostomy.

- **Pyelovesical Bypass**
  Desgrandchamps et al introduced a technique of pyelovesical bypass with a composite prosthesis [194]. In the initial series, 21 patients were treated with a success rate of over 90% [194]. The authors concluded that subcutaneous pyelovesical diversion ensures a better quality of life than classical percutaneous nephrostomy in cancer patients at the palliative stage [195]. Similar encouraging data were reported by others [196].

- **Ureteral Stenting**
  These data suggest that in patients with a limited life expectancy permanent stents might be an option.

**Conclusion**

The decision regarding bladder sparing or radical cystectomy in the elderly/geriatric patient with invasive bladder cancer should be based on tumor stage and comorbidity best quantified by a validated score, such as the Charlson score. Chronological age is of limited relevance. Cutaneous ureterostomy is the most popular non-bowel urinary diversion in this setting, providing adequate quality of life. The issue of decompression of an obstructed urinary tract in a patient with advanced pelvic malignancy (particularly bladder cancer) remains a difficult clinical situation. The indication for drainage should only be made when the views and wishes of the patient and caregivers are taken into account. The prognosis remains very poor.

### 7. URINARY DIVERSION IN THE PEDIATRIC AGE GROUP—SPECIAL CONSIDERATIONS

In the pediatric age group, continent and incontinent types of urinary diversion can be applied, each with specific advantages and disadvantages [197]. Bladder augmentation and heterotopic continent cutaneous diversion are the options for continent urinary diversion in patients with and without neurogenic deficits. Orthotopic bladder substitution and continent anal diversion [198] should be offered only to patients with competent urethral or anal sphincters. For incontinent urinary diversion, a colonic conduit is the preferred solution in children [199].

Indications for urinary diversion in childhood include neurogenic bladder, functional or anatomical loss of the lower urinary tract, radical surgery for malignancies, and failure of reconstruction of the lower urinary tract (e.g., failure of primary bladder closure in patients with bladder extrophy).

#### a) Postoperative Considerations

The level of the neurological defect is a crucial aspect in patients with myelomeningocele. This determines whether a patient is ambulatory or wheelchair-bound, and whether she or he will be able to adequately perform clean intermittent catheterization (CIC). An important aspect is the transition from ambulatory to a wheelchair-bound state with aging and increasing obesity [200].

Urine storage at low pressures in an adequate capacity reservoir for preservation of the upper urinary tract and achieving urinary continence are the main goals of bladder augmentation or substitution in childhood.

#### b) Surgical Techniques

1. **Bladder Augmentation and Substitution**

Bladder augmentation is indicated in patients who are incontinent due to an overactive detrusor and/or a low-compliance bladder or small contracted bladder after radiation or multiple surgeries. Patients should be able to perform CIC via the urethra. If this is impossible for anatomic or orthopedic reasons, a "Mitrofanoff" cutaneous stoma is preferable for catheterization [201].

Gastric segments, small and large bowel, and the ureter can be used for bladder augmentation. The bladder is opened widely ("clam–technique") to prevent an hourglass phenomenon of the bladder, with the augmented segment becoming a diverticulum at the bladder dome.

In patients, who are unable to perform CIC via the urethra, the presence of the appendix is a distinct advantage. The appendix can be used as a continent
cutaneous stoma of an augmented bladder. The appendix is embedded in the taenia libera in a similar manner as in heterotopic continent cutaneous pouches [202]. The ileocecal valve can be used as an antireflux mechanism for ureters, which are implanted into the terminal ileum, which works even for severely dilated or short ureters [203, 204]. Non-dilated ureters can be implanted into the large bowel by the submucosal tunnel technique [205].

Complications from the use of gastric segments are hyponatremic, hypochloremic alkalosis and hematuria-dysuria syndrome in up to 37% of patients [206, 207]. A further late complication is development of secondary malignancies starting from the tenth postoperative year [208-211]. Therefore, the use of the stomach for bladder augmentation has become obsolete.

Ureterocystoplasty avoids most of the adverse effects of intestinal cystoplasties. However, the association of a small contracted bladder with a severely dilated ureter of a non-functioning kidney is rare. In 1973, Eckstein described the technique of ureterocystoplasty [212]. Its success depends very much on patient selection. A reaugmentation rate of up to 73% is reported [213-216].

In patients with bladder extrophy, bladder augmentation with or without closure of the bladder neck with a Mitrofanoff stoma is an option after failure of primary reconstruction [217-220]. In the long-term, these patients become continent with their Mitrofanoff stoma. However, the complication rate is high at 40% [220-222].

2. CONTINENT CUTANEOUS DIVERSION

When there are irreparable sphincter defects, small bladder capacity, obstruction of the upper urinary tract, patients being unable to perform transurethral CIC, and impossible reconstruction of the bladder neck, continent cutaneous diversion is a reasonable alternative to bladder substitution. Ileum [223-227], the ileocecal segment [228-235], and colon can be used for the construction of a continent pouch [236-238].

High continence rates are the advantage of continent cutaneous diversion as compared to bladder augmentation only. Using the embedded appendix or an ileal intussusception valve as the continence mechanism, more than 90% of patients were continent [239]. If the appendix is not available, the Yang-Monti technique is a viable option for the creation of a continent catheterizable tube [240, 241].

3. CONTINENT ANAL DIVERSION IN CHILDREN (SEE ALSO III. 5)

Ureterosigmoidostomy was the first form of continent urinary diversion to be performed and became a popular form of urinary diversion until the latter half of the last century [242-245]. In the long run, high postoperative complication rates and deterioration of the upper urinary tract became evident. Electrolyte imbalances, upper urinary tract infections, chronic renal failure, and uremia were common in the past [243, 244, 246-250]. However, refinements in surgical techniques, improved antibiotic treatment, and better suture materials allowed a revival of this surgical strategy as an attractive alternative for continent urinary diversion [245, 251, 252]. This is especially true for developing countries where cultural and economic difficulties are encountered in accepting and obtaining catheters for intermittent self-catheterization of a continent cutaneous urinary diversion and external appliances for incontinent urinary diversion [253]. Both a previous dilated upper urinary tract and an insufficient anal sphincter are contraindications [254].

The rectosigmoid pouch (Mainz Pouch II) is based on the classic ureterosigmoidostomy but applies the principles of detubularization and spherical reconfiguration of bowel to eliminate high-pressure peristaltic contractions and create a low pressure, high capacity rectosigmoid reservoir [198]. In a series of 35 children with a mean follow-up of 112 months, all were continent during the day and 3 (9%) had nighttime incontinence requiring pads. Ten (15%) of 69 ureters required reimplantation (7 for obstruction and 3 for reflux) [255]. Most of the submucosally imbedded ureters that required reimplantation were already preoperatively dilated. Implanting dilated ureters in a serosa-lined extramural tunnel provides better results [255-257]. The augmented and valved rectum, and the double-folded rectosigmoid bladder are further modifications of the ureterosigmoidostomy strategy with excellent continence rates [258-260]. However, as the surgery of the augmented and valved rectum technique is quite complex and requires temporary colostomy, the technique did not find wide acceptance.

4. INCONTINENT DIVERSION

For patients who are either physically or mentally unable to perform CIC and for patients with chronic renal failure, incontinent urinary diversion remains the diversion of choice. Ileum [261-263], the ileocecal segment [264, 265], transverse colon [266, 267], and sigmoid colon can be used for incontinent diversion [268, 269].

In 1937, Seifert described incontinent urinary diversion by a jejunum conduit and Bricker popularized the use of the ileal conduit in 1950 [261, 263]. Early results were promising and hence the procedure was also commonly used for urinary diversion in children. However, the number of reported complications increased with the length of follow-up [270]. Deterioration of the upper urinary tracts and renal function, calculus formation, and stoma stenosis.
resulted in late complication rates of 19-86% [250, 271-278]. In the 1970s, Hendren and Middleton concluded that this operation should be abandoned in children or any patient with potential longevity [273, 279]. The alternative form of incontinent urinary diversion is the colonic conduit introduced by Übelhör in 1952 and popularized by Mogg in the early 1960s [268, 269]. Elder and coworkers suggested that it had the same long-term complications as the ileal conduit [280]. However, they used an isoperistaltic and refluxing conduit. Using an isoperistaltic colonic conduit with an antirefluxive ureter implantation, good results after a mean follow-up period of more than 16 years were reported (range 5-26 years) [199].

c) Surgical Complications

The use of bowel segments for urinary tract reconstruction in children is challenging and surgical complications are common [197, 281-284]. After bladder augmentation, Herschorn et al reported a re-operation rate of 36% over 6 years [285]. Using the ileocecal segment for bladder augmentation and a cutaneous stoma for for CIC (Hemi-Indiana pouch), Husman and Cain reported a re-operation rate of 48% in 62 patients [186]. Using the Kock pouch in 20 children and adolescents, Abd-el-Gawad et al reported pouch-related complications after a follow-up of 6.5 years in 10 (88%) of 13 children and in 3 (43%) of 7 adolescents [287, 288]. In a series of 91 patients with bladder extrophy, Surer and colleagues observed stomal stenosis or stomal prolapse in 24, calculus formation in 24, bowel obstruction in 3, fistulae in another 3, and bladder perforation in 2 patients [283].

1. Ureterointestinal Stenosis

Ureteral implantation is a crucial point in urinary diversion. For implantation of the ureter into a bowel segment, refluxive and antirefluxive techniques are available [227, 289-293]. The incidence of ureterointestinal stenosis for refluxive techniques (e.g., Nesbit or Wallace technique) is between 2% and 7%, and for antirefluxive techniques (Le Duc, submucosal tunnel, serosa lined tunnel, afferent nipple valve) is between 2% and 8% [205, 294-298].

In a recent review article, Somani and co-workers demonstrated that the average incidence of ureterointestinal stenosis in patients with an ileal conduit was 11% in prospective and 8% in retrospective studies. In patients with a continent cutaneous diversion, the stenosis rate was 7% in prospective and 8% in retrospective studies, and in bladder substitution it was 7% in prospective and 5% in retrospective studies [148]. Most of these studies were performed in patients with bladder cancer and normal upper urinary tracts.

In patients with neurogenic bladder or in those after failure of primary reconstruction, dilatation of the upper urinary tracts is common when lower urinary tract reconstruction is indicated. Implantation of these ureters into the bowel has a higher complication rate as compared to normal ureters [197, 205]. Using a submucosal tunnel implantation into large bowel, 16% of the renal units required reimplantation. Using the serosa-lined extramural tunnel technique [293] in dilated ureters, the reimplantation rate was much lower (3%) [239].

Recently, the necessity of antirefluxing ureteral implantation in children has been discussed controversially [299-302]. Clearly, there is a need for a prospective randomized study assessing the impact of reflux from a potentially contaminated diversion. Until evidence is obtained that even low-pressure reflux will not harm the kidney in the long run, in young patients with a long life expectancy the kidneys should be protected by an appropriate antirefluxing technique.

2. Stomal Stenosis

In continent urinary diversion, stomal stenosis is the most frequent single complication, with an incidence of up to 32% [148, 239, 283, 284, 303].

It is treated by simple excision or incision of the scar at skin level. In children with an ileal conduit, stenosis of the stoma occurred in up to 42% [273-278]. In patients with a colonic conduit, the incidence was 16% after a mean of 119 years (range 5–20) postoperatively [304].

3. Bone Density

Among other mechanisms, chronic acidosis may play a major role in a decrease of bone mineral density after bladder augmentation or urinary diversion.

4. Growth Retardation

It is very unlikely that the changes in position on the growth curve after enterocystoplasty are a consequence of enterocystoplasty. It seems to be a non-specific phenomenon that must be considered in any clinical population of similar size and age distribution after a similar time period [305].

5. Vitamin B₁₂

About 1% of orally administered vitamin B₁₂ is absorbed by an additional, yet unknown pathway [306, 307]. Studies, unlike older textbooks suggest, demonstrate that the terminal ileum can not be considered the only site of vitamin B₁₂ absorption [306-311].

After urinary diversion with ileal segments, substitution therapy is performed in up to 35% of patients [312, 313, 314, 315. 316]. However, in the literature there are only reports of 5 patients with clinical symptoms (1 with neurological symptoms) seemingly related to vitamin B₁₂ deficiency [314, 316, 317].
A randomized study demonstrated that oral therapy (2 mg per day) is as effective as parenteral application (1 mg intramuscularly) of vitamin B₁₂ in patients with cobalamin deficiency [307]. Hence, oral treatment of low vitamin B₁₂ levels may be considered especially in children.

6. **Bowel Dysfunction**

There are relatively few reports in the literature concerning bowel dysfunction after urinary diversion. An increased stool frequency was reported after ileal or colonic conduit diversion in 4-33% of patients, after bladder augmentation, in 7-59% after substitution, and after continent cutaneous diversion in 3-23% [296, 318-324]. On the other hand, stool incontinence is surprisingly common with an estimated prevalence of up to 20% depending on age, gender, and population [325, 326].

**IV. RECOMMENDATIONS**

At high volume hospitals, orthotopic reconstruction has become the procedure of choice for urinary diversion in both men and women undergoing radical cystectomy. In these patients, the construction of a neobladder allows the elimination of a stoma and preservation of body image without compromising the cancer control. However, the patient must be committed to the labor-intensive rehabilitation process. He or she must also have adequate manual dexterity to perform self-catheterization should it become necessary. When involvement of the lower urinary tract by tumor excludes the use of a neobladder, a continent cutaneous reservoir may still offer some advantages over an ileal conduit. For patients who are not candidates for either type of continent diversion, the ileal loop remains a time-honored option.

Regrettably, almost all the many recommendations given by our committee are of **grade C**. Nevertheless, **grade C** recommendations can be very helpful, as long as the experts have the necessary experience. There are 3 important facts:

- Radical cystectomy and urinary diversion have been assessed the highest relative value of difficulty of the surgery or any procedure in urology (open, laparoscopic, and robotic), resulting in a low acceptance of orthotopic reconstruction as seen from population-based data.
- The morbidity of the procedure is up to 75% diversion-related.
- The perioperative and long-term complication rate is significant, even in the most experienced hands.

Based on these, our committee strongly recommends that this type of surgery only be performed at high volume hospitals. Our committee also considers a minimum annual case load of 25 surgeries, done by not more than 2 surgeons, to be the definition of a high volume center.

**V. REFERENCES**


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Committee 8

Urothelial Carcinoma of the Prostate

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IV. RECOMMENDATIONS
I. INCIDENCE

1. CARCINOMA IN SITU

In 1952 Melicow and Hollow described Bowen’s disease of the prostatic urethra [1]. Ortega et al were the first to describe carcinoma “in situ” (CIS) of the prostatic urethra in 1953 (Level 3)[2]. In approximately 90% of the cases, CIS is associated with a papillary or solid bladder tumor [3]. However, in about 10% of cases, it may present as an isolated lesion. It is often diagnosed in the context of multifocal disease of the bladder (Level 3)[2]. Prostatic urethra (PU) involvement by CIS is relatively rare (Level 3)[4]. Its prevalence and significance has been clarified by the use of routine random biopsies including the prostatic urethra in patients with superficial bladder tumors or positive urine cytology. In 1529 patients with primary bladder tumors who had random biopsies, 19% had carcinoma in situ, and 2.7% had CIS in the prostatic urethra (Level 3)[5]. The presence of PU CIS increased with the duration of bladder cancer: secondary tumor involvement of the prostatic urethra and ducts in bladder cancer may be detected in 10-15% of patients with high-risk superficial bladder disease within 5 years and in 20-40% within 15 years (Level 3)[6-8] (Fig.1). The majority of patients also relapse in the bladder (Level 3) [8].

The most frequently reported risk factors for PU CIS are multifocality of bladder cancer and CIS in the bladder [9-12]. Others found bladder neck location of the bladder cancer predictive of PU CIS [13;14].

2. PAPILLARY LESIONS

Primary papillary lesions in the prostatic urethra do occur in only 1-4% of cases [15-17]. In most cases a tumor in the prostatic urethra is associated with urothelial cancer elsewhere in the urinary tract [14]. Mungan et al reported multiplicity as the only risk factor of PU involvement in patients with non-muscle-invasive bladder cancer [18]. Although in cystoprostatectomy specimens the incidence of urothelial carcinoma of the prostatic urethra has been reported as high as 43% (27), most of these series consisted of patients with larger, muscle-invasive bladder cancer [19].

Figure 1. Urothelial carcinoma in situ involving prostatic urethra. Markedly atypical and pleomorphic tumor cells undermining urethral lining (highlighted in inset).

3. STROMAL INVASION

Stromal invasion is present in 37-64% of men with prostate involvement at cystoprostatectomy for invasive bladder cancer [19;20] (Fig. 2). It was generally shown to be a sign of poor prognosis [20-22]. Survival in men with PU involvement without stromal invasion was more than 60% 5 years after the cystoprostatectomy, whereas less than 30% of men survived when stromal invasion into the prostate was present [20]. Stromal invasion into the prostate was shown to be associated with an increased risk of nodal metastases [21].
Besides stromal invasion, a distinction can be made between contiguous and non-contiguous tumor growth into the prostate. The former describes direct invasion of the bladder tumor into the prostate, whereas the latter refers to synchronous presence of PU tumors. In a series of 320 cystoprostatectomy specimens, Ayyathurai et al describe contiguous tumor growth into the prostate in 9% of cases, and non-contiguous in 15% [20]. Several studies showed worse prognosis for contiguous versus non-contiguous growing tumors [20;23;24].

4. CYSTECTOMY SPECIMENS

Most reports of prostatic urethral involvement at the time of radical cystectomy are not only retrospective but lack careful pathologic assessment of the prostate and thus are likely to underreport the true incidence of involvement with urothelial carcinoma. However, the incidence of prostatic urethral involvement approaches 50% in series where detailed pathologic assessment of the prostate is performed [25;26].

In a prospective histopathologic study by Sakamoto et al, 31 of 134 cystoprostatectomy specimens in patients with primary bladder cancer revealed prostatic involvement (Level 3)[27]. They differentiated between superficial (perirectal) and deep prostatic glands and demonstrated that there was prostatic urothelial carcinoma involvement of superficial glands around the verumontanum in 93% of the cases, and at 5 and 7 o’clock in 84%; only 1 patient had deeper gland involvement without superficial gland involvement.

Esrig et al analyzed their findings of prostatic involvement in 143 of 489 cystectomy specimens (Level 3)[23]. Nineteen cases showed direct penetration from bladder to prostate and had a bad prognosis. The remaining 124 patients had different stages of indirect prostatic involvement. Thirty-seven had low grade tumor or CIS and 29 had prostatic disease involving the ducts only; these patients had a relatively good prognosis. Wood et al reported a 43% incidence of urothelial carcinoma of the prostate in cystectomy specimens (Level 3)[14]. In this series, 94% of those with prostatic involvement had disease present in the prostatic urethra, including 67% with CIS of the prostatic ducts or acini. Risk factors included CIS of the bladder neck or trigone, prior intravesical therapy, and ureteral involvement by urothelial carcinoma. In a prospective pathologic assessment, Reveco et al reported results of 121 consecutive cystoprostatectomy specimens analyzed by whole mount (Level 3)[28]. Of 121 prostates, 58 (48%) had urothelial carcinoma involving the prostatic urethra, of which 19 (33%) had apical involvement. All patients with prostatic apical involvement by urothelial carcinoma uniformly had involvement of more proximal (toward the base) portions of the prostate. These results validate the concept of cystoprostatectomy. Nixon et al reviewed 192 consecutive radical cystectomy specimens and noted prostatic urethral involvement in 30 (15.6%) specimens (Level 3)[11]. Of patients with CIS in the bladder specimen, 31.3% (25/80) had prostatic urethral involvement. Similarly, 34.7% (25/72) with multifocal urothelial carcinoma of the bladder had prostatic urethral involvement. Multivariate analysis revealed the risk of prostatic urethral involvement to...
be 12-15-fold higher if CIS or multifocal urothelial carcinoma of the bladder was present. More recent data showed a prostatic tumor location in 38% of 248 cystoprostatectomy specimens [25]. In the majority of men with prostatic involvement of urothelial cancer, the cancer originated from the urothelial mucosa, whereas in 4% the tumor extended through the bladder wall into the prostate [29].

Predictors of PU involvement in cystoprostatectomy specimens are:

- multiplicity [11;18;25].
- bladder neck tumor location [19;26].
- bladder carcinoma in situ [11;19].

**II. DIAGNOSIS OF SUPERFICIAL UROTHELIAL CARCINOMA OR CIS IN THE PROSTATIC URETHRA**

1. **DIAGNOSIS**

Urothelial carcinoma of the prostate is often understaged; correct diagnosis has to be achieved in order to avoid progression due to undetected stromal invasion (Level 3)[8;23]. Interestingly, prostatic involvement of urothelial cancer was the only predictor of understaging in recurrent high risk non-muscle-invasive bladder cancer: 53% understaging in men with prostate involvement versus 20% in men without. This suggests that prostatic sampling plays a role in management of non-muscle-invasive bladder cancer [30]. Cystoscopy was described as a valuable tool to diagnose PU involvement [11]. However, Rikken et al showed that cystoscopically hard to detect lesions, such as carcinoma in situ, can be expected in around 10% of men with a history of non-muscle-invasive bladder cancer at prostate biopsy diagnosis [31]. Transurethral resection of the PU had highest accuracy for detecting stromal invasion when compared to FNA or core-biopsy prostate sampling [32]. Still detection of TUR biopsies in the PU for stromal invasion was reported to be only 56% [33]. Even at cystoprostatectomy specimen pathology, an accurate protocol is required to prevent undersampling of the prostatic urethra [34].

The only way to approach 100% accuracy would be to perform an extensive transurethreal resection of the prostate, an impractical approach for routine staging of patients with bladder cancer (Level 3) [35]. Multiple random biopsies of the bladder and prostatic urethra are not recommended as a normal routine in superficial bladder cancer. There is a very low incidence of CIS in that location, but this means that CIS of the prostate will be undetected in patients with primary bladder tumors (Level 3)[35]. Solsona et al recommended a prostatic biopsy in patients with positive cytology or in those with macroscopic lesions in the prostate (Level 3)[35]. Donat et al reported a 39% rate of prostate relapse in patients with superficial bladder cancer (Level 3)[33]. They recommended a systematic transurethral loop biopsy extending through the bladder neck, trigone, and prostatic urethra, and ultrasound-guided biopsy of the prostate to evaluate patients with high grade superficial disease; they do not justify the proposed timing or frequency.

The staging of bladder carcinoma should include independent evaluation and staging of any prostatic lesion (Tables 1-4) (Level 3)[22]. Involvement of the prostate by CIS is almost always associated with bladder CIS (Level 3)[3]. Superficial disease in the prostate is sometimes evident as a papillary tumor. More commonly, it is silent and insidious with no evidence of macroscopic disease. Once stromal invasion is detected, the management changes completely (see Section III. Prostatic Stromal Invasion). Cystoscopy is a valuable measure of prostatic urethral involvement in macroscopic lesions, with a sensitivity of 83.3% and specificity of 95.1% (Level 3)[11]. But it is not always a valuable tool; in patients with recurrent superficial urothelial disease after BCG treatment, when considering suspicious or visible lesions, Orihuela et al had a 48% negative biopsy rate (Level 3)[36]. CIS in the prostatic urethra is common in high-risk superficial bladder cancer (9-25%), and can evolve to prostatic stromal disease (Level 3)[37]. Rikken et al stress the need to perform a biopsy of the prostatic urethra in every patient with high grade superficial bladder cancer, with the intention of identifying patients with tumors in that location to allow better therapeutic planning (Level 3)[31]. Eight of 9 patients with CIS of the prostatic urethra have coexistent CIS in the bladder. Resectoscope loop biopsies of the prostatic urethra are taken from the lateral lobes and floor beginning distal to the bladder neck and extending just proximal to the verumontanum. In 1 study, 76.5% of 17 prostatic urethral biopsies contained identifiable prostatic ducts, and ductal urothelial carcinoma was identified in 7 [33]. Hillyard et al recommended taking a biopsy of the prostatic urethra with the resectoscope loop from the lateral lobes distal to the bladder neck and performing a complete resection of the prostatic urethra (Level 3) [38]. Bretton et al also recommended performing a complete resection with 1 to 3 passes and separate identification to determine the extent of prostatic involvement (Level 3)[39].

**Survival is optimised if radical treatment precedes stromal invasion (Level 3)[8].** The detection of prostatic relapse, particularly early stromal invasion, is difficult. That is why frequent and lifelong biopsies of the bladder neck and prostate are recommended in patients with recurrent high grade papillary and in situ tumors of the bladder (Level 3)[8].
2. TREATMENT

a) General Comments

Local resection and staging of the often present bladder tumor are essential for management of PU urothelial cancers. Often the bladder cancer dictates treatment, in particular in the cases with a muscle-invasive bladder tumor. Management of superficial (non-stroma-invading) and non-superficial (stromal or contiguous) PU tumors will be discussed.

b) Management of High Grade or CIS PU Cancers

The prognostic implications of detecting CIS of the prostatic urethra are defined by the risk of progression (Level 3)[37]. Some authors feel that this finding mandates the need to offer radical cystoprostatectomy as primary therapy (Level 3)[40;41]. Esrig et al analyzed their findings of prostatic involvement at radical cystectomy; 37 of their patients with low grade tumors or CIS and 29 with ductal only prostatic disease had a relatively good prognosis (Level 3)[23]. Both the prostatic urethra and distal ureter have been considered extravesical locations of urothelial neoplasms that cannot be managed with intravesical therapy. Since Morales introduced bacillus Calmette-Guérin (BCG) as intravesical therapy of superficial urothelial carcinoma of the bladder, several authors have evidenced its efficacy both on bladder CIS and on CIS of the prostatic urethra (Level 3)[22;42-45]. Superficial tumors of the prostate can be treated conservatively if they are completely resected and treated with intravesical instillations. TUR with intravesical BCG provides a significantly better prophylaxis of tumor recurrence in Ta and T1 bladder cancer than TUR alone (Level 2)[46]. However, topical antineoplastic agents may neither gain sufficient access to the prostatic urothelium nor are incubated upon it for sufficient duration of time (Level 3)[47]. In a few patients, there is contact of the chemotherapeutic agent with the prostatic urethra, but in the majority it is only during micturition. In a non-randomized study comparing BCG and epirubicin, there seemed to be a better prostate response to BCG (Level 3)[47]. Hillyard et al advocated radical surgery in patients with ductal and stromal involvement; however, this is not justified with numbers (Level 3)[38]. Solsona et al also advocated radical surgery in patients with ductal involvement

Table 1. Classification of Prostatic Urothelial Carcinoma According to Chibber et al [49]

<table>
<thead>
<tr>
<th>Group 1</th>
<th>CIS of prostatic urethra and ducts, with or without similar disease in the bladder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 2</td>
<td>Superficial papillary bladder tumor of prostatic urothelium and major ducts with similar bladder tumor</td>
</tr>
<tr>
<td>Group 3</td>
<td>Invasive tumor of bladder base and neck with prostatic extension</td>
</tr>
</tbody>
</table>

Table 2. Classification of Prostatic Involvement According to Hardeman and Soloway [70]

<table>
<thead>
<tr>
<th>Stage 1</th>
<th>Tumor confined to prostatic urothelium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 2</td>
<td>Invasion of ducts and acini, but confined to the basal membrane</td>
</tr>
<tr>
<td>Stage 3</td>
<td>Stromal invasion</td>
</tr>
</tbody>
</table>

Table 3. TNM (2001) Classification of Prostatic Urothelial (Transitional Cell) Carcinoma (71)

| Tis pu CIS, affecting prostatic urethra |
| Tis pd CIS, affecting prostatic ducts |
| T1 Tumor invading subepithelial connective tissue |
| T2 Tumor invading prostatic stroma, spongiosum body, or periurethral muscle |
| T3 Tumor invading cavernous body prostatic capsule or bladder neck (extraprostatic extension) |
| T4 Tumor that invades surrounding organs |

Table 4. TNM Classification (2009) of T4 Urothelial (Transitional Cell) Carcinoma of the Bladder (72)

| T4 Tumor invades any of the following: prostate stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall |
| T4a Tumor invades prostate stroma, seminal vesicles, uterus, or vagina |
| T4b Tumor invades pelvic wall or abdominal wall |
c) BCG Penetration in the Prostatic Urethra

There is not complete agreement on the degree of BCG penetration of the prostatic urethra in bladder instillations. Some authors propose a primary resection of the bladder neck to obtain direct contact between the drug or immunotherapy and the prostatic urothelium [43;49]. Several studies on the prostatic tissue of patients who received BCG without prior resection of the prostate have demonstrated the presence of granulomas, indicating that BCG penetrates into the prostate (Level 3)[50-52]. Oates et al performed biopsy in 13 of 32 patients who received BCG because a prostatic nodule or enhanced consistency of the gland was palpated, and granulomas were found in all of them (Level 3)[52]. Mukamel et al diagnosed granulomas in 40% of the patients and distinguished an early period (1.5-3 months after BCG) during which these granulomas formed caseum (Level 3) [51]. At a later stage (4-14.5 months after BCG), they did not. Hillyard et al performed several cystograms in patients without resection of the bladder neck or prostate and only occasionally observed contrast medium in the prostatic urethra (Level 3)[58]. However, patients with previous TUR of the prostate show good opening of the bladder neck on the one hand, and reflux to the prostatic ducts on the other. Both changes could facilitate the penetration of BCG into the prostatic gland.

BCG instillations were shown to result in lower local recurrences in patients after TURP compared to men without TURP [18;39;46;53-55].

Leibovici et al found a clinically significant elevation of prostate specific antigen (PSA) in 41.6% of the patients receiving BCG therapy, which reverted to normal in 3 months (Level 3)[56]. The variation of PSA levels following instillation of BCG was evaluated (Level 3)[57]. The variation was higher in patients who had previously undergone TUR of the prostate (Table 5), which may be related to better penetration of BCG into the prostate. Given these results, resection of the bladder neck or prostate is advisable, with separate superficial and deep sampling at 5 and 7 o'clock on both sides of the verumontanum. This allows better initial staging and gives the best chance to detect prostatic duct involvement. This maneuver will also facilitate penetration of BCG in the prostate.

d) BCG Treatment

The response rate of bladder CIS to BCG immunotherapy is approximately 70%. When only the mucosa of the prostatic urethra is involved, this form of prostatic involvement should also respond to BCG. In fact, treatment of CIS of the prostatic urethra associated with superficial bladder tumor has resulted in complete response rates of 70-100% in the prostatic urethra and 47-72% when both the bladder and prostate are considered (Table 6). In the series of Bretton et al, therapeutic failure has always been evidenced as disease progression in the bladder; they believe that transurethral resection of the prostate contributed significantly to the successful control of tumor in the prostatic urethra (Level 3)[39]. Hillyard et al described 2 cases in which radical cystoprostatectomy was performed to treat tumor progression in the prostatic urethra or due to progression in the bladder (Level 3)[38]. Schellhammer et al reported an update of the series of Hillyard et al and described persistence or recurrence of disease in 9 of 17 patients (Level 3, [33]). Seven were treated with radical surgery. Four presented with recurrence or progression in the bladder, 1 in the prostate and 2 in both bladder and prostate. They obtained good results in 8 of 10 patients with mucosal carcinoma and in 4 of 7 patients with ductal involvement. Therefore, a more aggressive approach is warranted in cases with ductal or acinar involvement.

In selected cases, a disease-specific survival of 89% was reported at 7.5 years follow-up for 28 patients with CIS of T1 or lower grade PU cancers [55]. However, 28% required a cystectomy for local recurrence or progression. In a series of 33 patients, general progression of disease was evidenced in 8 cases, 3 of them at the prostatic urethra (Level 3). The therapeutic response of this form of disease reaches 70%, while the global vesicoprostatic response is only 40%. Palou et al showed an 82% response rate of BCG for intraprostatic duct CIS even without TURP [54]. Therefore, the results support the view that BCG is a valid option to treat carcinoma in situ of the prostatic urethra even without previous transurethral resection and that it achieves an improved response. However, with longer follow-up, disease progression occurs in 24% of the cases. These patients have a high disease-specific mortality.

Table 5. Total PSA Values During BCG Instillations in Patients With and Without TURP [57]

<table>
<thead>
<tr>
<th></th>
<th>TURP</th>
<th>No TURP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before BCG</td>
<td>1.2</td>
<td>2.1</td>
</tr>
<tr>
<td>1st instillation</td>
<td>7.7</td>
<td>3.4</td>
</tr>
<tr>
<td>2nd instillation</td>
<td>10.9</td>
<td>3.5</td>
</tr>
<tr>
<td>3rd instillation</td>
<td>8.8</td>
<td>3.8</td>
</tr>
<tr>
<td>4th instillation</td>
<td>7.1</td>
<td>4.5</td>
</tr>
<tr>
<td>5th instillation</td>
<td>6.2</td>
<td>4.7</td>
</tr>
<tr>
<td>One month</td>
<td>5.3</td>
<td>4.7</td>
</tr>
<tr>
<td>Three months</td>
<td>3.5</td>
<td>3.2</td>
</tr>
</tbody>
</table>
A good staging should be initially performed, comprising a transurethral resection of the prostate, together with strict follow-up and aggressive management of recurrence or persistence of ductal disease. Very few cases of recurrence in the prostatic urethra after BCG failure have been treated conservatively. Orihuela et al treated 5 patients, and only 2 patients with papillary lesions sustained complete response (Level 3)[36]. The other 3 patients with CIS or high grade tumors recurred and progressed. Initial management of superficial prostatic urethral disease with intravesical treatment with BCG has reasonably good results with a response rate of approximately 70%.

Patients who progress and those with urothelial carcinoma of the bladder undergoing radical cystectomy should be considered for prostatectomy as well, given the high degree of prostatic involvement (Level 3)[11;14;28].

3. FOLLOW-UP OF THE PROSTATIC URETHRA

With increasing numbers of patients receiving initially longer courses of intravesical therapy for high grade superficial bladder cancer or CIS rather than radical surgery, there will be an increased number of patients at risk of developing urothelial carcinoma of the prostate. Urothelial carcinoma of the prostate may occur in 8-48% of patients (Level 3)[11;14;36,39]. Prostatic urethral involvement tends to be more common in patients with CIS of the bladder, as well as those with multifocal tumors and involvement of the bladder neck (Level 3)[11;14;36,39].

In the series of Herr and Donat, with a minimum follow-up of 15 years, 39% of patients with superficial bladder cancer (72% with associated CIS treated with BCG) relapsed in the prostate at a median follow-up of 28 months (Level 3)[39]. In 62%, the tumors were noninvasive and in 38% there was stromal invasion. Solsona et al strongly recommend frequent random biopsies of the prostatic urethra during initial and repeated cystoscopic examinations (Level 3)[35]. Details of frequency and technique were not provided. For patients with positive cytology in follow-up in the absence of macroscopic bladder carcinoma, it is mandatory to evaluate the bladder and the prostatic urethra with multiple biopsies (Level 3)[35]. With a positive cytology during the first 6 months of follow-up after conservative management of a superficial bladder carcinoma, bladder recurrence is most likely to be the cause (Level 3)[58]. The prostatic urethra should be considered if there has been associated carcinoma in situ, tumor near the bladder neck, or multifocal disease (Level 3)[11;39]. If positive cytology appears in longer term follow-up, the upper urinary tract should be evaluated (Level 3)[59].

**SUMMARY**

Superficial urothelial cancers of the prostate are rare and most often associated with bladder cancers. In radical cystectomy specimens, the incidence of prostatic stromal invasion by urothelial carcinoma of the prostate may be related to the extent of pathologic evaluation and is associated with poor prognosis. Most reports of prostatic urethral involvement at the time of radical cystectomy are not only retrospective, but lack careful pathologic assessment of the prostate. Underreporting of the true incidence of prostatic involvement is common. Series of patients who underwent cystectomy for urothelial carcinoma of the bladder report an incidence of urothelial carcinoma of the prostate from 12-48% with stromal invasion in 7.6-16.6% [8;11;14;22-24;28;60-62]. Transurethral resection of the prostate may improve response to instillation therapy such as BCG. Careful follow-up is required since recurrence in the prostate predicts prognosis in non-muscle-invasive bladder cancer.

### Table 6. Conservative treatment of CIS in the prostatic urethra with BCG with or without TURP

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of patients (%)</th>
<th>Pathology</th>
<th>TURP</th>
<th>Global/prostate response</th>
<th>Follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bretton et al</td>
<td>23 (8.7)</td>
<td>CIS</td>
<td>Yes</td>
<td>56/100</td>
<td>42</td>
</tr>
<tr>
<td>Ovesen et al</td>
<td>10 (23.8)*</td>
<td>CIS</td>
<td>Yes</td>
<td>-/-80</td>
<td>26</td>
</tr>
<tr>
<td>Gofrit et al</td>
<td>20</td>
<td>CIS and exophytic</td>
<td>Yes</td>
<td>46.5/95.3</td>
<td>58.5</td>
</tr>
<tr>
<td>Palou et al</td>
<td>33 (20.7)*</td>
<td>CIS</td>
<td>No</td>
<td>39.4/69.6</td>
<td>64</td>
</tr>
<tr>
<td>Taylor et al</td>
<td>28</td>
<td>CIS and exophytic</td>
<td>No</td>
<td>35.7/50</td>
<td>90</td>
</tr>
<tr>
<td>Mungan et al</td>
<td>14</td>
<td>CIS and exophytic</td>
<td>No</td>
<td>NA/64</td>
<td>66</td>
</tr>
</tbody>
</table>

* Incidence in patients with bladder CIS
III. UROTHELIAL CARCINOMA PROSTATIC STROMAL INVASION

1. INCIDENCE

Adequate specimen processing by whole mount sectioning of the prostate is essential for determining the true incidence and pattern of stromal invasion. Using this technique, several contemporary cystoprostatectomy series provide evidence suggesting prostatic stromal invasion is more common than generally appreciated. Stromal invasion is present in 37-64% of men with prostate involvement at cystoprostatectomy for invasive bladder cancer [19,20]. Shen et al studied 214 consecutive cystoprostatectomy specimens and found invasive prostatic urothelial carcinoma in 39 patients (18%) [63]. A similar incidence of stromal invasion was observed by Richards et al (19%) [26] and by Pettus et al (20%) [19]. It should be noted that the prostatic stroma might be involved not only in those with invasive bladder cancer but also in men with non-invasive bladder cancer previously managed by transurethral resection and intravesical therapy. Herr and Donat evaluated 186 consecutive men with superficial bladder cancer and found a total of 14% to subsequently relapse with prostatic stromal involvement [8].

Stromal invasion is generally considered a sign of poor prognosis [20-22]. Survival in men with PU involvement without stromal invasion was more than 60% 5 years after the cystoprostatectomy, whereas less than 30% of men survived when stromal invasion was present [20]. Stromal invasion into the prostate was shown to be associated with an increased risk of nodal metastases [21].

2. MECHANISMS OF STROMAL INVASION

Prostatic stromal invasion is defined by the presence of irregular invasive tumor nests or single cells within the dense fibromuscular stroma of the prostate or admixed within benign prostate glands. Accompanying ductal/acinar carcinoma in situ and a desmoplastic inflammatory response often coexists.

Besides stromal invasion, a distinction can be made between contiguous and non-contiguous tumor growth into the prostate. The former describes direct invasion of bladder tumor into the prostate as an extravesical tumor extension (stage pT3b or greater) penetrating into the stroma directly through the prostatic capsule whereas the latter refers to synchronous presence of PU tumors as a pagetoid spread of urethral tumor into the stroma via the ducts and acini. In a series of 320 cystoprostatectomy specimens, Ayyathurai et al describe contiguous tumor growth into the prostate in 9% of cases and non-contiguous in 15% [20]. Several studies showed worse prognosis for contiguous versus non-contiguous growing tumors [20,23,24] (Table 7).

Table 7. Classification of Involvement of the Prostate According to Pagano et al [24]

<table>
<thead>
<tr>
<th>Stage</th>
<th>Patients (%)</th>
<th>Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contiguous</td>
<td>44 (61)</td>
<td>7%</td>
</tr>
<tr>
<td>Noncontiguous</td>
<td>28 (39)</td>
<td>46%</td>
</tr>
<tr>
<td>Urethral mucosa</td>
<td>6</td>
<td>100%</td>
</tr>
<tr>
<td>Ductal/acinar</td>
<td>14</td>
<td>50%</td>
</tr>
<tr>
<td>Stromal</td>
<td>8</td>
<td>40%</td>
</tr>
<tr>
<td>Extracapsular invasion</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>

A third pattern has been described as tumors located at the bladder neck trigone extending into the prostatic stroma through thin lamina propria of the bladder neck without histological evidence of extravesical or intravesical spread [33], but the prognostic significance remains unknown.

3. DIAGNOSIS

In men diagnosed with invasive urothelial carcinoma, accurate determination of prostatic involvement prior to cystoprostatectomy remains hampered by inadequate diagnostic tools. Wood et al were first to assess the diagnostic yield of transurethral prostate biopsies, needle biopsies of the prostate, and fine needle aspiration of the prostate to identify prostatic involvement in 25 consecutive patients [14].

While superficial prostate involvement was accurately identified in the majority of patients, the overall diagnostic accuracy for stromal invasion was poor with only 2 of the 5 patients being identified by TUR biopsies. In a more recent study from the same group, 6 of 35 cystectomy specimens (17%) harbored urothelial carcinoma involving the prostatic stroma (either tumor extension from the bladder involving periprostatic tissue or direct extension via the urethra) [64]. In the 5 patients who had a TUR biopsy prior to surgery, the diagnostic yield of prostatic involvement, including superficial urethral and stromal invasion, was 100%. Donat et al evaluated 246 male patients undergoing cystectomy for bladder cancer and analyzed the ability of transurethral loop biopsies to adequately determine the presence and extent of prostatic involvement [65]. Biopsies were obtained at the 4 and 8 o’clock positions from the bladder neck to the verumontanum. With a sensitivity of 53%, specificity of 77%, and positive predictive value of 45%, the authors concluded that transurethral biopsy, while remaining the primary diagnostic modality, is an imperfect tool for detecting stromal invasion by urothelial carcinoma.
4. PREDICTING PROSTATIC STROMAL INVASION

Given the lack of accurate diagnostic tools, clinical factors that might help clinicians predict stromal invasion would be particularly useful. Most studies, however, assessing predictors of prostatic involvement by urothelial carcinoma have combined superficial urethral involvement and stromal invasion into a single endpoint in their multivariate analyses. Wood et al identified carcinoma in situ (CIS) involving the trigone, bladder neck, periurethral structures, and ureter, and the use of intravesical instillations as predictors of prostatic urethral involvement [14]. Similarly, Pettus and colleagues found prostatic urothelial carcinoma in 77 of 235 cystoprostatectomy specimens (stromal invasion present in about half) and identified CIS at the trigone as a significant predictor of prostatic involvement (OR 6.3) [19]. In fact, only 6% of the patients with a bladder tumor proximal to the trigone and no associated CIS had pathological evidence of urothelial cancer involving the prostate. In a more recent series of 96 cystoprostatectomy specimens, Richards et al found prostatic stromal involvement in 18 patients (19%) [26]. After adjusting for clinical stage, lymphovascular invasion, and tumor multifocality, the presence of carcinoma in situ (OR 3.2) and location of tumor at or below the trigone (OR 3.3) were the only independent clinical predictors of stromal invasion. Taken together, even in the absence of positive findings on transurethral loop biopsies, the presence of cancer, in particular CIS, at the bladder neck trigone should be considered a strong risk factor for prostatic stromal invasion. Recently, in another study by Arce et al, they found in multivariate analysis of a series of 717 cystectomy specimens the presence of solitary T2-T3 bladder tumor at the trigone or bladder neck was predictive of invasive prostatic involvement [66].

In addition to lymph node status, it has been suggested that the outcome of men with stromal invasion can be stratified by the pattern and depth of stromal invasion as aforementioned. Spread of urothelial carcinoma into the ducts via the urethra may not be as ominous as extravesical tumor extension into the prostate or silent invasion into the stroma emanating directly from a bladder neck tumor. The recent study published by Barocas and colleagues demonstrated the overall survival of men with carcinoma in situ involving the prostatic urethra or involvement of prostatic ducts to be similar to the overall survival of men with no prostatic involvement [21]. The outcome of those with stromal invasion was uniformly poor irrespective of the mode of spread.

5. TREATMENT AND OUTCOME ANALYSES

The application of neoadjuvant systemic chemotherapy followed by radical cystoprostatectomy with extended pelvic lymph node dissection is the standard of care for men with prostatic stromal invasion by urothelial cancer. Ample evidence is now available to attest that prostatic stromal invasion is associated with a higher likelihood of lymph node metastases and a profound negative impact on survival independent of lymph node status. Shen and colleagues, for example, detected lymph node metastases in 74% of the patients with stromal invasion; the 5-year survival in this group was 32% [63]. Similar findings were reported by Barocas et al who found lymph node metastases in 74% of men with bladder tumor extending into the stroma and estimated the 3-year overall survival of men with stromal invasion with and without lymph node involvement to be 7% and 17%, respectively [21]. While lacking support from level I evidence, the importance of extended lymph node dissection in the context of stromal invasion cannot be overstated. It has been well acknowledged that the more extensive the dissection and the more nodes removed, the higher the staging accuracy and therapeutic benefit to patients [65,67,68]. Mapping studies have provided important data regarding the incidence and location of node metastases in patients with bladder cancer, specifically pT4 disease. Dangle et al have recently demonstrated that extending the lymph node dissection to include the presacral and common iliac nodes changed the pN stage from pN0 to pN1 in 69% of cases and from pN1 to pN2 in 33% of patients [65]. These findings reiterate results from an earlier mapping study by Leissner and colleagues who demonstrated that 7% of patients with lymph node spread had node metastases in the common iliac or presacral regions only [69].

4. CIS or tumor in the prostatic ducts warrants

IV. RECOMMENDATIONS

Non-invasive Urothelial Carcinoma of the Prostate

1. Macroscopic evidence of superficial bladder cancer in the prostatic urethra is highly specific. TUR of any macroscopic or suspicious lesion is required for determination of the stage and grade of tumors in the prostatic urethra. Once a non-muscle-invasive high-grade tumor or CIS of the bladder has been diagnosed, careful follow-up of the prostatic urethra is mandatory (grade C).

2. High- and low-grade non-invasive urothelial carcinoma and CIS of the prostate should be treated with intravesical BCG (grade C).

3. Evidence (level 3) shows that TUR may improve contact of BCG with the prostatic urethra and it looks that response rates to BCG are increased (grade C).

4. CIS or tumor in the prostatic ducts warrants
further study because very few patients have been treated. It is advisable for the clinician to perform radical surgery if there is any doubt, to avoid understaging in patients with prostatic duct involvement (grade C).

5. Patients with non-invasive urothelial carcinoma in whom conservative therapy fails should be considered for cystoprostatectomy (grade C).

6. Patients with intermediate- to high-risk superficial urothelial carcinoma of the bladder or CIS, especially with involvement of the bladder neck and multifocality, require monitoring of the prostatic urethra when prostatic duct involvement is observed (grade B or C).

**Prostatic Stromal Invasion**

1. The incidence of prostatic urothelial carcinoma in men with superficial or invasive bladder cancer ranges from 12-48%, and 7.6-16.6% have stromal invasion. The prostate is a site of relapse for patients with non-muscle-invasive bladder cancer after intravesical therapy (grade C).

2. Transurethral biopsy of the prostatic urethra is effective in identifying prostatic involvement but does not accurately reveal the extent of involvement, particularly with stromal invasion (grade C).

3. Retrospective and prospective studies are needed to determine prognostic factors for prostatic stromal invasion (grade D).

4. Radical cystoprostatectomy is the treatment of choice for locoregional control in patients with prostatic stromal invasion (grade B).

5. In patients with pT4 disease, the incidence of positive nodes ranges from 40-50%, and node mapping studies indicate that multiple sites are involved (grade C).

6. Data show that the extent of lymphadenectomy may have an impact on survival (grade C).

7. The number of patients with prostatic stromal invasion treated in radiation therapy trials is too small to allow definitive conclusions regarding survival outcome (grade C).

8. Although the data are limited and the number of patients with prostate stromal invasion cannot be determined from the literature, the use of radical cystectomy as a salvage procedure does not appear to diminish disease-specific or overall survival probability (grade C).

**REFERENCES**


Chemotherapy for Metastatic Urothelial Carcinoma

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Chemotherapy for Metastatic Urothelial Carcinoma

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I. BACKGROUND AND INTRODUCTION

Bladder cancer is a major health problem as defined by incidence, mortality, and cost of care. While a major part of the expense is directed towards treatment of non-muscle-invasive and organ-confined bladder cancer, the major morbidity and mortality is a result of recurrent and/or metastatic disease. Although urothelial cancer is typically a chemo-sensitive disease, only a small sub-set of patients with advanced disease achieve long-term disease-free status.

II. FIRST-LINE TREATMENTS

Cisplatin combinations such as M-VAC (Methotrexate, Vinblastine, Adriamycin, Cisplatin) were extensively studied in the 1980’s and yielded partial and complete remissions in patients with metastatic disease, with long-term survival reported in complete responders [1;2]. Patients with nodal disease only and a good performance status have a 35% complete response rate, with the majority enjoying long-term survival and apparent cure [3].

On the basis of trials comparing M-VAC to cisplatin chemotherapy [4;5] and to CISCA (cisplatin, cyclophosphamide, Adriamycin) combination therapy, M-VAC became the standard of care for the treatment of metastatic bladder cancer in the 1990s with reproducible response rates in the range of 40-70% and a median survival of approximately 1 year in several series [2;4;6].

Nevertheless, the toxicity of the M-VAC regimen, without growth factor support, consisting mainly of myelosuppression and mucositis, with a low but consistent therapy related death rate, has challenged routine use.

III. MODIFICATIONS OF M-VAC

Several phase II trials have evaluated administration of dose-dense M-VAC (DD-M-VAC) with either GM-CSF (granulocyte macrophage colony stimulating factor) or G-CSF (granulocyte colony stimulating factor). These studies have demonstrated the possibility of increasing the doses as much as 60% [7]. Unfortunately, in some of these trials, toxicity was also significantly increased [8-10].

The European Organisation for Research and Treatment of Cancer (EORTC) conducted a randomized trial comparing DD-M-VAC given on an every 2 week schedule with classic M-VAC. With DD-M-VAC, it was possible to deliver higher doses of doxorubicin and cisplatin as compared to classic M-VAC. Although there was not a significant difference found in median survival (approximately 15 months in both arms), 21.8% were alive on the DD-M-VAC arm versus 13.5% on the M-VAC arm at 5 years (HR=0.76, P=0.042). There was also a significant difference in favor of DD-M-VAC in response rate (72% vs. 58%, P=0.016), complete response rate (25% vs. 11%, P=0.006) and median progression-free survival (9.5 vs. 8.1 months, P=0.017) [7;11].

A phase III randomized trial comparing M-VAC plus prophylactic G-CSF with docetaxel-cisplatin (DC) plus G-CSF was reported by the Hellenic Cooperative Oncology Group [12]. Two hundred twenty patients were randomly assigned to M-VAC (109 patients) or DC (111 patients). The overall response rate (72% vs. 37.4%; P=0.017), median time to progression (TTP; 9.4 vs. 6.1 months; P=0.003) and median survival (14.2 vs. 9.3 months; P=0.026) favored the M-VAC regimen. After adjusting for prognostic factors, the difference in time to progression
remained significant, whereas the survival difference was non-significant at the 5% level. M-VAC caused more frequent grade 3 or 4 neutropenia (35.4% vs. 19.2%; P=0.006), thrombocytopenia (5.7% vs. 0.9%; P=0.46), and neutropenic sepsis (11.6% vs. 3.8%; P=0.001), but toxicity of M-VAC was considerably lower than that previously reported for M-VAC administered without G-CSF. It can be concluded from this study that not only was M-VAC supported by G-CSF more effective than DC but that it was also better tolerated than classic M-VAC as first-line treatment in advanced urothelial carcinoma (level of evidence 1b).

These trials confirm that classic M-VAC with appropriate hematopoietic growth factor support is an effective treatment. DD-M-VAC is another excellent option that may potentially lead to higher long-term cure rates.

### IV. DOUBLET CHEMOTHERAPY

Several phase II trials in both pretreated and untreated patients evaluated the combination of cisplatin and gemcitabine (GC). Different schedules and dosages in locally advanced and/or metastatic bladder cancer have been conducted [13] with overall response rates ranging from 41-57% and complete response from 18-22% [14-16]. Toxicity was generally acceptable and median survival rates were 12.5, 14.3, and 13.5 months, respectively.

These results led to a large industry-sponsored randomized trial of GC versus M-VAC. When first published, at a median follow-up of 19 months, overall survival in the M-VAC group was 14.8 months as compared to 13.8 months in the GC group [17]. This trial was not designed as an equivalency trial, and many more patients would have been needed to prove that the two regimens were equivalent in efficacy.

The toxicity profile was different in the two arms, with lower rates of grade 3-4 neutropenia (72% vs. 84%), neutropenic fever (2% vs. 14%), and grade 3-4 mucositis (1% vs. 22%) in the GC arm, and a lower rate of thrombocytopenia and anemia in the M-VAC arm. It is possible that some of the toxicities in the M-VAC group could have been avoided with the prophylactic use of G-CSF, which was not routinely prescribed. The quality of life profile was similar for both arms with the exception of a non-statistically significant improvement in “fatigue” in the GC group.

In an update of this trial [18], overall survival was similar in both arms with median survival of 14.0 months for GC and 15.2 months for M-VAC. The 5-year overall survival rates were 13.0% and 15.3%, respectively (P=0.53). The median progression-free survival was 7.7 months for GC and 8.3 months for M-VAC, with a hazard ratio of 1.09. The 5-year progression-free survival rates were 9.8% and 11.3%, respectively (P=0.63). On the basis of a more favorable risk-benefit ratio, many consider the GC regimen as a new standard treatment in metastatic urothelial cancer (level of evidence 1b).

Several phase II trials explored the combination of paclitaxel and cisplatin [19;20] with an overall response rate of approximately 50%. At least three trials evaluated the combination of docetaxel and cisplatin with complete responses ranging from 19-26% and partial responses from 34-58%, [21-23]. The toxicity of these regimens was considered moderate with neutropenia and neurotoxicity being most common. As noted above, a phase III trial demonstrated that this regimen was inferior to M-VAC plus G-CSF [12].

Several phase II trials have studied the combination of paclitaxel with varying doses (150-225 mg/m²) and carboplatin (AUC 5-6) reporting overall response rates of 14-65%, with complete responses in 0-40% [24-28]. This regimen is well-tolerated with predominantly mild hematologic and neurologic toxicities.

A phase III trial conducted by the ECOG compared M-VAC with paclitaxel-carboplatin [29]. Patients with previously untreated metastatic urothelial carcinoma were randomized to either standard M-VAC or paclitaxel 225 mg/m² plus carboplatin AUC 6 every 3 weeks. After 2.5 years, the study was closed due to slow accrual. Of the planned 330 patients, only 85 were enrolled. Compared with carboplatin-paclitaxel, patients treated with M-VAC had more severe myelosuppression, mucositis, and renal toxicity. Interestingly, a quality of life evaluation revealed non-significant differences between the two arms. At a median follow-up of 32.5 months, there was no significant difference in response rate (35.9% M-VAC vs. 28.2% PC, P=0.34) or median survival (15.4 months M-VAC vs. 13.8 months PC, P=0.41) between the two arms. Definitive conclusions are not possible, given that the trial was severely underpowered.

The combination of gemcitabine and pemetrexed has been tested in 64 chemo-naive patients with locally advanced and/or metastatic urothelial carcinoma. The overall response rate among 47 patients evaluable for response was 28% and overall response rate for the intention-to-treat population was 20%. Median response duration was 11.2 months and median overall survival 10.3 months. There was one toxic death due to neutropenic sepsis. The efficacy was not superior to that of single-agent gemcitabine [30].

The combination of gemcitabine and paclitaxel has been evaluated in both pretreated and untreated
patients with different doses and schedules [31-35] with responses in the range of 35-55%.

Given the activity observed in several two-drug combinations, partially non-overlapping toxicities, and different mechanisms of action, combination therapy in three-drug regimens was the next logical step.

V. TRIPLET DRUG COMBINATION WITH PLATINUM ANALOGUES

Investigators have attempted to enhance treatment efficacy by adding a third drug to the doublet combinations. Data emerging from the phase II studies have suggested that triplet regimens might produce higher response rates and improve median survival [36-38].

To elucidate the role of paclitaxel when added to GC, a large international Intergroup Study EORTC 30987 compared the triplet paclitaxel-cisplatin-gemcitabine (PCG) with the conventional GC doublet in 627 chemo-naive patients with locally advanced or metastatic urothelial carcinoma. The study was designed to identify a 4-month difference in median survival between the two treatment groups. Overall response rate was 57.1% for PCG (CR 15%) and 46.4% for GC (CR 10%, P=0.02). Median progression-free survival was 8.4 months and 7.7 months for PCG and GC respectively (P=0.10). Median survival was 15.7 months for PCG and 12.8 months with GC, with no significant difference in overall survival (P=0.10). Both treatments were well-tolerated, with more thrombocytopenia and bleeding on GC (12% vs. 7%) and more febrile neutropenia on PCG (13% vs. 4%). In a retrospective subgroup analysis, a survival benefit was seen in patients with the bladder as their primary tumor site and in those with no risk factors or one factor (risk factors were the presence of visceral metastases and a WHO performance status of 1) [39].

In light of the results, this triplet regimen cannot be recommended as first-line therapy (level of evidence 1b).

VI. CISPLATIN-INELIGIBLE PATIENTS

As the majority of patients with advanced urothelial cancer are older (median age 68 years) and renal function declines with age, alternative non-cisplatin-based therapy is needed [40]. In fact, approximately 40% of patients with advanced urothelial cancer are “cisplatin-ineligible” due to renal dysfunction alone [41], and the proportion of cisplatin-ineligible patients is likely much higher when including treatment-limiting factors such as poor performance status and comorbidities. Several phase II studies have investigated non-cisplatin-based chemotherapy regimens in “cisplatin-ineligible” patients, however, these trials have generally included heterogeneous eligibility criteria due to a lack of consensus regarding what actually constitutes “cisplatin-ineligibility.” Recently, a working group surveyed a large group of medical oncologists in an attempt to develop a uniform definition of patients “unfit” for cisplatin that could be used to standardize eligibility criteria for clinical trials in this patient population moving forward [42;43]. Based on the survey results and the available literature regarding the safety of cisplatin in patients with urothelial cancer and other solid tumors, a consensus definition was generated. According to this definition, patients are deemed “cisplatin-ineligible” if they meet at least one of the following: ECOG performance status of 2, creatinine-clearance less than 60 mL/min, common terminology for adverse events (CTCAE) grade 2 or greater hearing loss, CTCAE v4 grade 2 or greater peripheral neuropathy, or New York Heart Association Class III heart failure. These criteria are rooted in common clinical practice, are designed to optimize the general population of patients with urothelial cancer who are eligible for clinical trials, and may lead to a greater likelihood of developing a viable strategy for regulatory approval of therapeutic regimens for this important patient subset.

The most commonly used non-cisplatin-based combination chemotherapy regimen in patients with advanced urothelial cancer is gemcitabine and carboplatin. This combination has been evaluated as first-line treatment in phase II trials [44;45].

In one of the gemcitabine-carboplatin trials, 60 unselected patients with advanced urothelial carcinoma were treated with carboplatin AUC 5 day 1 and gemcitabine 1000 mg/m² days 1 and 8 every 21 days in a study of the Hellenic Cooperative Oncology Group [46]. The objective response rate was 38.4% with 11.7% complete responses and 26.7% partial responses. The median time to disease progression was 7.6 months and the median overall survival was 16.3 months. The median survival was comparable to that reported for the combination of M-VAC according to the Memorial Sloan-Kettering Cancer Center prognostic model (3) based on similar baseline prognostic features.

The authors concluded that the combination of gemcitabine and carboplatin appears to have considerable activity as the first-line treatment of unselected patients with advanced urothelial carcinoma with manageable toxicity, and that it deserved further evaluation in this setting.

The University of Michigan led a phase II trial of carboplatin, gemcitabine, and paclitaxel for advanced urothelial cancer in patients with advanced urothelial malignancy of any histology, no previous chemotherapy for metastatic disease, Southwest...
Oncology Group performance status of 2 or less, and serum creatinine levels of 2 mg/dL or less [38]. Of 49 patients accrued, 15 (32%) experienced a complete response while 17 (36%) patients had a partial response. Febrile neutropenia occurred in only 1.4% of patients while grade 3 neuropathy occurred in 4 patients. The median survival was 14.7 months. The trial was notable for significant responses and good median survival with a non-cisplatin regimen, including responses in patients with squamous histology, who historically tend to be resistant to cytotoxic therapy. On that basis, this regimen has been widely used for subjects who are not cisplatin-ideal even though it has never been formally compared to cisplatin-containing regimens.

A randomized trial in patients with surgically incurable advanced bladder cancer evaluated whether the carboplatin-based regimen M-CAVI (methotrexate, carboplatin, and vinblastine) offered an advantage over the cisplatin-based regimen M-VAC (methotrexate, vinblastine, doxorubicin, and cisplatin) [47]. In this 47 patient trial, the overall response rates were 39% for M-CAVI and 52% for M-VAC (P=0.3) with 3 complete responses among the patients receiving M-VAC and none in the M-CAVI group. The median disease-related survival was 16 months with M-VAC versus 9 months with M-CAVI (P=0.03). The authors concluded that M-CAVI was less toxic but less active than M-VAC (P= 0.03). The authors concluded that the GCa combination might be resistant to cytotoxic therapy. On that basis, this regimen has been widely used for patients such as those with renal dysfunction. The trial included a WHO performance status 2 and/or impaired renal function (GFR greater than 30 but less than 60 mL/min). Overall survival was not different between the two arms [8.1 months versus 9.3 months; HR 0.94 (95% CI, 0.72-1.22); P= 0.64]. However, severe acute toxicity (defined as grade 3-4 mucositis, grade 4 thrombocytopenia associated with bleeding, grade 3-4 neutropenic fever, grade 3-4 renal toxicity, death) was substantially greater for M-CAVI than GCa (21.2 % vs. 9.3%). This trial provides level 1 evidence for the use of GCa chemotherapy in patients deemed ineligible for cisplatin-based chemotherapy; however, adoption of a standard definition of "cisplatin-ineligible" and additional randomized studies of chemotherapy and novel agents in this patient population are desperately needed [42].

VII. SECOND-LINE TREATMENTS/SALVAGE CHEMOTHERAPY

MONOTHERAPY

Vinflunine, a microtubule inhibiting vinca alkaloid is the most thoroughly investigated agent in the second-line setting. One phase II trial recruited 51 patients, most of whom had progressed within 12 months, and demonstrated an 18% response rate and a median duration of response of 9.1 months [52]. Another phase II trial accrued 175 patients with disease progressing within 12 months of platinum-based chemotherapy and demonstrated a response rate of 15% and median duration of response of 6 months [53]. Subsequently, a randomized phase III trial accrued 370 patients and compared vinflunine plus best supportive care (BSC) to BSC alone as second-line therapy [54]. This trial accrued patients progressing after frontline platinum-containing chemotherapy for metastatic disease, and those who had received prior peri-operative chemotherapy only were excluded. More than 80% had progressed within 6 months after prior chemotherapy and greater than 70% of patients had visceral disease. An extension of survival, the primary endpoint, was not demonstrated by an intention-to-treat (ITT) analysis (6.9 vs. 4.6 months, P=0.287), but there was a statistical improvement in response rate (8.6 vs. 0%) and median progression-free survival (3.0 vs. 1.5 months). Approximately 30% of patients in both arms received subsequent systemic therapy, which may have confounded survival. Multivariate Cox analysis adjusting for prognostic factors demonstrated a significant extension of survival with vinflunine (P=0.036), reducing the risk of death by 23%. In another analysis of only the eligible population
(n=357), the median survival was significantly longer for vinflunine with BSC compared to BSC (6.9 vs. 4.3 months, P=0.04). Based on this study, vinflunine was approved by the European Medicine Agency (EMA) and is the only agent approved by a regulatory agency for this indication. The key grade 3 or 4 toxicities for vinflunine were neutropenia (50%), febrile neutropenia (6%), anemia (19%), fatigue (19%), and constipation (16%). A recent retrospective analysis of patients who received second-line vinflunine identified ECOG performance status greater than 0, hemoglobin less than 10 g/dL, and liver metastasis as poor prognostic factors [55].

Numerous other chemotherapeutic and targeted agents have been evaluated as second-line therapy in non-randomized phase II trials and modest or marginal activity has been demonstrated for some agents (Table 1). Eligibility criteria for these reported phase II trials have been highly variable and heterogeneous, enrolling patients treated with peri-operative chemotherapy followed by frontline therapy for metastatic disease or enrolling those who had received peri-operative chemotherapy alone and with no requirement for a defined treatment-free interval after frontline therapy. Prior treatment may not be clearly defined. This renders comparison of outcomes across trials difficult; the corollary is that going forward, it might be important to enroll homogeneous patients in predefined chemosensitive or chemoresistant strata. Generally, these trials report response rates of 5-25%, median progression-free survival of 2 to 3 months and median survivals of 6 to 9 months (Table 1) [56-70].

Taxanes (paclitaxel, docetaxel, nanoparticle-albumin-bound paclitaxel) have been evaluated following first-line GC, while gemcitabine and the taxanes, alone or in combination have been employed following M-VAC. Second-line pemetrexed, a multitargeted antifolate and active as first-line therapy, illustrates the degree of heterogeneous outcomes in previously-treated patients. One study demonstrated modest activity of 8% and did not attain the level of activity required to continue accrual to the second stage in another trial (60;64). Conversely, another phase II trial in presumably comparable patients employed pemetrexed in the second-line setting of metastatic urothelial carcinoma and demonstrated a response rate of 28% [71].

### VIII. COMBINATION THERAPY

Combination regimens have also been evaluated as second-line therapy in phase II trials (Table 1), although a potential incremental benefit compared to monotherapy remains undefined. A German randomized phase II trial of 102 patients compared the strategy of administering 6 cycles of second-line gemcitabine-paclitaxel with continuation beyond 6 cycles until progression [72]. None of the patients had received previous paclitaxel, and approximately half had received previous gemcitabine. The median disease-specific survival was 7-8 months and the median progression-free survival was approximately 3.5 months in both groups. The strategy of a fixed number of cycles versus continuation until progression could not be evaluated since a mean of only 4 cycles were delivered in both groups.

<table>
<thead>
<tr>
<th>Drug</th>
<th>N</th>
<th>RR %</th>
<th>PFS (mo)</th>
<th>OS (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ifosfamide (62)</td>
<td>56</td>
<td>20</td>
<td>2.4</td>
<td>5.5</td>
</tr>
<tr>
<td>Gemcitabine (66)</td>
<td>30</td>
<td>11</td>
<td>4.9</td>
<td>8.7</td>
</tr>
<tr>
<td>Gemcitabine (67)</td>
<td>35</td>
<td>22.5</td>
<td>-</td>
<td>5.0</td>
</tr>
<tr>
<td>Weekly Paclitaxel (68)</td>
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<td>7.2</td>
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<tr>
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<td>30</td>
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<td>9.0</td>
</tr>
<tr>
<td>Nab-paclitaxel (70)</td>
<td>35</td>
<td>44</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Paclitaxel-Gemcitabine (31)</td>
<td>41</td>
<td>60</td>
<td>-</td>
<td>14.4</td>
</tr>
<tr>
<td>Ifosfamide-Gemcitabine (105)</td>
<td>34</td>
<td>21</td>
<td>4.0</td>
<td>9.0</td>
</tr>
<tr>
<td>Carboplatin-Paclitaxel (73)</td>
<td>44</td>
<td>16</td>
<td>4.0</td>
<td>6.0</td>
</tr>
<tr>
<td>Pemtrexed (60)</td>
<td>47</td>
<td>27.7</td>
<td>2.9</td>
<td>9.6</td>
</tr>
<tr>
<td>Pemtrexed (64)</td>
<td>12</td>
<td>8</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ixabepilone (58)</td>
<td>42</td>
<td>11.9</td>
<td>2.7</td>
<td>8.0</td>
</tr>
<tr>
<td>Oxaliplatin (61)</td>
<td>18</td>
<td>6</td>
<td>1.5</td>
<td>7.0</td>
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<tr>
<td>Vinflunine (53)</td>
<td>175</td>
<td>15</td>
<td>2.8</td>
<td>8.2</td>
</tr>
<tr>
<td>Vinflunine (52)</td>
<td>51</td>
<td>18</td>
<td>3.0</td>
<td>6.6</td>
</tr>
<tr>
<td>Irinotecan (57)</td>
<td>40</td>
<td>5</td>
<td>2.1</td>
<td>5.4</td>
</tr>
<tr>
<td>Topotecan (69)</td>
<td>44</td>
<td>9.1</td>
<td>1.5</td>
<td>6.3</td>
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<tr>
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<td>Lapatinib (63)</td>
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<td>Sunitinib (77)</td>
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<td>6.9</td>
</tr>
<tr>
<td>Pazopanib (79)</td>
<td>18</td>
<td>22</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Index (-)=Not available or stipulated in publication; N=number of patients; RR=response rate; PFS=progression-free survival; OS=overall survival*
Another trial evaluated carboplatin-paclitaxel following prior cisplatin-based chemotherapy not including paclitaxel, and reported a response rate of 16%, median progression-free survival of 4 months, and median survival of 6 months [73]. A phase II trial evaluated a combination of salvage weekly cisplatin, gemcitabine, and ifosfamide in a heterogeneous group of patients who had received previous platinum-based chemotherapy [74]. The response rate was 40.8% but hematologic toxicities appeared prohibitive. Similarly, the combination of pemetrexed and gemcitabine has demonstrated moderate activity coupled with substantial myelosuppression [30;75]. Scant data support re-administration of second-line M-VAC following prior first-line M-VAC in those with an excellent previous quality of response and relatively prolonged time to progression [76]. M-VAC appears to have activity after GC, although this has not been formally reported.

### IX. LEVEL OF EVIDENCE AND GRADES OF RECOMMENDATION FOR SECOND-LINE AND SALVAGE THERAPY

Since a survival benefit was not demonstrated with vinflunine by intention-to-treat analysis in the only phase III trial conducted in this setting and modest efficacy (that appears similar to activity of other available agents), in our opinion, these data represent level 2a evidence and a grade B recommendation. Additionally, other agents that have been evaluated in smaller numbers of patients in phase II trials also represent level 2a evidence and a grade B recommendation. Given the poor outcomes with currently available agents and regimens and the palliative nature of such therapy, clinical trials should remain the preferred option for the second-line and salvage therapy of metastatic urothelial carcinoma (Tables 2 and 3). Given the observation that these patients progress rapidly and poor performance might frequently preclude systemic therapy, the strategy of early second-line therapy in patients with stable or responding disease after first-line chemotherapy is being investigated (Table 3).

### X. NOVEL AGENTS FOR ADVANCED UROTHELIAL CARCINOMA

A better understanding of the molecular biology of urothelial carcinoma is yielding promising, albeit unvalidated results. Molecular targets including angiogenic pathways (VEGF, angiopoietin/Tie2, FGFR3), growth factor tyrosine kinase receptors (EGFR, Her2, Met, IGF-1R), cytoplasmic signaling pathways of survival and proliferation (PI3K/Akt/mTOR, Ras), immune modulation (CTLA-4 antagonists), and strategies to target the putative tumor initiating stem cells. Given the rapid proliferation that characterizes metastatic urothelial carcinoma, chemotherapeutic agents targeting DNA replication and/or cell division may continue to play a role even in the era of biologic agents (Table 2). While early disease appears to segregate into two molecular pathways (papillary tumors are characterized by gain-of-function mutations affecting oncogenes such as RAS and FGFR3, and carcinoma in situ (Tis) and invasive tumors are characterized by loss-of-function mutations affecting tumor suppressor genes p53, RB, and PTEN). A critically important driver of urothelial carcinogenesis in the setting of advanced disease remains elusive.

#### 1. CHEMOTHERAPY

Eribulin is a synthetic derivative of the marine sponge product halichondrin-B that inhibits tubulin polymerization, and is being evaluated as monotherapy in the first- or second-line setting, and in combination with GC. Novel anti-mitotic agents that inhibit the kinesin spindle protein (AZD-4877), the polo-like kinase (BI-6727) and a potent methotrexate analogue, pralatraxe are all being evaluated in the second-line setting (Table 2). Nab-paclitaxel is being evaluated as a single agent in previously treated patients and in combination with carboplatin and gemcitabine as neoadjuvant therapy preceding radical cystectomy.

#### 2. ANGIOGENESIS-TARGETING AGENTS

Modest activity has been demonstrated in phase II trials of the multi-targeted VEGFR tyrosine kinase inhibitor, sunitinib as frontline or salvage therapy of metastatic urothelial carcinoma [77;78]. In the salvage setting of a heavily pretreated population that received sunitinib 50 mg daily for 4 of 6 weeks or 37.5 mg daily, a partial response was seen in 3 of 45 patients, and in 1 of 32 patients respectively. Clinical regression or stable disease was achieved in 33 of 77 (43%) patients. The median progression-free survival (2.4 months) and overall survival (6-7 months) were disappointing. There were substantial toxicities with one treatment-related death and 47 patients experiencing grade 3 or 4 toxicities. While sunitinib has demonstrated modest activity in the salvage setting (described earlier), a frontline trial enrolled cisplatin-ineligible patients with a creatinine clearance of 30-60 mL/min and ECOG performance status 1 or greater to receive sunitinib 50 mg daily for 4 weeks of every 6 weeks [77]. Of 14 evaluable patients, 2 partial responses (14.3%) were obtained, and 9 patients (64.3%) had SD lasting greater than 3 months and the median progression-free survival was 6 months. This agent is under further study in combination with GC as neoadjuvant treatment and as maintenance therapy in patients experiencing
complete response, partial response, or stable disease after first-line therapy.

Another single institution Italian experience with pazopanib (a multi-targeted VEGFR tyrosine kinase inhibitor) pre-treated patients was reported at the ESMO meeting in October 2010. Of 18 heavily pre-treated patients with a median of 5 (3–12) prior regimens, 4 (22%) patients obtained a partial response and 11 (61%) had stable disease [79].

Sorafenib did not demonstrate significant activity as first- or second-line therapy by itself, but its evaluation in combination with frontline gemcitabine plus carboplatin is ongoing (Table 2) [80;81].

A randomized phase II trial is evaluating salvage docetaxel alone or with vandetanib (a VEGFR and EGFR targeting agent) in patients who have received up to 3 prior regimens (Table 3).

Dovitinib, a multtargeted inhibitor of VEGF and FGF receptors is being evaluated in the second-line setting after evaluation of FGF/R-3 expression (Table 2 and 3). A phase II trial evaluating first-line GC plus bevacizumab for metastatic urothelial carcinoma demonstrated promising activity (overall response rate 58%, median progression-free survival 8.2 months, median overall survival 19.1 months), accompanied by a significant rate of venous thromboembolism that was ameliorated with gemcitabine dose reduction [82]. Based on these promising results, the CALGB has launched a critically important first-line phase III trial that compares GC with GC-bevacizumab. Another phase II trial is evaluating the combination of carboplatin, gemcitabine, and bevacizumab for cisplatin-ineligible patients [83]. Separate phase II trials are evaluating neoadjuvant GC or DD-M-VAC plus bevacizumab followed by radical cystectomy with a goal of improving pathologic complete remissions and long-term outcomes.

Aflibercept (VEGF-trap), a VEGF receptor fusion protein that has greater affinity for VEGF than bevacizumab and also targets placental growth factor (PIGF), demonstrated poor activity as second-line monotherapy [84]. Based on preliminary evidence for activity in a phase I trial, a randomized phase II trial in the second-line setting will evaluate the value of adding AMG-386 (angiopoietin neutralizing peptibody) to carboplatin-paclitaxel [85]. Another randomized phase II trial is planning the second-line evaluation of a combination of docetaxel with monoclonal antibodies against either VEGFR1 (IMC-18F1) or VEGFR-2 (IMC-1121B) (Table 3).

**TABLE 2. Key Ongoing or Planned Non-randomized Trials Employing Novel Agents for Urothelial Carcinoma**

<table>
<thead>
<tr>
<th>Line of Therapy</th>
<th>Drug/Regimen</th>
<th>Molecular Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>First or second</td>
<td>Eribulin</td>
<td>Tubulin</td>
</tr>
<tr>
<td>First</td>
<td>GC-Eribulin</td>
<td>Tubulin</td>
</tr>
<tr>
<td>Neoadjuvant</td>
<td>GCa-Nab-paclitaxel</td>
<td>Tubulin</td>
</tr>
<tr>
<td>First (cisplatin-ineligible)</td>
<td>GCa-Bevacizumab</td>
<td>VEGF</td>
</tr>
<tr>
<td>Neoadjuvant</td>
<td>DD-MVAC-bevacizumab</td>
<td>VEGF</td>
</tr>
<tr>
<td>First</td>
<td>GCa-Sorafenib</td>
<td>VEGFR, PDGFR, Raf</td>
</tr>
<tr>
<td>Neoadjuvant, first-line</td>
<td>GC-Sunitinib</td>
<td>VEGFR, PDGFR</td>
</tr>
<tr>
<td>Neoadjuvant</td>
<td>GC-Sorafenib</td>
<td>VEGFR, PDGFR</td>
</tr>
<tr>
<td>First-line</td>
<td>GC-Tlenalidomide</td>
<td>Immune-modulation, angiogenesis</td>
</tr>
<tr>
<td>Neoadjuvant</td>
<td>Dasatinib</td>
<td>Src</td>
</tr>
<tr>
<td>Second</td>
<td>AZD-4877</td>
<td>Kinesin spindle protein</td>
</tr>
<tr>
<td>Second</td>
<td>Pralatrexate</td>
<td>Folate</td>
</tr>
<tr>
<td>Second</td>
<td>Volasertib</td>
<td>Polo-like kinase</td>
</tr>
<tr>
<td>Second</td>
<td>Pazopanib</td>
<td>VEGFR, PDGFR</td>
</tr>
<tr>
<td>Second</td>
<td>Dovitinib</td>
<td>VEGFR, PDGFR, FGFR</td>
</tr>
<tr>
<td>Second</td>
<td>Tamoxifen</td>
<td>Estrogen receptors</td>
</tr>
<tr>
<td>Second</td>
<td>Everolimus</td>
<td>mTOR</td>
</tr>
<tr>
<td>First-line cisplatin-ineligible, second-line</td>
<td>Everolimus-Paclitaxel</td>
<td>mTOR and tubulins</td>
</tr>
<tr>
<td>First-line</td>
<td>GC-Tensirolimus</td>
<td>mTOR</td>
</tr>
</tbody>
</table>

selected patients. An ongoing randomized phase II trial is evaluating the combination of cetuximab with front-line GC.

In a phase II trial of patients with EGFR and/or Her2 expression, lapatinib demonstrated partial responses in 3% and response plus stability 16 weeks or longer in 12% of patients with a trend towards apparent anti-tumor effect in those with EGFR or Her2 expression 2+/3+ by immunohistochemistry (IHC) [63]. A randomized British trial is evaluating maintenance lapatinib or placebo in patients with EGFR and/or Her2-expressing tumors with stable or responding disease after frontline chemotherapy (Table 3). In the EORTC Genitourinary Group, escalating doses of lapatinib in combination with GC are under evaluation in a dose-finding study.

In one study, patients with metastatic urothelial or squamous carcinoma whose tumors expressed Her2/neu (by IHC, serology, or fluorescence in situ hybridization) in the primary or metastatic site were treated with first-line trastuzumab in combination with paclitaxel, carboplatin, and gemcitabine in a phase II trial [88]. Thirty-one (70%) of 44 patients responded (5 complete responses and 26 partial responses), although it is unclear if these patients unequivocally had Her2-driven tumors since gene amplification was infrequent. Median time to progression and survival were 9.3 and 14.1 months, respectively. Disappointingly, a randomized phase II trial that attempted to compare GC with or without trastuzumab as front-line therapy and another phase II trial that attempted to evaluate trastuzumab as second-line monotherapy for Her2 over-expressing metastatic urothelial carcinoma closed early due to a lower than expected frequency of Her2 overexpression. Also, a phase II trial is evaluating trastuzumab in combination with paclitaxel and radiotherapy as a bladder-conserving regimen in patients with localized/locally advanced urothelial carcinoma of the bladder.

**Table 3. Key Ongoing or Planned Randomized Trials of Systemic Therapy**

<table>
<thead>
<tr>
<th>Line of therapy</th>
<th>Phase</th>
<th>Eligibility</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-line III</td>
<td>Chemo-naive or ≥1 year after peri-operative chemotherapy</td>
<td>GC</td>
<td>GC-Bevacizumab</td>
<td>VEGF</td>
<td></td>
</tr>
<tr>
<td>First-line II</td>
<td>Chemo-naive or ≥1 year after peri-operative chemotherapy</td>
<td>GC</td>
<td>GC – Cetuximab</td>
<td>EGFR</td>
<td></td>
</tr>
<tr>
<td>First-line II</td>
<td>Cisplatin- ineligible</td>
<td>GCa</td>
<td>GCa-Vandetanib</td>
<td>VEGFR, EGFR</td>
<td></td>
</tr>
<tr>
<td>Second-line II</td>
<td>Consolidation following response/stability after frontline therapy</td>
<td>Docetaxel</td>
<td>Docetaxel - Cetuximab</td>
<td>EGFR</td>
<td></td>
</tr>
<tr>
<td>Second-line II</td>
<td>Consolidation following response/stability after frontline therapy</td>
<td>Placebo</td>
<td>Sunitinib</td>
<td>VEGFR, PDGFR</td>
<td></td>
</tr>
<tr>
<td>Second-line II</td>
<td>Consolidation following response/stability after frontline therapy</td>
<td>Placebo</td>
<td>Lapatinib</td>
<td>Her2, EGFR</td>
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<tr>
<td>Second-line II</td>
<td>Progression after frontline regimen</td>
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<td>Cetuximab - Paclitaxel</td>
<td>EGFR</td>
<td></td>
</tr>
<tr>
<td>Salvage II</td>
<td>Progression after ≤3 prior regimens</td>
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<td>Docetaxel - Vandetanib</td>
<td>VEGFR, EGFR</td>
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</tr>
<tr>
<td>First or second-</td>
<td>Progressive disease, intolerant or ineligible for cisplatin</td>
<td>Placebo</td>
<td>Sunitinib</td>
<td>VEGFR, PDGFR</td>
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<td>line II</td>
<td>Progressive disease</td>
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<td>Docetaxel-IMC18F1</td>
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<tr>
<td>Second-line II</td>
<td>Progressive disease</td>
<td>Carboplatin-paclitaxel</td>
<td>Carboplatin-paclitaxel-AMG386</td>
<td>Angiopoietin/Tie2</td>
<td></td>
</tr>
</tbody>
</table>

Index * From www.Clinicaltrials.gov accessed October 20, 2010, GC=gemcitabine plus cisplatin, GCa=gemcitabine, carboplatin, IMC1121B=monoclonal antibody against VEGFR2, IMC18F1=monoclonal antibody against VEGFR1
4. OTHER MOLECULAR TARGETS

Expression of the IGF-1R appears to increase with stage and correlate with poor outcomes [89]. A phase II trial is planning the evaluation of combination GC and cixutumumab, a fully human monoclonal IgG1 antibody against IGF-1R, as first-line therapy for metastatic urothelial carcinoma.

Based on ER-β expression in urothelial carcinoma and the inhibitory effect of selective estrogen receptor modulators in preclinical models, salvage therapy with oral tamoxifen is being evaluated (Table 3) [90;9].

The mTOR inhibitors, everolimus and temsirolimus are being evaluated as monotherapy or in combination with chemotherapy (Table 2). Immune-modulation with ipilimumab, a monoclonal antibody against CTLA-4 has demonstrated immune-modulating activity in the neoadjuvant setting, and a trial is being planned in combination with frontline chemotherapy (Table 2) [92]. Lenalidomide is another agent with immune-modulating and anti-angiogenic activity and is being evaluated in combination with frontline combination chemotherapy (Table 2). Src inhibitors have demonstrated preclinical activity, and a trial is evaluating dasatinib as neoadjuvant therapy with correlative endpoints [93;94].

XI. NEW TRIAL DESIGNS AND THE DEVELOPMENT OF TAILORED THERAPY

Innovative clinical trial paradigms may enable the rapid evaluation and approval of novel agents. The consolidation second-line strategy following frontline therapy in stable or responding patients employing biologic agents is being pursued with sunitinib and lapatinib. Neoadjuvant therapy before surgery in localized disease permits rapid in vivo assessment of pathologic response and biologic activity.

The goal of personalized therapy may be attainable. Factors predictive of response may facilitate personalized therapy and enable judicious patient selection even in the early stages of drug development. Low levels of DNA-repair genes (ERCC1 and BRCA1) and tumor gene expression profiling or genomics based on in vitro drug sensitivities in the NCI-60 cancer cell line panel appear to be associated with better long-term outcomes [95-99]. A vigorous and multidisciplinary international effort to validate these observations will enable more rapid advances.

XII. PREDICTIVE MODELS

Selection of patients with a high likelihood of benefit would potentially be extremely beneficial and advance the field. Several studies have made progress towards this end. In the neoadjuvant setting, Takata et al have employed a cDNA microarray platform to profile gene expression from biopsies of 27 patients with invasive bladder cancer who were subsequently treated with M-VAC neoadjuvant chemotherapy [100]. Based on supervised analyses designed to discover genes differentially expressed between 14 M-VAC responders (defined as downstaging to T1 or less) and 13 non-responders (defined as T2 or greater stage), a set of 50 genes was identified, 25 overexpressed and 25 underexpressed, that differed significantly between these groups. Splitting their data into an 18 sample learning and 9 sample test set, they developed a 14-gene M-VAC response classifier based on the learning samples that correctly classified 8 of 9 test set samples. Quantitative RT-PCR to assess expression of these genes for classification purposes was used to validate these results [100]. However, such signatures are of much greater potential value if they are independently and prospectively validated on novel test sets. To that end, the same group performed a validation study of their predictive platform on 22 additional cases, profiled as before [97]. The signature correctly predicted response in 19 of 22 additional cases, providing a sensitivity of ~100% with a specificity of ~73%. Most importantly, in terms of potential application of this classification scheme for patients with invasive bladder cancer, in this independent test set, the positive predictive value for the assay was approximated at ~79% (11 of 14 cases), while the negative predictive value was approximated at ~100% (8 of 8 non-responders identified).

A second study examined cisplatin-based combination chemotherapy (M-VAC and GC) in 30 patients with locally advanced or metastatic invasive bladder cancer (T4b, N2-3, or metastatic M1). An oligonucleotide microarray platform was used to profile the gene expression of tumors from these patients and related it to survival [98]. A set of 50 genes was differentially expressed between these groups; interestingly, all 55 were underexpressed, that differed significantly between these groups. Splitting their data into an 18 sample learning and 9 sample test set, they developed a 14-gene M-VAC response classifier based on the learning samples that correctly classified 8 of 9 test set samples. Quantitative RT-PCR to assess expression of these genes for classification purposes was used to validate these results [100]. However, such signatures are of much greater potential value if they are independently and prospectively validated on novel test sets. To that end, the same group performed a validation study of their predictive platform on 22 additional cases, profiled as before [97]. The signature correctly predicted response in 19 of 22 additional cases, providing a sensitivity of ~100% with a specificity of ~73%. Most importantly, in terms of potential application of this classification scheme for patients with invasive bladder cancer, in this independent test set, the positive predictive value for the assay was approximated at ~79% (11 of 14 cases), while the negative predictive value was approximated at ~100% (8 of 8 non-responders identified).
differential response rates of 39% versus 74%, while survivin positive and negative tumors exhibited response rates of 47% and 70%, respectively. Double negative tumors exhibited a high response rate of 82%, whereas double positive tumors exhibited a response rate of only 27%. This resulted in an odds ratio for response in double negative tumors of 11.9 (95% CI, 3.2-42.3). Based on these findings, the authors proposed that if emmprin and survivin immunohistochemical detection were independently validated in large patient cohorts and staining were inter-institutionally standardized, these markers might be used to stratify patients into high and low likelihood of response groups, with likely responders treated by traditional cisplatin-based methods and likely non-responders assigned to investigational therapies [98].

In the adjuvant setting, a study [101] assessed the gene expression of the chemotherapy response modifiers multidrug resistance gene 1 (MDR1) and excision repair cross-complementing 1 (ERCC1) to determine if they are useful in identifying a group of patients benefiting from cisplatin-based adjuvant chemotherapy. Formalin-fixed paraffin-embedded tumor samples from 108 patients with locally advanced bladder cancer, who had been enrolled in AUO-AB05/95, a phase III trial randomizing a maximum of 3 courses of adjuvant cisplatin and methotrexate (CM) versus methotrexate, vinblastine, epirubicin, and cisplatin (M-VEC), were included in the study. Tumor cells were retrieved by laser-captured micro-dissection and analyzed for MDR1 and ERCC1 expression using a quantitative real-time reverse transcription-polymerase chain reaction assay. Importantly, expressions of MDR1 and ERCC1 were independently associated with overall progression-free survival. The correlation of high MDR1 expression with inferior outcome was stronger in patients receiving M-VEC, whereas ERCC1 analysis performed equally in the CM and M-VEC groups.

Gene expression-based predictive models may not only be predictive of single drug therapeutic response, but could also be combined to successfully predict combination responses [99;102-104]. This approach uses a novel algorithm term “CoXpression Extrapolation” (COXEN), which uses expression microarray data as a “Rosetta Stone” for translating between drug activities in a cancer cell line panel to drug activities in a set of clinical tumors. This technique has been used in bladder cancer and has also successfully predicted clinical outcome in breast and ovarian cancer. More than 500 patients have been evaluated, of which 233 patients were enrolled in clinical studies.

In summary, while not yet extensively validated in a sufficient number of samples obtained from prospective clinical trials, there is the potential that gene expression-based or immunohistochemical-detected biomarkers could become part of the diagnostic workup and management in the future (level of evidence 2b, Grade of recommendation: Not recommended outside a clinical trial or biomarker study). Unfortunately, the majority of these promising biomarkers have not yet undergone appropriate assay validation in prospectively collected samples so that full biomarker qualification studies can be performed. Implementation of molecular markers on which to base treatment decisions in bladder cancer lagged behind other diseases but it is hoped that the strategies discussed above can be validated in prospective studies in order to move the field forward.

RECOMMENDATIONS

- Combination cisplatin regimens are a standard of care for patients with a Grade A recommendation for first-line advanced urothelial cancer with adequate renal function.

- In patients with renal impairment, advanced age or poor performance status, carboplatin and gemcitabine is a Grade A recommendation and for patients with renal impairment only use of gemcitabine/carboplatin/paclitaxel can be considered (Grade C).

- Use of triplet regimens adding paclitaxel to gemcitabine plus cisplatin is not recommended.

- For second-line therapy after a platinum-based treatment, vinflunine has been adopted as a standard in Europe but not in North America.

- Use of vinflunine is a grade B recommendation.

- Novel agents and approaches are urgently needed in the treatment of urothelial cancer and clinical trial accrual needs to be actively encouraged by urologists, medical oncologists, and radiation oncologists. In this regard, the standard of care for a majority of patients with advanced bladder cancer is the best clinical trial available.

XIII. ABSTRACT

Advanced metastatic urothelial carcinoma of the bladder and other bladder cancers are responsive to chemotherapy. Cisplatin-containing chemotherapy regimens such as M-VAC, dose dense M-VAC (DD-M-VAC) and cisplatin with gemcitabine can improve quality of life and overall survival. Cisplatin-based regimens can produce complete responses in approximately 15% of patients, which can be durable. Major unmet needs exist for patients who...
fail first line standard cisplatin-based regimens, are precluded from cisplatin treatment because of renal impairment, or are not suitable for cisplatin due to comorbid conditions or advanced age. For cisplatin-ineligible patients, the combination of carboplatin with gemcitabine has emerged as a standard of care. For patients with platinum-refractory cancer, several chemotherapeutic agents have demonstrated activity. These include: vinflunine, taxanes, ifosfamide, folate modulators, and anthracyclines; of these, only vinflunine has been compared to best supportive care in a phase III trial. Novel targeted agents under investigation may be of interest in the second line or maintenance setting. To date, no second line agent has yet demonstrated definitive clinical benefit in a randomized controlled trial. Therefore, a clinical trial remains an excellent option for all patients with advanced urothelial cancer.

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Non-urothelial Cancer of the Urinary Bladder

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Non-urothelial Cancer of the Urinary Bladder

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I. NON-UROTHELIAL BLADDER CANCER

Non-urothelial bladder cancer refers to a heterogeneous group of malignancies, which are considerably less prevalent than urothelial carcinoma. Data from several contemporary epidemiologic studies highlighting the relative percentage of the various histological subtypes of bladder tumors by geographic region is depicted in Figure 1 [1,2].

The relative scarcity of these tumors has precluded the development of large-scale prospective clinical trials. In a recent review of the National Cancer Institute’s Surveillance Epidemiology and End Results (SEER) database, [3] slightly more than 3700 non-urothelial tumors were identified over a 34-year period from over 125,000 cases of bladder cancer. Of these non-urothelial tumors, only small cell carcinoma appears to have demonstrated a slight increase in incidence during that time period (Figure 2).

As a result of these data, the level of evidence provided regarding screening recommendations, staging, and treatment strategies of non-urothelial malignancies is limited. Nevertheless, the clinician must be aware of these tumors, which often warrant a different clinical approach than urothelial carcinoma. Each of the tumors will be addressed individually, and evidence-based recommendations will be provided when applicable.

Squamous Cell Carcinoma (SCC)

SCC may occur de novo, or in individuals who have been infected with the parasite Schistosoma hematobium. It is important to recognize the distinction between these two populations of patients, because the epidemiology, natural history, and treatment recommendations are different. Each will be discussed separately in the sections below.

II. SCC NOT ASSOCIATED WITH SCHISTOSOMIASIS

1. EPIDEMIOLOGY

Often referred to as non-Bilharzial SCC, this represents the most common non-urothelial bladder malignancy, accounting for 2-5% of cases in most contemporary cystectomy series [4-8]. These tumors are most often diagnosed during the seventh decade of life.

The incidence of SCC demonstrates less of a male predominance than does urothelial carcinoma. Compiling data from 915 patients in 10 series of patients with SCC, Johansson and Cohen [9] reported that the ratio of males to females was 1.4:1. Similar to urothelial carcinoma, however, women are more likely than men to present with advanced disease [10]. Data from the Netherlands Cancer Registry [11] corroborates this higher incidence of T3 and T4 tumors noted in women relative to men (21.7% vs. 14.5% in T3, and 14.5% vs. 8.4% in T4).

Data from Surveillance, Epidemiology, and End Results (SEER) program conducted between 1973 and 1997 [12] shows that there is a large racial disparity in the incidence of SCC. With an annual incidence of 1.2 per 100,000 person-years, African Americans were twice as likely to develop these tumors as Caucasians, who had an annual incidence of 0.6 per 100,000 person-years.

2. ASSOCIATION WITH SPINAL CORD INJURY (SCI)

In the United States, patients with SCI represent the largest cohort of patients affected by SCC. This
Figure 1. Percentage and histologic subtype of non-urothelial bladder cancers seen in various tumor registries worldwide (1,2).

Figure 2. Age-adjusted incidence rates of nonurothelial bladder cancer by histological subtypes in the USA, nine SEER registries, 1973-2007 (3).
condition is believed to arise as a result of chronic urinary tract inflammation, a factor which may contribute to the higher likelihood of SCC in patients with chronic cystitis, persistent calculi, and bladder diverticula [13].

Historically, the incidence of bladder cancer in patients with SCI was believed to be as high as 2.3-10%, with most cases representing SCC [14-16]. SCI patients with indwelling catheters were found to have the highest risk for the development of SCC; up to 10% of these individuals developed SCC at 10 years [14]. Interestingly, studies determined that patients performing clean intermittent self-catheterization were significantly less likely to develop SCC than those SCI patients with indwelling catheters [17, 18].

Recently, these concepts have been scrutinized by data emerging from several contemporary series. A United States Department of Veterans Affairs review of admission data from 33,560 SCI patients identified only 130 patients with bladder cancer, for an overall incidence of 0.39% [19]. Some 42 patient records were available for review, including 23 (55%) with urothelial carcinoma, 14 (33%) with SCC, and 4 (10%) with adenocarcinoma. It is noteworthy that in 26 patients with indwelling catheters, the incidences of SCC and urothelial carcinoma were equal, implicating chronic inflammation and tobacco abuse as competing risk factors.

In another study of 2900 SCI patients from several centers in the southwest United States, bladder cancer was detected in only 8 (0.32%) patients, none of whom had an indwelling catheter [20]. Another study evaluated 15 SCI patients with SCC, who were followed over a 24-year period from a VA Center in Northern California [21]. Interestingly, the majority of these patients had never had an indwelling catheter. Finally, in the largest study to date, Pannek et al. [22] evaluated 43,561 SCI patients from multiple urologic centers in Eastern Europe. In all, 48 patients with bladder cancer were identified, for an overall incidence of 0.11%. Only 7% of patients in this series had indwelling catheters, and the prevalence of SCC was only 0.02%.

Based upon these epidemiologic data, guidelines regarding the necessity, frequency, and the diagnostic testing needed for bladder cancer screening in the SCI patient population cannot be determined. Initial reports, in which a high percentage of patients with spinal cord injury developed SCC are flawed, primarily related to the retrospective manner in which data were obtained, small patient cohorts, and less rigorous statistical evaluation than would be expected for a more contemporary evaluation. Although the incidence of SCC in a contemporary SCI population appears to be less than 1%, it is recommended that these patients should be monitored, particularly if they have indwelling catheters or have a history of tobacco abuse. Any history of hematuria should be evaluated.

3. SMOKING

The relationship between SCC and cigarette smoking is not clear; Johansson and Cohen [9] found a higher incidence of SCC in smokers. SEER data support a direct correlation between quantity of cigarettes smoked and relative risk of developing SCC [23]. Indirect evidence from the Swedish Cancer Registry [24], however, does not support an association between SCC and smoking. A review of this data, which plotted trends in bladder cancer in Sweden between 1960 and 1993, revealed that, despite a rising incidence of urothelial carcinoma in Swedish women (which correlated with an increased prevalence of smoking), the incidence of SCC remained relatively constant.

4. ETIOLOGY

Because urinary tract infections are more common in women, a relationship between squamous metaplasia, leukoplasia, and the development of SCC was proposed by Connery [25] and by Holly and Mellingler [26]. In a series of 20 patients with long-standing leukoplasia, O’Flynn and Mullaney [26] observed the development of 5 cases of SCC. Although squamous metaplasia is not considered a premalignant lesion, it is often found in areas adjacent to SCC [13]. Many studies, however, have confirmed that there is a high prevalence of squamous metaplasia in the general population, and that it is not necessarily implicated in the development of SCC [28].

A few case reports have documented associations between cyclophosphamide, bacille Calmette-Guérin (BCG), human papillomavirus, and SCC of the urinary bladder [29, 30]. Other studies have revealed possible genetic and chromosomal changes that may be associated with SCC. Abnormalities of chromosomes 3, 8, 10, 13, and 17 have been detected in SCC [31]. Studies on uroplakin II gene expression found a significant difference in expression between urothelial carcinoma and SCC, with expression being greater in SCC. Uroplakins are the major differentiation products of the urothelium that control the various pathways of urothelial differentiation [8].

5. CLINICAL AND PATHOLOGIC FEATURES

The presenting symptoms in patients with non-schistosoma-related SCC are not distinguishable from urothelial carcinoma. Hematuria is the main clinical feature in 63-100% of patients. Irritative bladder symptoms are seen in two-thirds of patients. Weight loss, back or pelvic pain, and frank obstructive symptoms are less common and suggest advanced disease [4-6,32]. A urinary tract infection is present in 30-93% of patients at the time of diagnosis [4-6,33,34], and symptoms have often been present
for a prolonged period of time before the diagnosis is made [4,4,8,33].

Relatively few series of patients from Europe and the Americas have addressed pure SCC. Most of these are retrospective observational series that are more than 10 years old, and use older staging and grading systems. Despite this, we know that the majority of patients present with a bulky, solitary tumor that extensively involves the bladder wall. These tumors are sessile lesions, often with ulceration and areas of squamous metaplasia adjacent to the primary tumor. A predilection for the trigone has been noted, but SCC can arise anywhere within the bladder. Tumors may occupy a bladder diverticulum and have been described in association with bladder calculi [35].

SCC is often locally advanced at the time of diagnosis. Debbagh et al [36] reported that 10 of 14 (71%) patients in their series had a palpable tumor on rectal examination, and 11 (79%) had upper urinary tract obstruction. Pretreatment imaging studies may demonstrate hydronephrosis in 33-59% of cases [5,6,8]. Of 114 patients with SCC of the bladder in one series, 92% had T2 to T4 disease at the time of diagnosis, and most tumors were high grade [5]. As with urothelial carcinoma, clinical understaging is seen in as many as 73% of patients [6,37].

6. TREATMENT

Pure SCC of the bladder has a poor prognosis, with most patients succumbing within 1 to 3 years of diagnosis. Failure to provide loco-regional control is the hallmark of the difficulty in managing these patients. In a series of 120 patients from the Royal Marsden Hospital, the overall 5-year survival rate was 16%, with only 8% of patients developing metastatic disease [33].

a) Radiation

Irrespective of whether radiation is used as neoadjuvant or as primary treatment, results have been uniformly poor [6,32]. In a report by Quilty and Duncan [34], 51 patients were treated with radical radiotherapy, delivered with a 3-field beam-directed technique, covering the entire bladder, to a prescribed dose of 55 Gy over 4 weeks. Patients were treated prone, immediately after emptying their bladders. Only 4 patients in this series had T2 cancer, with a median survival of 14.3 months, and a 3-year survival of 26.8%. Of 48 patients treated with radiation therapy by Rundle et al [6], the 5-year survival for patients with T2 and T3 disease was 16.7% and 4.8%, respectively. No patient with T4 disease was alive beyond 11 months. Similarly, in a series of 17 patients with T2 and T3 tumors who were treated with radiation therapy alone, Johnson et al [5] reported a 20% 5-year survival rate, which was not statistically different than the 34.6% 5-year survival rate seen in 7 patients in which preoperative radiation was followed by radical cystectomy.

b) Radical Surgery

While most of the surgical series are subject to selection bias, radical cystectomy seems to offer some advantages in patients with SCC. Richie et al [37] reported a 5-year survival rate of 48% in 25 patients treated with radical cystectomy. While the investigators stated that this compared favorably with results in patients with urothelial carcinoma, they did not include in the analysis 3 patients (9%) who died during the perioperative period and an additional 5 patients in whom insufficient pathologic or follow-up data were obtained. Given the small cohort of study patients, and adjusting for these cases, the 5-year survival rate is significantly lower than was reported. Tumor stage was identified as the most important predictor of outcome.

Similarly Serretta et al [8] reported on 19 patients with pure SCC of the bladder undergoing radical cystectomy. With a mean follow-up of 52 months, 63% had died of local recurrence, with only one patient developing distant metastases.

Emerging data on the surgical management and outcome of treated SCC continues to be derived from relatively small single center series. In a recent series of 45 patients [38], in which 67% presented with T3 tumors, 37% of patients were alive without disease and 29% had died of disease at a median follow-up of 15 months following cystectomy. Similarly, Kassouf et al [39] reported a 50% recurrence in 10 of 20 patients who had undergone cystectomy at only 5 months. The majority of patients who died of SCC had isolated pelvic recurrence in the absence of disseminated metastases, emphasizing the importance of local surgical control.

c) Prognostic Comparison with Urothelial Carcinoma

Several large contemporary cystectomy series in the literature have compared outcomes in patients with urothelial carcinoma with those in patients with SCC. In a large series from Japan [40], evaluating 1042 patients treated with urothelial carcinoma and 89 patients with SCC, there was no significant difference observed in 5-year post-cystectomy survival (68.0% urothelial carcinoma vs. 60.8% SCC). In a review of SEER data between 1988 and 2003 [41], patients with SCC had worse outcomes than those with urothelial carcinoma except for those patients with localized cancers who were treated by cystectomy.

d) Neoadjuvant Radiation

Several studies have retrospectively evaluated the efficacy of pre-cystectomy irradiation. Data is limited because of the small number of patients studied, and the lack of randomized clinical trials. Johnson et al [5] integrated preoperative radiation therapy followed
by cystectomy and reported a 5-year survival rate of 34%. Swanson et al [42] reported similar results with the same approach. Patients with T2 disease showed the highest survival figures. Given the relative rarity of these tumors, the advanced stage of presentation, and the overwhelmingly poor overall survival with these tumors, it would be difficult to devise clinical trials of sufficient power to demonstrate a difference in the outcome between the two groups.

e) Impact of Urinary Diversion

The impact of the type of urinary diversion in patients with SCC is the subject of some discussion in the literature. In a series of 19 patients undergoing radical cystectomy and urinary diversion, all 3 patients with an orthotopic ileal neobladder developed recurrence at the anastomosis between the neobladder and the urethra [43]. In another series reported by Stenzl et al [44], intraoperative frozen section biopsies were obtained from the bladder neck before orthotopic reconstruction. No local recurrences occurred in the 5 female patients in this series.

f) Chemotherapy

The role of neoadjuvant or adjuvant chemotherapy in the treatment of patients with pure SCC of the bladder is uncertain. SCC is considerably less responsive to standard chemotherapy regimens used for urothelial carcinoma [45, 46]. Neoadjuvant M-VAC has been tried with no objective response [47]. Newer combination regimens consisting of gemcitabine, paclitaxel, and docetaxel, when combined with a platinum compound, may yield sustained disease remission in up to 50% of cases; these hold promise for the future [48].

g) Prevention and Early Detection

Several screening protocols have been advocated in an attempt to diagnose these tumors earlier, thereby improving outcomes. Broecker et al [49] recommended annual cystoscopy and urine cytology in patients with SCI. Others have suggested routine random bladder biopsies every 1 to 2 years. Navon et al [50] advocated urine cytology or random bladder biopsies in patients with spinal cord injuries for more than 10 years or in those with recurrent or chronic urinary tract infection. Celis et al [51] showed that psoriasin, a calcium-binding protein expressed by squamous epithelia, is a potential marker for SCC. Other biomarkers, such as SCC antigen and bcl-2 and p53 oncoproteins, may have a possible role in early diagnosis [52]. The role of these new markers in the early detection and follow-up of bladder SCC requires further study before they can be recommended.

**RECOMMENDATIONS**

In summary, non-schistosoma-related SCC is an uncommon form of bladder cancer that usually presents at an advanced stage, generally recurs loco-regionally, and has an extremely poor prognosis. Death is most often related to loco-regional failure, and not to disseminated metastasis.

The current literature supports cystectomy as the treatment of choice, when possible (grade B) [53].

**III. SQUAMOUS CELL CARCINOMA IN ASSOCIATION WITH SCHISTOSOMIASIS (BILHARZIASIS)**

1. **Epidemiology**

This type of cancer is prevalent where urinary *Schistosoma hematobium* is endemic. It is often referred to as schistosoma-related SCC or bilharzial SCC. The highest incidence of SCC of the bilharzial bladder occurs in Egypt [1]. In a report by Ghoneim et al [54], SCC accounted for 59% of 1026 cystectomy specimens. A high incidence of SCC is also found in Iraq, the Jizan region in southern Saudi Arabia, Yemen, and Sudan. In Africa, the disease has been reported in the Gold Coast region and in South Africa. However, the incidence in these countries is lower because *Schistosoma hematobium* is less endemic and less severe [55]. With a mean age at presentation of 46 years, the mean age of schistosoma-related SCC patients is 10 to 20 years younger than that seen with non-schistosoma-related SCC [56]. In areas in which schistosomiasis is endemic, some 80% of cancer specimens have shown histologic evidence of bilharzial infestation [55]. A lag period of approximately 30 years has been reported between infection with the parasite and subsequent development of the disease. The male-to-female ratio is 5:1 [57]. This male predominance is attributed to sustained contact with infected water supplies that laborers often endure while working in various outdoor environments (Figure 3).

Contemporary epidemiological studies have demonstrated a decline in the incidence of bilharzial SCC, as public health efforts have been successful in eradicating schistosomiasis in many areas of the Nile delta and in rural Egypt [58-62]. Interestingly, despite the decline in SCC, the incidence of bladder cancer remains high. This is believed to be a result of the high prevalence of tobacco use that has now created a significant rise in the incidence of urothelial cancer. Figure 4 depicts some of these trends [63].
2. Etiology
Evidence from animal models suggests that the biogenesis of bladder cancer is a multistage process. It involves initiation by carcinogens, followed by promotion of tumor growth [64]. Schistosoma-related bladder cancer may be initiated by exposure to an environmentally or locally-produced chemical carcinogen that is excreted in urine. This carcinogen reacts with the mucosal surface of the bladder to produce irreversible and potentially carcinogenic changes in the DNA of some urothelial cells. Chronic bacterial infection, which commonly complicates urinary schistosomiasis, has been implicated in the production of nitrosamines, which are well-known potent carcinogens derived from precursors in the urine. Additionally, bacterial infections may induce the secretion of beta-glucuronidase, which has been shown to split conjugated carcinogens to yield free carcinogenic products [65,66].

The possibility that carcinogenic products may be of parasitic origin is not supported by several recent investigations [55]. However, local mechanical irritation by Schistosoma eggs appears to be an important promoting factor [66]. Vitamin A deficiency may explain the high frequency of squamous metaplasia of the bladder epithelium and the predominance of SCC in patients with bilharziasis. Recent laboratory studies have shown that overexpression of cyclooxygenase-2 is associated with increasing pathological stage and grade and a worse outcome after radical cystectomy [67,68]. Abdulamir et al found that bilharzial and non-bilharzial SCC have different molecular profiles of tumor development of progression [69].

3. Clinical and Pathological Features
Patients usually present with symptoms of cystitis, including painful micturition, frequency, and hematuria. A diffuse, irregular filling defect is usually detected on cystogram. Computed tomography (CT) scanning or magnetic resonance imaging (MRI) is helpful for diagnosis and staging, which relies on cystoscopy, biopsy, and bimanual examination under anesthesia [70]. Urine cytology may provide valuable diagnostic information in patients with schistosoma-related SCC [71]. In fact, cytokeratin shedding in urine has been used as a biologic marker for the early detection of SCC [72].

Figure 3. Gender disparities in stage of bladder SCC at diagnosis. Data derived from the Netherlands Cancer Registry (11).

Figure 4. Changing Patterns of Egyptian Bladder Cancer Data abstracted from NCI- Cairo (4).
Most patients present for treatment at an advanced stage, and 25% of cases are inoperable when first seen [56]. This is because of the nonspecific symptoms of schistosoma-related SCC, which often mimic simple bilharzial cystitis.

Similar to urothelial bladder cancer, clinical understaging occurs in a high percentage of cases [70] and schistosoma-related SCC is often locally advanced at the time of diagnosis. In a study of 608 patients with schistosoma-related SCC, pT1 disease was found in 2.6%, pT2 in 10.5%, pT3 in 80.0%, and pT4 in 6.9% [54]. Lymph node metastases were only present in 18.7% of cystectomy specimens. Interestingly, the vast majority of tumors were low and medium grade (49.7% and 33.2%, respectively), a factor that may account for the low incidence of lymph node positivity [73].

Grossly, tumors are generally of the nodular, fungating type and are located in the dome or posterior or lateral walls of the bladder. Five gross types have been identified: nodular (60%), ulcerative (23%), verrucous (7%), papillary (7%), and diffuse (3%) [55]. A variety of atypical changes in the bladder mucosa, including metaplasia, dysplasia, and, rarely, carcinoma in situ, may be associated with the disease [74].

4. TREATMENT

a) Radiation

The growth characteristics of carcinoma of the bilharzial bladder have been studied with the goal of evaluating its potential response to radiation therapy [74]. Two growth features were noted: [1] high cell mitotic rate with a potential doubling time of 6 days, and [2] an extensive cell loss factor. Tumors with such growth characteristics were expected to exhibit a better response to radiation therapy [75]. Nevertheless, early experiences with external beam radiation therapy for definitive control of these tumors were disappointing [76]. Factors that interfered with the efficiency of radiation treatment in these cases included coexisting Schistosoma-related urologic lesions, which interfere with local tissue tolerance, and considerable tumor bulk, which reduces local tumor control. Furthermore, the presence of radio-resistant hypoxic tumor cells is suspected in light of the capillary vascular pattern of this cancer [77].

b) Endoscopic Resection

In view of the usual high tumor volume and its advanced stage, transurethral resection is not definitive treatment in the management of this disease. Endoscopic resection should be used only for obtaining a biopsy specimen for histopathologic diagnosis.

c) Segmental Resection (Partial Cystectomy)

Segmental resection is an attractive alternative to
with oral antibilharzial drugs such as praziquantel. Parasite) and mass treatment of the rural population through snail control (the intermediate host of the parasite). Primary prevention entails control of bilharziasis with SCC alone. Ninety-two patients were divided into 2 groups, and followed for 60 months. Patients who received preoperative radiation showed a trend towards longer survival, although this was not statistically significant. In low-stage tumors, regardless of grade, survival was not influenced by preoperative irradiation, as it was in high-stage tumors.

The presence of a large proportion of hypoxic cells within bulky tumors could explain the modest improvement that was observed after this regimen. To enhance the therapeutic value of irradiation, misonidazole, a hypoxic cell sensitizer, was given before the radiation regimen was delivered [84,85]. A prospective trial was divided into 3 arms: cystectomy only, 20 Gy of preoperative radiation followed by cystectomy, and preoperative radiation followed by cystectomy with misonidazole added as a radio-sensitizer. The addition of misonidazole did not provide any additional survival advantage to patients who were given preoperative radiotherapy (level 1 evidence).

f) Chemotherapy
Several agents have been evaluated by Gad-el-Mawla et al [86] in order to treat patients who are initially not believed to be surgically resectable. All trials were phase 2 studies in which a single agent was used, and the optimal results were obtained with epirubicin. Neoadjuvant and adjuvant epirubicin chemotherapy were used in a prospective, randomized study involving 71 patients with invasive cancer in bilharzial bladders. Two-thirds of treated patients had SCC. Disease-free survival rates were 73.5% and 37.9%, favoring the chemotherapy group [87]. Additional long-term follow-up results have not been published.

Bilharzial SCC does not appear to be responsive to chemotherapy that has traditionally been used for urothelial carcinoma. In a recent multicenter study that consisted of 120 patients treated with neoadjuvant cisplatin and gemcitabine [88], patients with SCC had no survival benefit over those who underwent cystectomy alone.

g) Prevention and Early Detection
Bilharzial SCC is a preventable malignant disease. Primary prevention entails control of bilharziasis through snail control (the intermediate host of the parasite) and mass treatment of the rural population with oral antibilharzial drugs such as praziquantel. Secondary prevention includes early detection with urine cytology and selective screening of the population at risk. The yield of a single screening study done in a rural area in Egypt was 2 per 1000 individuals [71]. Such a detection rate would not justify regular screening.

**RECOMMENDATIONS**

In summary, bilharzial SCC is the most common form of bladder cancer in endemic areas. It most often presents at an advanced stage but with low-grade cells. Cystectomy is the standard treatment, but long-term survival remains disappointing (grade B). Limited evidence (Grade B) supports a potential role of neoadjuvant chemotherapy and radiation therapy, but it is not yet sufficient to facilitate a recommendation.

**IV. ADENOCARCINOMA**

1. EPIDEMIOLOGY

Adenocarcinoma of the bladder is the third most common histologic type of bladder carcinoma. In regions in which schistosomiasis is not endemic, it comprises 0.5–2.0% of all bladder tumors [89-91]. The incidence in areas where schistosomiasis is endemic is higher, at 5.2-11.4% [54, 92,93]. Annual incidence rates for adenocarcinoma are correspondingly very low. One study from the United States using SEER data identified just 32 patients (0.7%) with adenocarcinoma from 4045 patients with newly diagnosed bladder cancer over a 1-year period (1977-1978) [94]. Similar to urothelial carcinoma, adenocarcinoma shows a male predominance. In a total of 11 series comprising 247 patients, the gender ratio between males and females was 2.7:1 [9].

The relative rarity of this tumor makes determination of risk factors difficult [94]. Nevertheless, there appears to be a higher likelihood of developing adenocarcinoma in patients with a history of schistosomiasis, endometriosis, bladder augmentation, and other irritative conditions of the urinary bladder [95,96]. Adenocarcinoma also carries the unique distinction of being the most common tumor arising in the bladder of patients with exstrophy. Such patients carry a 4% lifetime risk of developing adenocarcinoma [97]. Adenocarcinoma of the urinary bladder is classified as either: primary adenocarcinoma, urachal adenocarcinoma, or secondary (metastatic) adenocarcinoma. Secondary tumors are indicative of local extension of a primary colonic, prostatic, or ovarian cancer [98]. Primary, urachal, exstrophy-associated, and metastatic adenocarcinoma will be discussed separately.
2. PRIMARY ADENOCARcinoma

a) Epidemiology

El-Bolkainy and associates reported an incidence of 8.1% in a series of 229 cases of bladder cancer [56]. Between 1970 and 1995, 1870 cystectomies were carried out in the Urology and Nephrology Center of Mansoura. Of these, 185 cases (9.9%) proved to be primary non-urachal adenocarcinoma of the bladder on histopathologic examination [55]. Similarly, between 1994 and 2003, 3659 cystectomies were performed at the National Cancer Institute, Cairo and Minia Oncology Centre, Egypt. Of these, 192 (5.2%) were for primary non-urachal adenocarcinoma of the bladder [92]. In addition to these 2 large schistosoma-associated series of patients, two recent series from the United States have been evaluated. Using the SEER database, Wright et al identified 1374 cases of primary adenocarcinoma of the bladder recorded between 1973-2002 [99]. Lughezzani et al [100] also evaluated SEER data and found a total of 306 (2.5%) primary adenocarcinoma patients among 12,003 bladder cancer patients undergoing cystectomy between 1988 and 2006.

b) Clinical features

Primary adenocarcinoma of the bladder presents with hematuria in most patients, which may be associated with irritative voiding symptoms and, occasionally, mucus passage in the urine [89, 93,101-104]. Cystoscopically, the tumor is usually sessile, but can be papillary [103]. It can arise anywhere along the lateral walls, trigone, dome, and anterior wall of the bladder [93,101,103,104]. Multiple tumors are present approximately 50% of the time [54,101]. Adenocarcinoma is virtually always invasive with only 1 series documenting 2 non-invasive tumors [105]. Interestingly, both patients were alive at 51 and 61 months following TUR alone.

Similar to urothelial carcinoma, the in situ form of adenocarcinoma appears to portend a poor prognosis. Chan et al [106] reviewed all the case files for a series of 19 patients who had bladder biopsies performed at Johns Hopkins Hospital between 1984 and 2000 confirming the presence of adenocarcinoma in situ. Nearly 80% of these patients also exhibited some form of concomitant urothelial carcinoma in situ. Although none of the patients progressed to develop primary adenocarcinoma of the bladder, 74% ultimately received treatment for invasive carcinoma (often for an aggressive histological subtype: 5 cases of small cell and 4 cases of micropapillary urothelial carcinoma). Clearly, it is difficult to determine whether the urothelial or adenocarcinoma component of the in situ disease determined prognosis, but certainly the co-existence of both entities mitigated a poor outcome.

Primary adenocarcinoma of the bladder has a very poor prognosis regardless of the treatment modality utilized. Five-year survival varies from 11-57%; the small number of patients in each series precludes individual comparison of treatment undertaken. Consistently reported independent prognostic factors for survival include age, stage, grade, and lymph node involvement [92,93,96,99,100,105].

c) Pathological features

In order for a diagnosis of primary adenocarcinoma of the bladder to be made, it must be clearly distinguished from urothelial carcinoma with areas of glandular metaplasia. The pathogenesis of primary non-urachal adenocarcinoma is based on the ability of the urothelium to undergo metaplastic changes [108]. Mostofi [109] proposed that the metaplastic potential of the urothelium has 2 distinct patterns. Progressive invagination of hyperplastic epithelial buds into the lamina propria (von Brunn’s nests) leads to the formation of cystitis cystica. Subsequently, metaplasia of the urothelial lining of these cysts, which become columnar mucin-producing cells, results in the production of cystitis glandularis, which is a premalignant lesion. As a result, careful follow up of patients with cystitis glandularis is necessary [109]. Chronic bladder irritation and infection are the predisposing factors for these changes [107,110]. This explains, at least partly, the higher incidence of these tumors among patients with cystitis resulting from schistosomiasis.

Histologically, adenocarcinoma may be non-mucin-producing or mucin-producing. Most of these tumors are mucin-producing, but the gross passage of mucus during micturition remains uncommon [105,110]. This is because most of the mucus is secreted into the extracellular (interstitial) matrix of the urinary bladder, rather than into the bladder lumen [93]. Occasionally, mucin is secreted within the lumen of the acini. In other cases, mucin accumulates within the intracellular space displacing the nucleus to a peripheral crescent, giving the cells a signet ring appearance. It is generally accepted that this histological subtype denotes a poor prognosis [111-114].

No uniformly accepted grading system for adenocarcinoma of the bladder exists. On the basis of histopathologic findings, Anderstrom et al classified vesical adenocarcinoma into 5 patterns: glandular with columnar, sometimes enteric–appearing cells; colloid carcinoma; papillary adenocarcinoma; signet ring cell carcinoma; and clear cell carcinoma [96]. Several other histologic subtypes have been described, including mucinous, enteric (colonic) type, adenocarcinoma not otherwise specified (NOS), clear cell, hepatoid, and mixed type [104]. Unfortunately, no clear data exists regarding the impact of these different histologic patterns on survival or prognosis. The exception is signet ring cell carcinoma, which usually follows a very rapid
course, resulting in death in the majority of patients within 6 months [111].

d) Treatment

Several treatment strategies have been used in the management of primary adenocarcinoma of the bladder. In general, the available series are too small to permit meaningful comparisons between differing treatment approaches.

1. Surgical Resection

Surgical strategies include transurethral resection (TUR), partial cystectomy, and radical cystectomy. The therapeutic yield after TUR, with or without adjuvant radiotherapy, is poor (19-31% 5-year survival) [102,115]. Partial cystectomy for localized disease in a mobile part of the bladder has been advocated by several authors, including a series of 15 patients who had a 5-year survival of 54% [96]. Other series however, have shown poorer 5-year survival rates of 16-37% following partial cystectomy [91,116].

The reported 5-year disease-free survival in several cystectomy series range from 0-80% in several historical series [91,96,115-120]. Contemporary series quote more consistent 5-year survival rates, ranging from 35-55% [92,93,99,100]. Such survival rates are not dissimilar to those of patients with either urothelial or squamous cell carcinoma [54,121]. Indeed, Lughezzani et al [100] showed that while patients with primary bladder adenocarcinoma are significantly more likely to present with high stage disease, stage and grade, the adjusted survival was equivalent to that of patients with urothelial carcinoma.

A number of factors have been shown to have independent prognostic significance in patients with adenocarcinoma of the bladder. Those consistently reported include age, stage, grade and lymph node involvement. Potential molecular prognostic factors have also been assessed. El Sobky et al [122] assessed the prognostic significance of markers of angiogenesis in bilharzial primary bladder adenocarcinoma. Fifty-five cases of primary bladder adenocarcinoma were assessed for immunohistochemical markers of angiogenesis (anti-CD31), microvessel density (MVD) and DNA ploidy in relation to survival. Only lymph node involvement and MVD were independent prognostic factors for survival. However, previously defined clinical prognostic factors (stage and grade) did not predict survival in this series suggesting possible selection bias in the series (only 55 cases were assessed from a previously reported larger cohort of 185 patients). The prognostic significance of DNA ploidy has been assessed by other groups with conflicting results. Shaaban et al [123] showed that DNA ploidy did not correlate with tumor stage or grade but was predictive of lymph node metastases. Others have found no correlation between DNA ploidy and outcome [93,12] whereas Song et al [124] showed that DNA ploidy significantly correlated with tumor progression and subsequent poor outcome. In short, there are no molecular markers predictive of outcome for primary adenocarcinoma that have been validated in an independent patient cohort.

2. Radiation Therapy

Adenocarcinoma is not a radioresponsive disease, with 5-year survival rates of less than 20% in patients treated by external beam irradiation alone [91,106,114]. The addition of preoperative irradiation to partial cystectomy did not improve the survival in 2 early studies [91,96]. One of the 2 large Egyptian cystectomy series for adenocarcinoma did assess the benefit of adjuvant radiation treatment [93]. Patients receiving adjuvant radiation experienced improved outcome (61% vs. 37% 5-year survival), but the study was not a randomized trial and patient selection may have accounted for the survival differences.

3. Chemotherapy

Reports of the use of chemotherapy in the treatment of primary bladder adenocarcinoma are limited. The literature is confined to case reports or very small case series. The most successful chemotherapy regimens utilize 5-fluorouracil (5-FU), which is extrapolated from its use for gastrointestinal malignancies. Most of the published series involve small numbers and the response is universally unsatisfactory [126-130].

3. Urachal Adenocarcinoma

a) Epidemiology

Urachal carcinoma is extremely rare and represents less than 1% of all bladder tumors [121,131-133]. Previous reports consistently suggested that 33% of bladder adenocarcinomas were urachal in origin [105,118,120,131]. More recently, literature suggests that just 10% of such tumors are urachal [99]. Tumors present at a significantly younger age (median age at presentation 47-56 years) and the male:female distribution is less pronounced than for other forms of bladder adenocarcinoma at 1.3:1 [99,103,132-134].

b) Clinical and pathological features

Due to the frequent extravesical location of the tumor, presentation is often late. The most common presenting symptoms are hematuria, dysuria, and frequency. Less common symptoms and signs include mucosuria, abdominal pain, abdominal mass, and, rarely, umbilical discharge [133,134]. Cross sectional imaging can be a useful diagnostic tool (Figure 5). CT appearances consistent with urachal adenocarcinoma include a mixed solid/ cystic midline mass, an unencapsulated caudal tumor component involving the bladder wall with
a cystic encapsulated supravesical portion, mass calcification, and presence of low attenuation areas (consistent with mucin content) [135,136].

There are no known risk factors for development of urachal adenocarcinoma. The presence of a urachal anomaly per se does not increase the risk of urachal adenocarcinoma [137] However, patients with a urachal mass who experience hematuria or are over 55 years of age, have a 17- and 3-fold increased likelihood of urachal carcinoma, respectively [138].

The histological appearance of urachal carcinoma is indistinguishable from enteric type adenocarcinoma [131,139]. Recognized histological forms include: enteric, mucinous, signet cell, and adenocarcinoma not otherwise specified [140]. Two theories propound as to the origin of these unique tumors. According to Begg et al [141], this type of tumor arises from enteric rests left behind following cloacal closure during embryological development. The alternative theory suggests development along a metaplastic pathway [110,131].

Several diagnostic classification systems exist for urachal adenocarcinoma. Sheldon and Mostofi [110,131] listed several strict criteria for diagnosis including tumor located at the dome of the bladder, absence of cystitis cystica or cystitis glandularis, predominant invasion of the muscularis or deeper tissues with a sharp demarcation between the tumor and surface bladder urothelium that is free of glandular or polypoid proliferation, presence of urachal remnants within the tumor, extension of tumor into the bladder wall with involvement of the space of Retzius, anterior abdominal wall, or umbilicus, and no evidence of a primary neoplasm elsewhere. These criteria are felt to be too strict by many, who have adopted the more pragmatic approach of the group at the MD Anderson Cancer Center of considering all adenocarcinomas located at the bladder dome or midline as adenocarcinoma until proven otherwise [131].

Sheldon et al initially described the staging system that is still widely used for urachal carcinoma [131]:

- Stage I - tumor confined to the urachal mucosa
- Stage II - local invasion confined to the urachus
- Stage III - local extension into A) bladder, B) abdominal wall, C) peritoneum, or D) local viscera
- Stage IV - metastases to A) regional lymph nodes or B) distant sites

The Mayo clinic group proposed a simpler staging system (Stage 1, confined to urachal mucosa, stage 2, extending beyond the urachus/bladder, stage 3, regional lymph node metastasis, stage 4, distant metastasis) [138]. Given the similar survival between patients with stage 3 and 4 disease, the MD Anderson group suggested consolidation of these stages.

![Figure 5](image-url)

Figure 5. 59 year old woman with urachal adenocarcinoma. The anterior bladder wall is thickened (red arrows), with mild perivesical fat stranding, and prominence of the urachus (blue arrows). A large discrete mass is not noted here.
2 stages to create a simplified three tier staging system [133]. Notwithstanding these modifications, the Sheldon staging system is still the most widely used system in current practice.

c) Treatment

1. Surgical Resection

Correct identification that a bladder tumor is urachal in origin is imperative as this dictates modification of standard bladder cancer surgical techniques, to include complete excision of the urachus and umbilicus. Surgical treatment options include either 1) partial cystectomy with en bloc excision of the urachus, posterior rectus fascia, peritoneal reflections, and umbilicus, or 2) radical cystectomy with en bloc excision of the urachus/umbilicus. There are no randomized trials comparing these surgical techniques, but durable results appear achievable with either approach. Reported 5-year survival rates following partial cystectomy with en bloc urachal/umbilical excision range from 31-83% [91,96,99,105,118,120,132-134,138,139,142]. The more contemporary series estimate a 40-50% 5-year survival with either partial or radical cystectomy [132,138]. Some authors emphasize the need to utilize frozen section at the time of surgery to ensure negative surgical margins are achieved when performing a partial cystectomy [133,138].

There are currently no data to support the therapeutic benefit of bilateral pelvic lymphadenectomy as part of the surgical management of urachal tumors. Lymphadenectomy undoubtedly allows more accurate disease staging and thereby provides prognostic information. However, in the absence of effective adjuvant therapies, its routine use cannot be endorsed.

There is very little available information describing the feasibility or oncologic outcome associated with minimally-invasive approaches (laparoscopic or robotic) for urachal tumors [143-145]. None of the follow-up data from these case reports are mature enough to compare outcomes with those of conventional open surgery.

Survival rates for patients with urachal adenocarcinoma appear to be superior to those of patients with non-urachal adenocarcinoma [99,105]. Factors predictive of disease recurrence following surgical resection include positive surgical margins and high disease stage [133,138]. The Mayo clinic series showed low stage, low pathologic grade, the undertaking of total urachectomy, and negative surgical margin status to be associated with improved outcome on univariate analysis. Interestingly, stage and undertaking total urachectomy no longer retained statistical significance on multivariate analysis [138]. The authors (probably correctly) attribute this to the low number of patients studied and emphasize that total urachectomy should be undertaken as part of surgical treatment of all urachal tumors.

2. Chemotherapy

A number of chemotherapeutic regimens have been assessed in patients with either metastatic disease at presentation, or high risk of disease recurrence following surgical resection (positive surgical margins or presence of lymph node metastases). Most reports involve single patients or very small case series. In common with primary bladder adenocarcinoma, the most promising regimens appear to be 5-FU based [127,133]. Of 20 patients receiving chemotherapy in the MD Anderson Cancer Center series for metastatic disease, there were only 4 patients with significant objective responses, of whom 3 had received a 5-FU based regimen. Subsequently the group is presently performing a multi-center phase II clinical trial, using 5-FU, gemcitabine, cisplatin, and leucovorin [146].

There are no diagnostic tumor markers for urachal adenocarcinoma. However, elevated Ca19-9 and CEA levels have been reported by a number of authors [133,147,148]. These tumor markers have been shown to correlate well with response to chemotherapy [133].

4. ADENOCARCINOMA IN BLADDER EXSTROPHY

a) Epidemiology

Adenocarcinoma is the most common bladder cancer in patients with bladder exstrophy. Patients with exstrophy have a reported 4% lifetime risk of developing this type of malignancy [97]. In a review of 40 patients with untreated bladder exstrophy, McIntosh and Worley [149] found that 33 cases were adenocarcinoma, the mean age at diagnosis was 44 years, and two-thirds of the patients were male. Even with the advent of urinary diversion surgery, the risk of developing carcinoma in the bladder remnant is significant. Smeeulders et al reported on a series of 102 patients born with bladder exstrophy, who were followed for a minimum of 35 years [97]. There were 4 cases of bladder cancer, which was calculated to be 694 times greater than the risk in the normal adult population. Three of the 4 patients had undergone a simple cystectomy before the age of 5, and all were males. This implies that there was retention of a portion of the bladder in these individuals, which is speculated to become malignant in the presence of sperm or secretions from the male genitourinary tract.

b) Pathology and clinical features

The histopathology of the bladder in exstrophy patients has been well-described [150]. The development of adenocarcinoma of these bladder remnants is thought to arise from either metaplasia of the urothelium, which is exposed to inflammatory...
stimuli, or as a result of the displacement of ectopic colonic or rectal epithelium that occurs during division of the cloaca. The fact that the majority of the bladder malignancies occur during the fifth and sixth decades of life and that adenocarcinoma has been found to arise in other conditions resulting in defunctionalized bladders and after augmentation enteroplasty favors the “metaplasia theory” [151-153]. The prognosis of these tumors is poor as a result of late presentation. As a result, all patients with exstrophy who have retained their bladders should be followed closely, although no specific follow-up regimen can be recommended based upon the existing literature.

5. SECONDARY (METASTATIC) BLADDER ADENOCARCINOMA

Secondary bladder adenocarcinomas are tumors that involve the bladder by either direct extension from adjacent organs, reimplantation from adenocarcinoma located higher up within the urinary tract, or lympho-hematogeneous spread. A retrospective review of surgical specimens collected over a 90-year time period [154] showed that secondary bladder tumors comprised 2.3% of 5533 surgical specimens assessed. The most common sites of secondary tumor origin were, in order of their occurrence, colonic, prostatic, rectal and cervical. Over 50% of tumors assessed were adenocarcinomas. Indeed, secondary adenocarcinoma of the bladder is more common than primary adenocarcinoma [155]. Some of these secondary adenocarcinomas are histologically distinct, allowing rapid identification of tumor origin, such as prostatic tumors. However, many present the clinician with a diagnostic challenge when trying to determine tumor origin, which is clearly of importance in planning subsequent disease management. In the first instance, the clinical history, endoscopic exams, and radiological studies are valuable in identifying tumor origin. When such studies are not informative, immunohistochemical staining of tumor biopsy specimens may be undertaken. Two groups have reported that lack of CDX2 and villin staining indicates that an adenocarcinoma sampled from the bladder is unlikely to be colorectal in origin [156,157]. Positive PSA staining is pathognomonic of prostatic origin and vimentin staining indicates endometrial/ovarian origin [158]. Many other immunostains have been assessed, including CK7, CK20, CEA and Ca19-9, however, most lack the specificity to confidently discriminate tumor origin [158]. Similarly, assessment of mucin produced by the tumor has failed to add clarity when assessing tumor origin [159]. Urine cytology can be useful at identifying tumors of secondary origin, for example, prostatic or colonic, although it lacks sensitivity in the diagnosis of primary bladder adenocarcinoma[160].

Approximately 10% of colorectal adenocarcinomas will be attached to adjacent structures, with the urinary bladder being one of the most common organs involved [161,162]. Talamonti et al reported on a series of 70 patients undergoing en bloc bladder resection for colorectal carcinoma [163]. There were 58 primary and 12 recurrent tumors in the series. Median survival was 34 months in patients with negative surgical margins and 11 months for patients with positive margins. There were no 5-year survivors. A more recent series by Carne et al [164], retrospectively evaluated 53 patients who had secondary involvement of the bladder with a colorectal cancer over a 15-year period. The most common site of the primary tumor was the sigmoid colon [46/53], with the remainder invading from the rectum [2/53], the ascending colon [4/53], and the transverse colon [1/53]. All 4 patients undergoing blunt dissection of the tumor from the bladder, without resection of the involved bladder, developed local recurrences and subsequently died of their disease. There were no local recurrences in 4 patients undergoing total cystectomy and 3 of the 4 patients with follow-up were alive, 2 without and 1 with disease. Finally, in the 45 patients who underwent partial cystectomy, there were a total of 8 (19%) local recurrences. The authors emphasized the importance of obtaining frozen sections of the resection margins at the time of partial cystectomy. However, whether frozen sections were taken in the patients who had local recurrences was not reported.

TREATMENT RECOMMENDATIONS

• The treatment of adenocarcinoma depends upon its subclassification. Primary adenocarcinoma is poorly responsive to radiation and chemotherapy and should be treated with radical cystectomy (Grade B).
• Urachal adenocarcinoma should be treated with en bloc resection of the urachus and umbilicus with partial or radical cystectomy (Grade B).
• The incidence of adenocarcinoma is much higher in exstrophy patients. Any patient with bladder exstrophy who has retained his or her bladder should be closely followed, though an exact regimen cannot be defined based on currently-available evidence (Grade C).
• Patients with metastatic primary or metastatic urachal adenocarcinoma of the bladder should be considered for enrollment into a clinical trial using 5-FU based chemotherapy (Grade C).
• In patients with locally advanced colonic or rectal tumors that secondarily involve the bladder, patients may undergo complete resection of the involved portion of the bladder, either with partial cystectomy and verified negative margins or radical cystectomy (Grade B).
V. SMALL CELL CARCINOMA

1. EPIDEMIOLOGY

Primary small cell carcinoma is a neuroendocrine tumor that is rare, with just under 300 cases reported in the English-language literature. Despite this, this histologic subtype accounts for 0.48-0.7% of all cases of primary bladder tumors [165-169].

The incidence of small cell carcinoma appears to be increasing in the United States. A recent review of SEER data identified 642 cases of small cell carcinoma of the urinary bladder between 1991 and 2005 [169]. During that time period, there was a 300% increase in the incidence of this tumor, from 0.05 to 0.14 cases per 100,000 population. Additionally, relative to all other bladder tumors, small cell carcinoma increased from 0.3% to 0.6% of all histologic types of bladder cancer.

2. CLINICAL FEATURES

Most of the data regarding the clinical features of small cell carcinoma of the bladder is derived from only a few series and case reports. The vast majority of patients diagnosed with small cell carcinoma are male, with a propensity for it to affect patients in their late 60s and early 70s [169-171]. Caucasians account for 90% of patients with small cell carcinoma in the SEER-cancer registry [169].

Similar to other bladder malignancies, hematuria is the presenting complaint in close to 90% of patients [171,172]. On occasion, paraneoplastic syndromes may herald the diagnosis [173,174].

Small cell carcinoma usually cannot be visually distinguished from urothelial carcinoma on cystoscopy. Urine cytology may be helpful in providing a suspicion of small cell carcinoma. A retrospective analysis of 29 urine specimens from patients diagnosed with small cell carcinoma showed that 56% could be diagnosed by urinary cytopathology [175]. The other cases were interpreted as high grade urothelial carcinoma. Five patients had both small cell carcinoma and urothelial carcinoma.

At the time of presentation, 90% of patients with small cell carcinoma have muscle-invasive disease, approximately 50% have T3 or T4 disease [169], and 24-67% have metastases [169,170]. Small cell carcinoma metastasizes most commonly to lymph nodes, liver, bone, lung, and brain [170].

3. PATHOLOGIC FEATURES

Microscopically, small cell carcinoma of the bladder resembles small cell carcinoma of the lung. The tumor is comprised of a population of relatively uniform cells with scant cytoplasm and hyperchromatic nuclei. This gives a characteristic appearance of round blue cells under the microscope with routine hematoxylin and eosin staining. Frequent mitotic figures and extensive necrosis are common in small cell carcinoma, and are indicative of its often aggressive behavior [176].

The diagnosis of small cell carcinoma may be confirmed by immunohistochemical stains for neuron-specific enolase, chromogranin A, and synaptophysin [168, 177]. In more complex cases, additional immunohistochemical stains for pan-cytokeratin and p63 may be needed to distinguish it from urothelial carcinoma [177].

A number of studies have shown that small cell carcinoma exists as either pure small cell carcinoma or in combination with urothelial carcinoma [170-172]. Rarely, small cell carcinoma may coexist with squamous cell carcinoma or adenocarcinoma [171, 178]. The implications of this are that in pure small cell carcinoma, the chemotherapeutic regimen should be specifically directed to small cell carcinoma. Extremely poor responses have been noted in those patients treated with regimens that are specific for urothelial carcinoma (MVAC or taxol, methotrexate, and cisplatin) [179].

4. TREATMENT

Local treatment with either radiation therapy [170] or surgery alone [170, 171,179] yields very poor results in patients with clinically localized small cell carcinoma of the bladder. Based upon the treatment paradigm developed for small cell lung cancer, primary chemotherapy followed by either radiation therapy or cystectomy seems to provide the optimal means of managing patients with this tumor [180-184]. Based upon the chemotherapeutic regimen used for small cell lung cancer, the agents used are etoposide and cisplatin, possibly alternating with ifosfamide and doxorubicin.

a) Chemotherapy and cystectomy

In the small series reviewed by Sved et al [170], 13 of 18 patients who underwent cystectomy plus chemotherapy were alive at a mean of 27 months. Similarly, Walther [165] reported favorable response rates in seven patients treated with systemic etoposide and cisplatin in neoadjuvant and adjuvant protocols. In a retrospective analysis from MD Anderson Cancer Center, median and 5-year disease-free survival was significantly improved in patients who received preoperative chemotherapy [179]. In this study, 5-year survival was 36% for 25 patients who underwent cystectomy alone compared with 78% in those who received preoperative chemotherapy. Interestingly, an evaluation of the surgical specimens indicated that 10/12 patients receiving a regimen directed towards small cell carcinoma (either etoposide and cisplatin or ifosfamide and doxorubicin) had no residual tumor in the bladder versus 3 of 9
patients receiving chemotherapy directed towards urothelial cancer (MVAC or taxol, methotrexate, and cisplatin).

b) Chemotherapy and radiation therapy

Radiation therapy has been used as an alternative to cystectomy in many centers, and seems to provide comparable results when used with neoadjuvant chemotherapy. In the largest series to date, 17 patients with localized small cell bladder cancer were treated over a 14-year period using platinum-based chemotherapy followed by radiation therapy to 56-70 Gy [184]. The median overall survival was 32.5 months, with 88% of patients showing an initial complete response. In another retrospective study evaluating 10 patients, the 2- and 5-year survival rates in patients treated with chemotherapy and radiation were 70% and 44%, respectively [185]. Of note, local recurrences warranting surgery have occurred with this approach [184].

c) Chemotherapy alone

This is primarily used in patients with metastatic disease. Similar to small cell lung cancer, there is an initial response seen in most patients. In a phase II trial evaluating 30 patients with metastatic small cell bladder cancer [185], 72% of patients had a complete response, and 28% of patients had a partial response. The durability of the responses is short-lived, however, as the median overall survival with this disease is between 5 and 13.3 months [184,186].

Second line therapy has been evaluated in isolated case reports using vinorelbine [187]. Prophylactic brain irradiation has also been evaluated, but limited data is available. [185,188]

CONCLUSIONS

Small cell carcinoma of the bladder is an aggressive disease that often presents in advanced stages. Because of the rarity of this lesion, evidence is limited. Aggressive multimodal therapy is warranted, yet altogether this subtype of bladder cancer carries a dismal prognosis.

VI. OTHER BLADDER TUMORS

1. BLADDER SARCOMA

Malignant soft tissue tumors represent the most common histologic type of the non-epithelial bladder tumors. Half of bladder sarcomas are leiomyosarcoma, 20% are rhabdomyosarcoma, and the remainder are angio-, osteo-, and carcinosarcoma [189]. The histological pattern of leiomyosarcoma is characterized by interwoven bundles of spindle-shaped cells. The incidence is higher in patients with previous local radiation treatment or systemic chemotherapy [190]. Most patients present with hematuria, and the diagnosis is made early. The majority of the tumors are high grade and may attain very large size before recognition (see Figure 6). Tumor grade is established on the basis of mitotic rate and proliferation indices rather than nuclear atypia [190]. The preferred treatment for localized disease is radical cystectomy with negative margin resection. In the largest series to date, encompassing 10 patients, the 5-year survival rate was 80%. Metastatic sarcomas are treated with multimodality protocols. Doxorubicin and ifosfamide are the most active single agents available [191].

2. CARCINOSACROMA AND CARCINOMATOID TUMORS

Carcinosarcoma is a rare type of primary tumor composed of an admixture of malignant epithelial (carcinoma) and malignant soft tissue elements (sarcoma). The term sarcomatoid has been used to describe a malignant spindle cell tumor with epithelial differentiation [192]. In a series of 41 patients, Lopez-Beltran reported that both carcinosarcoma and sarcomatoid tumors had similar presentations [192]. The most common epithelial component was urothelial in both types. Most patients had locally advanced tumors at the time of diagnosis. Despite aggressive surgical management, the outcome is poor. Treatment failure occurs within 1 to 2 years following treatment [192]. Metastatic disease showed a favorable response to cisplatin and gemcitabine [193].

3. PARAGANGLIOMA AND PHEOCHROMOCYTOMA

These are extra-adrenal neoplasms derived from neural crest cells. Bladder pheochromocytoma accounts for 0.05% of bladder tumors. It may be derived from embryonic rests of chromaffin cells in the detrusor sympathetic plexus. It accounts for 10% of extra-adrenal pheochromocytoma. Malignancy was demonstrated in 10% and characterized by local invasion, regional lymph node metastases, or distant spread. Bladder pheochromocytoma may be hormonally active and presents with attacks of paroxysmal hypertension, headaches, palpitations, blurred vision, and sweating associated with the act of micturition [194]. If the disease is suspected, cystoscopy should be performed under adrenergic blockade in the operating room. The gross appearance is often a solitary, submucosal, or intramural nodule. Biopsy should be avoided. The diagnosis depends on CT scan or MRI for anatomical location and the extent of the lesion. Isotopic scanning using ¹³¹iodine metaiodinebenzylguinidine (MIBG) is the study of choice for localizing small pheochromocytomas with more than 90% specificity [195]. Positron emission tomography was recently used with high sensitivity as well [194].
The standard treatment is local excision via partial cystectomy combined with pelvic lymph node dissection. The surgery is employed under the same precautions as in adrenal pheochromocytoma with controlled adrenergic blockade.91

It may be difficult to distinguish benign and malignant lesions if the disease is localized. Lifelong follow-up is important as the malignant pheochromocytoma may show local recurrence with or without metachronous metastases.

4. BLADDER PSEUDOTUMORS

Bladder pseudotumors are rare and may resemble malignancy. The etiology and histogenesis remain unclear. Some of these lesions present as “postoperative spindle-cell tumors.” It may be difficult to distinguish them from leiomyosarcoma on a histopathologic basis [196]. However, absence of significant nuclear atypia, less than three mitotic figures per high power field, and presence of spindle cells with myxoid degeneration and eosinophilic cytoplasm favor pseudotumor. Some tumors may show a fascicular growth pattern with deposition of interstitial collagen [197]. Local recurrence or distant metastases are rare following tumor excision. If the diagnosis is clear, transurethral resection or partial cystectomy is sufficient. Radical cystectomy may be required if the diagnosis is difficult to distinguish from bladder sarcoma.

5. MELANOMA

Primary bladder melanoma is very rare. It affects the urethra more than the bladder. Secondary melanoma of the bladder was found in patients with widespread metastatic melanoma of the skin [190, 198]. The patient’s history and careful examination of the skin is essential to confirm the primary nature of the tumor. The histologic picture of bladder melanoma is similar to other melanomas. It is composed of large malignant cells arranged in nests with variable amounts of pigments. The cell origin of bladder melanoma is undefined. Treatment of primary bladder melanoma is radical surgery. The prognosis is poor [199, 200].

6. LYMPHOMA

Bladder lymphoma is usually a part of metastatic spread of systemic disease. Primary lymphoma is very rare. Microscopic analysis shows diffuse infiltration of lymphoid cells into the normal structures of the bladder [201]. Primary lymphoma is more common in women [202]. It is mostly localized and of low grade with good prognosis [201]. Local irradiation is the recommended treatment with a high recurrence-free survival [201, 202].

VIII. SUMMARY OF THE RECOMMENDATIONS

Squamous Cell Carcinoma

Patients with SCI should be aware of the risk of development of SCC. A surveillance schedule, however, cannot be determined from the currently available evidence. (Grade D)

Cystectomy is the best primary therapy for SCC,
whether it is related to schistosomiasis or is not associated with schistosomiasis (Grade B).

Neoadjuvant chemotherapy or radiation therapy prior to cystectomy for SCC is not advisable, given the information available to date (Grade D).

In patients with metastatic disease, epirubicin-based chemotherapy regimens offer a higher likelihood of an initial complete response than other agents. The long-term survival benefits remain to be determined (Grade A).

Adenocarcinoma

Patients with bladder extrophy who have retained their bladders should be closely followed, but no particular regimen can be recommended on the basis of currently available evidence (Grade D).

Patients with primary adenocarcinoma of the urinary bladder should be treated with radical cystectomy, when possible (Grade B). There is no role for neoadjuvant radiation or chemotherapy, based upon the available literature (Grade D).

Patients with urachal adenocarcinoma should be treated with en bloc excision of the urachus and the umbilicus with either partial or radical cystectomy (Grade B).

Patients with metastatic adenocarcinoma of the bladder should undergo complete resection of the involved portion of the bladder, with partial cystectomy with verified negative margins or with the use of radical cystectomy (Grade B).

Small Cell Carcinoma

When small cell carcinoma is identified on a TURBT specimen, the patient should undergo a full metastatic work-up including a CT of the abdomen and pelvis, a bone scan, a chest x-ray, and a neurologic examination. (Grade C)

Patients with small cell carcinoma of the urinary bladder require aggressive combination therapy to achieve cures, such as combined chemotherapy and radical cystectomy or chemotherapy and radiation therapy. (Grade B)

Bladder Sarcoma

Patients with bladder sarcoma should be treated with radical cystectomy with negative surgical margins (Grade C).

Those with metastatic sarcoma should be treated with a multimodality protocol (Grade C).

Carcinosarcoma and Sarcomatoid Tumors

Carcinosarcoma and sarcomatoid tumors have a poor prognosis and surgical management is inadequate. Multimodality therapy is recommended (Grade C).

Paraganglioma and Pheochromocytoma

The standard treatment for patients with paraganglioma and pheochromocytoma is partial cystectomy with pelvic lymphadenectomy, with the same precautions taken as for any other pheochromocytoma with preoperative adrenergic blockade (Grade C).

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ICUD Guidelines on Bladder Cancer: Diagnosis and Evaluation

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• A group of 17 experts from 5 countries
  – thoroughly assessed 125 references related to diagnosis and screening of bladder cancer
  – > 250 page document
• No new level 1 or 2 studies since last ICUD guidelines published
  – Most reports level 3 or 4, few level 2b
• Most recommendations are Grade C
  – some B and D
Screening Recommendations

• Bladder cancer screening is not helpful in improving survival (Grade C)
• If undertaken, screening should be confined to high risk patients (Grade C).
• Screening in high-risk can consist of annual cytology & dipstick (Grade C).
  – Further studies of screening are warranted
Hematuria

• No correlation between degree of hematuria & diagnosis of bladder cancer (Grade B).
  – Microscopic hematuria is variable & intermittent in bladder cancer

• Lack of hematuria on a single urinalysis does not exclude bladder cancer (Grade C).
Evaluation

- Imaging of the upper tracts necessary in investigation of hematuria (Grade B).
- For asymptomatic microscopic hematuria without risk factors for urothelial carcinoma, urine cytology or cystoscopy can be used (Grade B).
- In patients with irritative voiding symptoms and hematuria, carcinoma in situ (CIS) must be ruled out (Grade C).
Cystoscopy and Cytology

• Cystoscopy alone is the most cost effective method to detect recurrence of bladder cancer (Grade C).

• Among urinary markers, urine cytology is the gold standard for surveillance (Grade B).

• Cytopathologists should use uniform nomenclature (Grade C).
Cystoscopy and Cytology

- Bladder wash cytology provides better diagnostic yield than voided urine cytology (Grade B).
- At cystoscopy minimal manipulation should be performed prior to bladder wash. Residual urine mixed with bladder lavage specimen should be sent for cytology (Grade D).
Cytology

- For follow-up urine cytology is most useful for diagnosis of high-grade tumor recurrence (Grade B).
- Cytology valuable for differentiating high-grade from low-grade urothelial carcinomas (Grade B).
- No consensus on other urinary markers in the diagnosis of bladder cancer (Grade D).
- Markers – eg FISH – may be most useful in the setting of a negative cystoscopy and atypical cytology. (Grade C).
Endoscopic Techniques

• White light cystoscopy (WLC) is the gold standard for evaluation of the lower urinary tract (Grade B).

• Fluorescence cystoscopy
  – improves the rate of detection of CIS (Grade B).
  – decreases risk of residual tumor after TURBT (Grade B).
  – useful for positive cytology but negative findings on WLC (Grade C).
Imaging

• Imaging of the upper tracts necessary in investigation of haematuria (Grade B).

• CT urography most useful
  – intravenous urography, regular CT, ultrasound & MRI are options (Grade C).

• Imaging for staging should be obtained prior to TURBT
  – or >2 weeks after TURBT to avoid artifacts (Grade C).
Imaging

- CT & MRI not accurate for staging of primary bladder tumors but may be demonstrate metastatic disease (Grade B).
- With invasive bladder tumors, metastatic work-up includes chest radiography, liver function tests, and alkaline phosphatase measurement (Grade C).
- Bone scan for patients with bone pain or elevated alkaline phosphatase concentration (Grade B)
Technique

- Insufficient information to support specific energy modality for TURBT (Grade D).
- Patients undergoing TURBT should be given appropriate prophylactic antibiotics (Grade B).
Technique of TURBT

• Document shape, size & location of the tumor (Grade C).

• Document appearance base of the tumor (Grade C).
  – these details provide important prognostic information

• Obtain separate tumor base & margin biopsies for larger tumors (Grade C).

• Attempt complete tumor resection except in patients with diffuse CIS (Grade C).
Technique

• If ureteral orifice is resected,
  – cutting current should be used.
  – Functional study should be performed 3-6 weeks later (Grade C).

• Diverticulum
  – Aggressive resection risks perforation.
  – Low-grade, noninvasive tumors may be treated TUR or fulguration with or without intravesical therapy (Grade C).
A second TURBT should be performed in all patients with a high-grade T1 lesion or select HG Ta lesion (Grade B).

The optimal timing of repeat TURBT is 4-6 weeks after the first resection (Grade C).
Technique: Random Biopsies

• Not routinely recommended (Grade C).
• Indicated in
  – Patients with positive findings on urine cytology & normal cystoscopy (Grade B).
  – Candidates for partial cystectomy (Grade C).
Prostatic Urethral Biopsy

- Indicated in cases of multifocal urothelial carcinoma of the bladder, CIS & visible abnormalities of the prostatic urothelium (Grade B).
- Prostate biopsy not useful in counselling patients for neobladder, but useful in identifying cT4 disease (Grade C).
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INTERNATIONAL CONSORTIUM FOR UROLOGIC DISEASES – EUROPEAN ASSOCIATION OF UROLOGY
INTERNATIONAL CONSULTATION ON BLADDER CANCER 2011:
CONSENSUS GUIDELINES BY THE PATHOLOGY OF BLADDER CANCER WORK GROUP

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And
Members of the Pathology of Bladder Cancer Work Group

Vienna Austria, March 18, 2011

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What’s New in this Consensus Offering?:
An Update on:

• The knowledge of the histoanatomy of the bladder as it pertains to the diagnosis and staging of bladder cancer
• The prognostic significance of histologic grading by the WHO (2004)/ISUP system, its contributions, shortfalls and opportunities for refinement
• The information needed from the clinicians by the pathologist in order to provide optimal pathologic reporting of bladder cancer
• On nomenclature for inverted lesions of the bladder
What’s New in this Consensus Offering?: An Update on:

- The histologic types of bladder cancer and the variants of urothelial cancer, some relatively recently described, with a focus on definition for diagnosis and their implied clinico-pathologic significance

- Role of immunohistochemistry and molecular studies in contemporary routine practice diagnosis, prognostication or prediction of bladder cancer

- The reporting of bladder cancer in transurethral resection of bladder tumors (TURBT) and cystectomy specimens
Urothelial denudation

- Seen with instrumentation with CIS
- Extensive or complete denudation in a bladder biopsy should be reported as correlation with concurrent cytology results may yield a positive diagnosis of malignancy in the patient
Urothelial hyperplasia

- Papillary or flat
- Thickened urothelium without cytologic atypia
- Flat hyperplasia may be seen adjacent to low grade papillary tumors
- Papillary hyperplasia is suggested to be a precursor lesion for a subset of papillary urothelial neoplasms
Squamous Metaplasia

- Should be reported and specified whether keratinizing or not and whether focal or multifocal
- Current evidence does not support any precursor potential with focal changes, although multifocal and/or extensive lesions precede or may be associated concurrent with neoplasia
Glandular Metaplasia

- Cystitis cystica & cystitis cystica glandularis are proliferative lesions
  - They may be associated with intestinal metaplasia

Glandular metaplasia is not a risk factor for adenocarcinoma or UCa
- Multifocal disease
- Metaplasia with dysplastic changes
  - Associated with risk for adenocarcinoma
pT1 – invasion into the lamina propria
67-75% 5-year survival

pT2 – invasion into the m. propria
60-63% 5-year survival

pT3 – invasion into the perivesical fat
31-50% 5-year survival

pT4 – invasion of adjacent organs
10-25% 5 year survival
Muscularis Mucosae Muscle

- Hyperplastic Muscularis Mucosae:
  - Patterns frequently observed but exceed thickness of previously described MM

- To avoid confusion in diagnosis, documentation of “MM-only invasion” by carcinoma is not recommended in the main pathologic diagnosis, and should be reported as “urothelial carcinoma with lamina propria invasion (at least pT1)

- Involvement of MM may be included in a comment to provide information on depth/extent of invasion
M. mucosae muscle patterns

Typical
Wispy or thin muscle bundles

Variant
Hypertrophic MM muscle
Muscularis Propria

• Several terms are currently being used to describe both MP (deep muscle, muscle proper or detrusor muscle) and MM (superficial muscle). These terms are not recommended and use of standardized nomenclature of “MP muscle bundles” is recommended.

• It is important to document the presence or absence of MP in a biopsy irrespective of involvement.

• Some institutions recommend not mentioning the presence or absence of MP in low grade tumors and require documentation in high grade tumors only.
Muscularis Propria

- In cystectomy specimens, a more objective and reproducible anatomical or extent of disease criterion is needed between pT2a and pT2b subcategories.
- Substaging of pT2 disease and recognition of pT3 disease is not tenable in TURBT specimens.
Documenting Amount of Muscularis Propria in Specimen

- Formal studies are lacking
  - Amount of MP included in the specimen (isolated and rare versus established groups)
  - MP in the area of the tumor or not in the vicinity
- Information may be useful in the management of invasive cancer
- Inclusion of the information is optional but may be communicated in a multidisciplinary setting
Muscle Involved by UCa, Indeterminate Type

- Muscle bundles indeterminate between MM and MP should be reported with terminology such as "invasive urothelial carcinoma with invasion of muscle, indeterminate type" to prompt the urologist for a restaging biopsy procedure.
Adipose Tissue

- Adipose tissue is frequently present in the LP and MP of the urinary bladder, usually scant in the former and abundant in the latter.
- Involvement of adipose tissue by tumor in biopsy or TURBT specimens should not be automatically interpreted as pT3 disease.
- There is limited reliability of pT3a vs pT3b subcategorization as gross involvement of perivesical fat (extravesical fat) may not always be readily recognizable and may be mimicked by reactive changes.
Assessment of pT2 vs. pT3 – cystectomy alone
Lamina Propria Invasion

- There are problems with interobserver reproducibility in the diagnosis of early LP invasion
- When early invasive urothelial carcinoma is suspected, diagnosis through examinational of additional levels, or in a consensus manner either with other pathology colleagues or thru quality assurance meeting is encouraged
Microinvasive Urothelial Carcinoma

• To diagnose early invasion, stringent criteria such as: only focal invasion, less than 1 high power field, or 0.5 mm from the nearest basement membrane, should ideally be employed.

• Studies are needed to establish a clinically significant definition of microinvasive urothelial carcinoma. Until there is understanding of the definition, it is recommended that only stringent criteria be used or the term microinvasive carcinoma not be used.
Substratification or Substaging of Lamina Propria Invasion (pT1)

- Depth of invasion may be established either:
  - Up to MM: \( \text{pT1a} \) or beyond the MM or vascular plexus: \( \text{pT1b} \);
  - Up to MM: \( \text{pT1a} \), in to MM: \( \text{pT1b} \), or beyond the MM or vascular plexus: \( \text{pT1c} \)

- Currently substaging is not recommended due to the lack of widely accepted and reproducible criteria although there is much need for such studies

- It is recommended for the pathologist to provide an estimate of the LP invasion in pT1 tumors with respect to depth and/or quantity of invasion (e.g. focal, multifocal, extensive, etc.)
Minimal (micro) invasion
Extensive invasion
Grading of Urothelial Carcinoma

- The non-invasive urothelial lesions and neoplasms can be flat, papillary (exophytic) and inverted (endophytic). All 3 growth patterns may be seen in a single tumor.

- The World Health Organization (WHO) (2004) / International Society of Urologic Pathologists (ISUP) classification system is the recommended system. It has also been endorsed by the WHO 2004 Blue Book, the 4th Series Armed Forces Institutes of Pathology Fascicle on Bladder and the 7th edition AJCC Cancer Staging Manual.
WHO (2004)/ISUP Grading System

Flat Lesions:
- Normal
- Hyperplasia
- Reactive
- Dysplasia
- CIS
- Atypia of unknown significance

Papillary Lesions:
- Non invasive
  - Papilloma
  - PUNLMP
  - Low grade
  - High grade
- Invasive
  - High grade
  - Low grade (rare)

Inverted Lesions:
- Non invasive
  - Papilloma
  - PUNLMP
  - Low grade
  - High grade
- Invasive
  - High grade
The diagnosis of papillary urothelial neoplasia is made on the basis of the presence of a fibrovascular core.

Grading is performed based primarily on cytology & some architectural features.
Inverted Neoplasms

- Papillary tumors may be associated with a variable degree of inverted growth patterns; although focal areas of inverted growth are not uncommon, prominent or exclusive inverted growth is much rarer and when encountered may pose problems related to grading or assessment of invasion.

- From the clinical standpoint during cystoscopy, inverted tumors made be polypoid, dome-shaped or frequently raise the suspicion of invasive urothelial carcinoma.
Exophytic tumor  Inverted tumor

Courtesy R. Montironi, Italy
Inverted High Grade without invasion

Inverted High Grade with invasion
Urothelial Dysplasia

- Overall features are those of a neoplastic atypia but which fall short of the criteria for CIS; dysplasia is not further graded.
- There is some evidence, largely genetic, that dysplasia shares some abnormalities with CIS and therefore likely represents a precursor lesion.
- Few studies, most dated, indicate a 5-19% risk of developing cancer.
Urothelial Dysplasia

- The diagnosis of de novo dysplasia (i.e. in a patient without history of bladder neoplasia) should not be made or should be made with great caution as the vast majority of patients, in the limited studies, do not progress to cancer.

- While dysplasia likely represents a marker of urothelial genetic instability, the diagnosis should not by itself invoke any therapy; continued surveillance is recommended.
UROTHELIAL DYSPLASIA
Urothelial CIS

- Biologically, therapeutically and prognostically significant flat lesion
- There is a spectrum of nuclear and architectural atypia. CIS defined by WHO (2004) / ISUP includes cases diagnosed previously as severe dysplasia and even some cases previously diagnosed as moderate dysplasia
- Development of invasion is seen in 20 to 30% of the cases
### WHO (2004) / ISUP: Prognostic Significance

<table>
<thead>
<tr>
<th></th>
<th>Papilloma</th>
<th>PUNLMP</th>
<th>LG pap ca</th>
<th>HG pap ca</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence</td>
<td>9-18</td>
<td>17-62</td>
<td>34-78</td>
<td>34-74</td>
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<tr>
<td></td>
<td></td>
<td>(34)</td>
<td>(50)</td>
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<tr>
<td>Grade progression</td>
<td>2%</td>
<td>11</td>
<td>7-12</td>
<td>-</td>
</tr>
<tr>
<td>Stage progression</td>
<td>0</td>
<td>0-4</td>
<td>3-18</td>
<td>27-61</td>
</tr>
<tr>
<td>Survival</td>
<td>100</td>
<td>93-100</td>
<td>82-96</td>
<td>65-90</td>
</tr>
</tbody>
</table>

- Does not predict risk at individual patient level
- Need for incorporation with other clinical parameters in nomograms to provide personalize risk stratification
Contributions of WHO (2004) /ISUP

- Establishment of uniform terminology and common definitions for papillary neoplasms
- Establishment of detailed criteria of various preneoplastic conditions and various grades of tumor
- Correlation with urine cytology terminology, facilitating cyto-histologic correlation and making it easier for urologists to manage patients
- Creation of a category of tumor that identifies a tumor with a negligible risk of progression (PUNLMP), whereby patients avoid the label of having cancer which has psychosocial and financial implications. Neither is a benign lesion (papilloma) diagnosed in these patients, so they may still be followed up closely.
Contributions of WHO (2004) /ISUP

- Identification of a distinct group of patients (high-grade papillary UCa) who would be ideal candidates for intravesical therapy
- Removal of ambiguity in diagnostic categories in WHO 1973 system (e.g., TCC grade 1-2, TCC grade 2-3)
- Stratification of bladder tumors into prognostically significant categories
- Emergence of molecular correlates for high grade tumors and tumors at the low-grade end of the spectrum which may help provide ancillary grading tools, and possibly guide in future refinements of the current grading system
Grade heterogeneity is not uncommonly encountered in papillary urothelial neoplasia.

There are studies showing that pure HG papillary U Ca has a higher disease progression rate than tumors with mixed high-grade and low-grade areas.

The WHO (2004)/ISUP system recommends grading of heterogeneous tumors to be based on the highest grade present in a tumor.
Grading Papillary Urothelial Neoplasm with Histologic Heterogeneity

• There is no current widely acceptable definition or criteria to provide quantitative estimate of size of smallest focus required to “upgrade” a lesion.

• Studies are needed to establish quantitative/semi-quantitative criteria that need to be present to alter assignment of grade in tumors with grade heterogeneity.
Grading Papillary Urothelial Neoplasm with Histologic Heterogeneity

- The distinction between PUMLMP and low grade papillary U Ca is not that critical in an individual patient.
- Distinction of low grade from high grade carcinoma is more important.
- When assigning the tumor grade in tumors with borderline grade histology, other tumor parameters such as multifocality, previous grade of the tumor, size of lesions, frequency of recurrence, presence of concurrent CIS, positive cytology may be factored in the grading.
- Currently, no reliable or acceptable IHC or molecular markers to assist in grading.
Papillary Hyperplasia with Cytologic Atypia

- Terminology used when criteria of papillary neoplasia are not fulfilled but there is a background of cytologic atypia
  - Dysplasia with early papillary formations
  - CIS with early papillary formations
- Usually occurs in the backdrop of treatment setting
- These terms are only descriptive diagnoses and outcome studies are not available
CIS with early papillary features
Dysplasia with early papillary features
Grading Invasive Cancer

Practice in the United States

• Almost all cases, once diagnosed as invasive, are called high grade
• Exceptionally rare cases are called low grade including variants such as nested variants
• Most studies show that once invasive, depth of invasion is more important
Grading Invasive Cancer

Practice in the Europe

- Further grading of high grade (WHO 2004/ISUP system)
  - G2 and G3 categories (of WHO 1973 system)
- Incorporated into algorithms such as the EORTC system
- Criteria for distinction of G2 versus G3 not well defined but studies show prognostic significance in at least pT1 tumors
Conventional Urothelial Ca
# Histologic Variants of Bladder Cancer

<table>
<thead>
<tr>
<th>Prognosis:</th>
<th>Therapy:</th>
<th>Diagnosis:</th>
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<tbody>
<tr>
<td><strong>Aggressive</strong></td>
<td><strong>Sarcomatoid Ca</strong></td>
<td><strong>Nested variant</strong></td>
</tr>
<tr>
<td>• Micropapillary</td>
<td>• Small cell</td>
<td>• UCa with small tubules</td>
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<tr>
<td>• Small cell</td>
<td>• Large cell</td>
<td>• Plasmacytoid UCa</td>
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<tr>
<td>• Sarcomatoid</td>
<td>• Neuroendocrine</td>
<td>• UCa with clear cell features</td>
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<tr>
<td>• With rhabdoid</td>
<td>• Lymphoepitheliomatoid</td>
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<tr>
<td>• Signet ring adenocarcinoma</td>
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<tr>
<td>• Giant cell carcinoma</td>
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<tr>
<td><strong>Favorable</strong></td>
<td><strong>Micropapillary</strong></td>
<td></td>
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<tr>
<td>• Pure LELC</td>
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<tr>
<td>• Verrucous Ca</td>
<td></td>
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<tr>
<td>• Carcinoid tumor</td>
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</table>
Histologic Variants of Bladder Cancer

- Bladder carcinoma can demonstrate many different morphologies; major categories include urothelial carcinoma, squamous cell carcinoma, adenocarcinoma and small cell carcinoma.
- All forms of bladder carcinoma originate from changes in the overlying urothelium.
- Urothelial carcinoma is the most common category of bladder carcinoma, comprising approximately 95% of all bladder carcinomas.
- Urothelial carcinoma may be subdivided into conventional and variant subtypes.
Histologic Variants of Bladder Cancer

- Variant forms include the 15 subtypes; it remains unclear what percentage of variant form impacts survival in most cases
- Most variants often admixed with conventional UCa, squamous or glandular differentiation
- Level I evidence is limited for most bladder carcinoma variants, given their relative rarity. Prospective or consecutive cases studies in large series evaluating the impact of various histologic variants on outcome or therapy have not yet been performed
Histologic Variants of Bladder Cancer

• The percentage of variant component required to make a diagnosis of a particular variant is not defined.

• When mixed with conventional or other variants of U Ca, the relative percentages of the different histologies must be specified.

  • e.g. “U Ca with micropapillary histology (40%), conventional U Ca histology (50%) and with squamous differentiation (10%)”
Papillary tumor

Micropapillary U Ca
Micropapillary UCa
Sarcomatoid UCa

Small cell Ca
Plasmacytoid UCa

Lipoid-rich UCa
UCa with Squamous and Glandular Differentiation

- Controversial and limited data
- Some studies have shown a worse prognosis when compared with pure urothelial cancer
- Others show no differences between stage matched cohorts
- The presence of divergent differentiation in a TURBT may predict locally advanced cancer at cystectomy
Squamous Cell Carcinoma

- **Invasive squamous cell carcinoma**
  - Schistosomosal
  - Non-schistosomosal

- **Verrucous carcinoma**
  - Should be pure in morphology
  - If associated with destructive invasion, should be classified as squamous cell carcinoma invasive with verrucous features
Molecular Subtyping of UCa

• There are promising emerging tests which have the potential to impact prognostication and prediction to therapy in UCa
• Prospective studies determining their efficacy and best practices for performing the tests are underway (e.g. the UROMOL study in Europe investigating and validating gene expression profile)
• Further studies need to be defined for professional and technical quality assurance and optimal patient care
IHC Markers in Staging UCa

Smoothelin

- Contractile protein
- Fully differentiated muscle cells
- Hyperplastic muscularis mucosae (-) to weak
- Diffuse positivity in muscularis propria

• Caution: Susceptible to variation in antibody titer
• Must be interpreted in the context of morphology
Reporting of Bladder Cancer

- Guidelines: CAP and European Society of Uropathology etc.
- Reporting in synoptic pattern is preferred
- Clinical information important for pathology diagnosis
  - Cystoscopic impression
  - Previous history of bladder cancer
  - Previous history of therapy (intravesical or systemic)
  - History of stones, indwelling, catheter, etc.
- A deeper bite for assessment of MP involvement in TURBTs should be preferably submitted separately, for larger tumors
Reporting at Cystectomy

**No residual cancer in cystectomy:**
- ? pT0 or pT2 (if TURBT showed muscle invasive disease)
- By AJCC 6th edition: pT2
- Studies in literature have shown “pT0” (no tumor at cystectomy) have better prognosis than pT2 tumor at cystectomy
- Need conference multidisciplinary input to resolve reporting tumor (-) cystectomies
Reporting of Bladder Cancer

- Minimum number of lymph nodes in cystectomy not established
- Size of largest metastatic focus and extranodal extension, if present should be documented
- Frozen section is not an optimal method for a primary diagnosis of invasive urothelial carcinoma or to perform pathologic staging prior to a cystectomy
Chapter 3: Biological Markers

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Disclosures

Patents

• Method to determine prognosis after therapy for prostate cancer
  Granted 2002-09-06

• Methods to determine prognosis after therapy for bladder cancer
  Granted 2003-06-19

• Prognostic methods for patients with prostatic disease
  Granted 2004-08-05

• Soluble Fas urinary marker for the detection of bladder transitional cell carcinoma
  Granted 2010-07-20
Definition of Biological Marker

- NIH definition: “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention”

- For our purposes: a biomarker is the end result of a bioassay, a laboratory technique for processing biological material from humans, expressed quantitatively or categorically

- Imaging results could also be included as a biomarker if we interpret “bioassay” broadly enough

- Measurement outcome of a biomarker:
  - binary (e.g., positive or negative)
  - categorical (e.g., high, medium, low)
  - quantitative (e.g., the level of some urine/serum protein), or
  - more complicated (e.g., a genomic signature or “metagene”)


Clinical Uses of Biomarkers

- **Clinical practice**
  - Determine the risk of developing disease
  - Early detection/screening
  - Establish diagnosis
  - Determine prognosis
  - Predict response to therapy
  - Therapeutic target
  - Monitor disease/treatment response

- **Clinical Trials**
  - Stratifying study populations
  - Conducting interim analysis of efficacy/safety
  - Applied toward regulatory approval

**Diagnostic Markers**

**Prognostic Markers**
Biomarker Conundrum for Bladder Cancer

- PubMed Search on “bladder cancer” AND (“biomarker” OR “biomarkers” OR “molecular marker” OR “molecular markers”) yields 4125 hits (3/17/2011)

- Number of biomarkers routinely used by urologists: cytology

- Why haven’t biomarkers lived up to their promise?
“A variety of issues and barriers can affect the movement of clinical tests from research to clinical practice.”
Analytical and regulatory barriers to the application of biomarkers

- Status of intellectual property protection
- Availability of standard reference materials for the assay
- Complexity of assay format
- Implementation of quality control to assure reproducibility and accuracy
- Sufficient market testing size to assess methods of commercialization
- Lack of clear guidelines for good manufacturing/laboratory practice and quality control requirements for all phases of biomarker development
- Cost and effort required to accumulate clinical data under appropriately designed, Institutional Review Board-approved prospective trials
- The interval required for resolution of patent issues, assay standardization, validation, testing, and regulatory approval

Shariat et al., Eur Urol 2007
Why haven’t biomarker studies led to translation?

- Biomarker research done in context of usual clinical care, not clinical trials
- Biomarker assays not standardized
- Most biomarkers findings not reproducible
  - Biomarkers that appear biomedically and statistically significant at one center - NOT significant in other centers
- Lack of minimal set of CDEs, use cases, metadata
- Pre-analytical variation not controlled or annotated
- Usually small, single institution studies
Bringing the ideal marker to clinical practice

- **Easier**: performed easily and promptly in a clinical environment
- **Better**: does the biomarker add to established predictors?
- **Faster**: available in an efficient and timely manner
- **Cheaper**: cost-effectiveness

*Shariat et al., Eur Urol 2008*
Roadmap to Biomarker Evaluation

- **Preclinical Exploratory**
  - **PHASE 1**: Promising directions identified

- **Clinical Assay and Validation**
  - **PHASE 2**: Clinical assay detects established disease

- **Retrospective Longitudinal**
  - **PHASE 3**: Biomarker detects preclinical disease and a “screen positive” rule defined

- **Prospective Screening**
  - **PHASE 4**: Extent and characteristics of disease detected by the test and the false referral rate are identified

- **Cancer Control**
  - **PHASE 5**: Impact of screening on reducing burden of disease on population is quantified
# Modification of the structured phase-approach to the systematic discovery, evaluation, and validation of biomarkers

<table>
<thead>
<tr>
<th>PHASE</th>
<th>GOALS/AIMS</th>
<th>EXPERIMENTATION</th>
<th>SAMPLE DETAILS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preclinical</td>
<td>Exploratory; nominate and rank candidate biomarker profiles</td>
<td>Preclinical study for hypothesis generation</td>
<td>Possible bias: small size and convenience sampling</td>
</tr>
<tr>
<td>Testing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>Develop an assay with clinically reproducible results</td>
<td>Reproducibility and robustness of assay; No assessment of benefit</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>Test on small sample to determine benefit</td>
<td>Marker optimization, establish prediction rules, determine cut-offs</td>
<td>Sample population assay developed from candidate biomarker profile</td>
</tr>
<tr>
<td>II</td>
<td>Determine operating characteristics &amp; internal validation</td>
<td>Retrospective design</td>
<td>Sample population should be the target population</td>
</tr>
<tr>
<td>III</td>
<td>External validation</td>
<td>Retrospective or prospective, Generalizability, Impact on clinical decision-making</td>
<td>Multi-institutional, large study</td>
</tr>
<tr>
<td>IV</td>
<td>Assess whether biomarker reduces the burden of disease</td>
<td>Post-approval reporting and testing for other disease processes or disease stages</td>
<td></td>
</tr>
</tbody>
</table>
Flow of Biomarkers thru Validation Funnel

Industry → BRLs → Biomarker Discovery

BRLs → Characterization (Phases 1 & 2)

Characterization (Phases 1 & 2) → Cross-sectional Study

Cross-sectional Study → Longitudinal Study

Statistically Derived Panels of Biomarkers
Introduction: State the marker examined, the study objectives, and any pre-specified hypotheses.

Materials and Methods: Patients: Describe the characteristics (e.g., disease stage or co-morbidities) of the study patients, including their source and inclusion and exclusion criteria. Describe treatments received and how chosen (e.g., randomised or rule-based).

Specimen characteristics: Describe type of biological material used (including control samples) and methods of preservation and storage.

Assay methods: Specify the assay method used and provide (or reference) a detailed protocol, including specific reagents or kits used, quality control procedures, reproducibility assessments, quantitation methods, and scoring and reporting protocols. Specify whether and how assays were performed blinded to the study endpoint.

Study design:
- State the method of case selection, including whether prospective or retrospective and whether stratification or matching (e.g., by stage of disease or age) was used. Specify the time period from which cases were taken, the end of the follow-up period, and the median follow-up time.
- Precisely define all clinical endpoints examined.
- List all candidate variables initially examined or considered for inclusion in models.
- Give rationale for sample size; if the study was designed to detect a specified effect size, give the target power and effect size.

Statistical analysis methods:
- Specify all statistical methods, including details of any variable selection procedures and other model-building issues, how model assumptions were verified, and how missing data were handled.
- Clarify how marker values were handled in the analyses; if relevant, describe methods used for cutpoint determination.

Results:

Data:
- Describe the flow of patients through the study, including the number of patients included in each stage of the analysis (a diagram may be helpful) and reasons for dropout. Specifically, both overall and for each subgroup extensively examined report the numbers of patients and the number of events.
- Report distributions of basic demographic characteristics (at least age and sex), standard (disease-specific) prognostic variables, and tumour marker, including numbers of missing values.

Analysis and presentation:
- Show the relation of the marker to standard prognostic variables.
- Present univariate analyses showing the relation between the marker and outcome, with the estimated effect (e.g., hazard ratio and survival probability). Preferably provide similar analyses for all other variables being analysed. For the effect of a tumour marker on a time-to-event outcome, a Kaplan–Meier plot is recommended.
- For key multivariable analyses, report estimated effects (e.g., hazard ratio) with confidence intervals for the marker and, at least for the final model, all other variables in the model.
- Among reported results, provide estimated effects with confidence intervals from an analysis in which the marker and standard prognostic variables are included, regardless of their statistical significance.

If done, report results of further investigations, such as checking assumptions, sensitivity analyses, and internal validation.

Discussion:
- Interpret the results in the context of the pre-specified hypotheses and other relevant studies; include a discussion of limitations of the study.
- Discuss implications for future research and clinical value.

NCI-EORTC

McShane et al., 2005
Levels of evidence for grading clinical utility of biomarkers: Tumor Marker Utility Grading System (TMUGS)

<table>
<thead>
<tr>
<th>Level</th>
<th>Type of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Evidence from a single high-powered prospective study that is specifically designed to test marker or evidence from meta-analysis and/or overview of Level II or III studies. In the former case, the study must be designed so that therapy and follow-up are dictated by protocol. Ideally, the study is a prospective randomised trial in which diagnostic and/or therapeutic clinical decisions in one arm are determined based at least in part on marker results, and diagnostic and/or therapeutic clinical decisions in control arm are made independently of marker results. However, may also include prospective but not randomised trials with marker data and clinical outcome as primary objective.</td>
</tr>
<tr>
<td>II</td>
<td>Evidence from study in which marker data are determined in relationship to prospective therapeutic trial that is performed to test therapeutic hypothesis but not specifically designed to test marker utility (i.e. marker study is secondary objective of protocol). However, specimen collection for marker study and statistical analysis are prospectively determined in protocol as secondary objectives.</td>
</tr>
<tr>
<td>III</td>
<td>Evidence from large but retrospective studies from which variable numbers of samples are available or selected. Therapeutic aspects and follow-up of patient population may or may not have been prospectively dictated. Statistical analysis for tumor marker was not dictated prospectively at time of therapeutic trial design.</td>
</tr>
<tr>
<td>IV</td>
<td>Evidence from small retrospective studies which do not have prospectively dictated therapy, follow-up, specimen selection, or statistical analysis. May be matched case controls, etc.</td>
</tr>
<tr>
<td>V</td>
<td>Evidence from small pilot studies designed to determine or estimate distribution of marker levels in sample population. May include ‘correlation’ with other known or investigational markers of outcome, but not designed to determine clinical utility.</td>
</tr>
</tbody>
</table>

Hayes et al. JNCI 1996
The only useful function of a statistician is to make predictions, and thus to provide a basis for action.

W.E. Deming

Modeling strategies

- Logistic regression
- Cox proportional hazards regression (caveat: competing risks lead to overestimation of the probability of an event)
- Recursive partitioning and regression trees
- Artificial neural networks

Shariat et al., Cancer 2008
It is NOT sufficient to show that it is:
1. significantly related to the outcome
2. statistically significant in a multivariate model including the standard clinical and pathologic factors
3. more significant than the standard clinical and pathological factors in a multivariate model

A variable that is statistically significant in a multivariate model might not improve the model’s predictive accuracy
- Odds ratio and hazard ratio do not meaningfully describe a biomarkers ability to classify patients
- Neither the p-value
Gain in predictive accuracy

It is necessary to show that adding a biomarker to an existing model based on the most important clinical and pathologic factors improves the predictive accuracy of the model.

- Does the biomarker add predictive/prognostic information to the current risk group classification?
- Does the classifier improve the predictive inaccuracy and proportion of explained variation?
- Does the classifier improve the Area Under the ROC Curve (AUC) or C-index (Concordance Index)?
A biomarker is optimal for the patients in the training set used to develop it (overly optimistic results)

Therefore biomarker-based models need to be validated on data not used to develop it:

- Internal validation on original dataset
- External validation on independent dataset (best!!!)
Statistics in marker research

- Attention to sound statistical practice
  - should be delivered as early as possible
  - will help maximize the promise of biomarkers for patient care
- Studies should include a measure of predictive accuracy
- External validation using data from a completely different study provides the highest irrefutable evidence that a model is valid
- Other issues such as over-reliance on statistical significance tests, over-fitting of models, small sample sizes, and lack of pre-specification of the validation process continue to be problematic
- Statistical methodology is an area of research

Shariat et al., Urol Oncology, 2010
Clinical States Model of Bladder Cancer

Initial Bladder Evaluation: No Cancer Diagnosis → Non-invasive UCB → Invasive UCB → Metastatic UCB

Death From Other Causes → Death From UCB

Shariat et al., Eur Urol 2003
Potential indications for marker use
- Screening (*Voiding symptoms, hematuria, risk populations e.g., occupational exposure/lifestyle*)
- Reflex testing
- Follow-up of patients with bladder cancer
Why are new markers attractive?

• Cystoscopy gold standard for diagnosis and surveillance
• Invasive, expensive, time consuming
• Up to 10% of significant lesions still missed by cystoscopy
• Cystoscopy
  – 0-2 years → Every 3 months
  – 2-4 years → Every 6 months
  – 5 years + → Annually

• Cytology
  – Obtained at time of cystoscopy

But…only 40% complete recommended surveillance protocol
Cytology

- Cells readily available in urine
- Relies on abnormal cellular morphology
- Reasonable specificity (87-95%)
- **Poor sensitivity** (12-48%)
- Higher sensitivity for high grade disease
- **Useless**: infection during intravesical Rx
- Need for **highly trained cytopathologist**
- Interpreter dependent
- Low inter- and intra-observer reproducibility

**Accuracy affected by:**
- Collection technique
- Pelvic radiation, intravesical therapy, instrumentation
- Cytopathologist
Variability of urinary cytology is very high

- Positive in 38% to 65% of recurrent UCB
- Sensitivity for grade 3: 33% to 95%
- Sensitivity for stage ≥ T2: 37% to 100%
- Accuracy from poor (63%) to excellent (89%)
  - even after adjusting for age and gender
  - regardless of tumor stage and grade
Gold Standard?

Sensitivity of Cytology (Review of Literature)

<table>
<thead>
<tr>
<th></th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
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</thead>
<tbody>
<tr>
<td>Before 1990</td>
<td>37%</td>
<td>75%</td>
<td>94%</td>
</tr>
<tr>
<td>After 1990</td>
<td>11%</td>
<td>31%</td>
<td>60%</td>
</tr>
<tr>
<td>All studies</td>
<td>21%</td>
<td>53%</td>
<td>78%</td>
</tr>
</tbody>
</table>

Halling et al. JUrol 2002
Ideal Tumor Marker

• Potential to replace, delay, or complement cystoscopy and/or cytology

• Characteristics
  - Non-invasive
  - Rapid
  - Objective
  - Reproducible
  - Cost-effective
  - Easy to perform and interpret
  - High sensitivity and specificity

• For monitoring, two different paradigms:
  - **Low risk tumors**: reduction of diagnostic cystoscopies
  - **High risk tumors**: recognition of tumor recurrence as early as possible and prevention of progression
<table>
<thead>
<tr>
<th>Test/marker</th>
<th>Marker detected/Marker type</th>
<th>Specimen</th>
<th>Assay type</th>
<th>FDA approval</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytology</td>
<td>Tumor cells</td>
<td>Voided urine</td>
<td>Microscopy</td>
<td>n.a.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Barbotage specimen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematuria detection</td>
<td>A: Hemoglobin</td>
<td>A: Voided urine</td>
<td>A: Dipstick, B: Interference-microscopy /RBC analyzer</td>
<td>-</td>
<td>A: Bayer Corp. B: -</td>
</tr>
<tr>
<td></td>
<td>B: Red blood cells</td>
<td>B: Voided urine</td>
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<td></td>
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<tr>
<td>BTA-Stat</td>
<td>Complement factor H-related protein (and also Complement factor H)</td>
<td>Voided urine</td>
<td>Dipstick immunoassay</td>
<td>Diagnosis, follow-up</td>
<td>Bard/Bion Diagnostics</td>
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<tr>
<td>BTA-TRAK</td>
<td>Complement factor H-related protein (and also Complement factor H)</td>
<td>Voided urine</td>
<td>Sandwich ELISA</td>
<td>Diagnosis, follow-up</td>
<td>Bard/Bion Diagnostics</td>
</tr>
<tr>
<td>NMP-22</td>
<td>Nuclear mitotic apparatus protein</td>
<td>Voided urine</td>
<td>Sandwich ELISA</td>
<td>follow-up</td>
<td>Matritech, Inc.</td>
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<tr>
<td>NMP-22</td>
<td>Nuclear mitotic apparatus protein</td>
<td>Voided urine</td>
<td>Point-of-care device</td>
<td>Diagnosis high risk, follow-up</td>
<td>Matritech, Inc.</td>
</tr>
<tr>
<td>BLCA-4</td>
<td>Nuclear matrix protein</td>
<td>Voided urine</td>
<td>ELISA (using a rabbit polyclonal antibody)</td>
<td>-</td>
<td>Eichrom Technologies</td>
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<tr>
<td>Survivin</td>
<td>A member of inhibitors of apoptosis gene family</td>
<td>Voided urine</td>
<td>Bio-dot test</td>
<td>-</td>
<td>Fujirebio Diagnostics</td>
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<tr>
<td>UBC</td>
<td>Cytokeratin 8 and 18 (cytoskeletal proteins)</td>
<td>Voided urine</td>
<td>Sandwich ELISA or a point of care test</td>
<td>-</td>
<td>IDL Biotech.</td>
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<tr>
<td>CYFRA 21-1</td>
<td>Cytokeratin 19 (a cytoskeletal protein)</td>
<td>Voided urine</td>
<td>Immunoradiometric assay or ELISA</td>
<td>-</td>
<td>Bio Int; Roche Diag</td>
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<tr>
<td>DD23</td>
<td>185-kDa tumor associated Antigen</td>
<td>Exfoliated cells</td>
<td>Immunocytochemistry</td>
<td></td>
<td>UroCor Labs</td>
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<td>uCyt+</td>
<td>Carcinoembryonic antigen, 2 bladder tumor cell-associated mucins</td>
<td>Voided urine, Exfoliated cells</td>
<td>Immunocytochemistry</td>
<td>Follow-up</td>
<td>Scimedx, Inc.</td>
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<tr>
<td>UroVysion</td>
<td>Alt in chromosomes 3, 7, 17 and 9p21</td>
<td>Voided urine, Exfoliated cells</td>
<td>Multi-colored, multi-probe FISH</td>
<td>Diagnosis, follow-up</td>
<td>Abbott, Vysis</td>
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</table>
## Urine Biomarkers for Detection and Surveillance

<table>
<thead>
<tr>
<th>Marker</th>
<th># Studies</th>
<th># Pts</th>
<th>Sensitivity</th>
<th>Range</th>
<th>Specificity</th>
<th>Range</th>
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<tbody>
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<td>BTA</td>
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<td>436</td>
<td>48</td>
<td>32-58</td>
<td>92</td>
<td>91-92</td>
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<td>BTAtstat</td>
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<td>1377</td>
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<td>29-74</td>
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<td>56-86</td>
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<td>BTAttrak</td>
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<td>360</td>
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<td>60-83</td>
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<td>60-79</td>
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<td>NMP22</td>
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<td>838</td>
<td>71</td>
<td>47-100</td>
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<tr>
<td>FDP</td>
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<td>168</td>
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<td>45-65</td>
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<td>Hb-dipstick</td>
<td>2</td>
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<td>Lewis X</td>
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<td>Na</td>
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<td>Microsatellite</td>
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<td>79-100</td>
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<td>73-95</td>
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<td>Cytology</td>
<td>26</td>
<td>2213</td>
<td>35</td>
<td>13-75</td>
<td>94</td>
<td>85-100</td>
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</table>

Shariat et al., Minerva Urol, 2009
## Marker Sensitivity and Specificity: Meta-analyses

<table>
<thead>
<tr>
<th>Marker</th>
<th>Median Sensitivity (range)</th>
<th>Median Specificity (range)</th>
<th>Total Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytology</td>
<td>55 (48-62)*</td>
<td>94 (90-96)*</td>
<td>3,444</td>
</tr>
<tr>
<td>Cytology</td>
<td>34 (20-53)</td>
<td>99 (83-99)</td>
<td>2,767</td>
</tr>
<tr>
<td>Cytology</td>
<td>35 (13-75)</td>
<td>94 (85-100)</td>
<td>5,545</td>
</tr>
<tr>
<td>Cytology</td>
<td>44 (38-51)*</td>
<td>96 (94-98)*</td>
<td>14,260</td>
</tr>
<tr>
<td>BTA stat</td>
<td>70 (66-74)*</td>
<td>75 (64-84)*</td>
<td>1,160</td>
</tr>
<tr>
<td>BTA stat</td>
<td>71 (57-82)</td>
<td>73 (61-82)</td>
<td>2,534</td>
</tr>
<tr>
<td>BTA stat</td>
<td>58 (29-74)</td>
<td>73 (56-86)</td>
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<td>NMP22</td>
<td>67 (60-73)*</td>
<td>78 (72-83)*</td>
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<td>NMP22</td>
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<td>NMP22</td>
<td>68 (62-74)*</td>
<td>79 (74-84)*</td>
<td>10,119</td>
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<td>NMP22 BladderChek</td>
<td>65 (50-85)</td>
<td>81 (40-87)</td>
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<td>Immunocyt</td>
<td>67 (52-100)</td>
<td>75 (62-82)</td>
<td>959</td>
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<tr>
<td>Immunocyt</td>
<td>84 (77-91)*</td>
<td>75 (68-83)*</td>
<td>3,041</td>
</tr>
<tr>
<td>This assessment</td>
<td>81 (42-100)</td>
<td>75 (62-95)</td>
<td>4,899</td>
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<tr>
<td>FISH (Urovysion)</td>
<td>72 (69-75)*</td>
<td>83 (82-85)*</td>
<td>2,477</td>
</tr>
<tr>
<td>FISH (Urovysion)</td>
<td>76 (65-84)*</td>
<td>85 (78-92)*</td>
<td>3,101</td>
</tr>
<tr>
<td>This assessment</td>
<td>72 (23-100)</td>
<td>80 (40-100)</td>
<td>2,852</td>
</tr>
</tbody>
</table>
### Sensitivity of Select Markers Based on Tumor Grade and Stage

<table>
<thead>
<tr>
<th>Marker</th>
<th># studies</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytology</td>
<td>8</td>
<td>0.12 (.04-.31)</td>
<td>0.26 (.17-.37)</td>
<td>0.64 (.38-.84)</td>
</tr>
<tr>
<td>Cytology</td>
<td>9</td>
<td>0.17</td>
<td>0.34</td>
<td>0.58</td>
</tr>
<tr>
<td>BTA stat</td>
<td>8</td>
<td>0.47 (.38-.56)</td>
<td>0.73 (.59-.83)</td>
<td>0.94 (.55-.99)</td>
</tr>
<tr>
<td>BTA stat</td>
<td>7</td>
<td>0.45</td>
<td>0.6</td>
<td>0.75</td>
</tr>
<tr>
<td>NMP 22</td>
<td>3</td>
<td>0.41</td>
<td>0.53</td>
<td>0.8</td>
</tr>
<tr>
<td>NMP 22</td>
<td>7</td>
<td>0.61 (.35-.81)</td>
<td>0.71 (.41-.90)</td>
<td>0.79 (.63-.89)</td>
</tr>
<tr>
<td>Immunocyt</td>
<td>1</td>
<td>0.78</td>
<td>0.9</td>
<td>1</td>
</tr>
<tr>
<td>FISH (Urovysion)</td>
<td>2</td>
<td>0.56</td>
<td>0.78</td>
<td>0.95</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Marker</th>
<th># studies</th>
<th>Ta</th>
<th>T1</th>
<th>&gt;T2</th>
<th>TIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytology</td>
<td>8</td>
<td>.15 (.09-.25)</td>
<td>.46 (.34-.59)</td>
<td>.55 (.35-.73)</td>
<td>.63 (.29-.87)</td>
</tr>
<tr>
<td>BTA stat</td>
<td>8</td>
<td>.57 (.47-.67)</td>
<td>.82 (.63-.92)</td>
<td>.91 (.74-.97)</td>
<td>.66 (.42-.83)</td>
</tr>
<tr>
<td>NMP 22</td>
<td>7</td>
<td>.60 (.42-.76)</td>
<td>.85 (.27-.97)</td>
<td>.89 (.50-.98)</td>
<td>.73 (.54-.86)</td>
</tr>
</tbody>
</table>
NMP22 improves prediction of UCB in high risk patients

May improve referrals from PCP
May improve timing of cysto in systems with limited resources

Lotan and Shariat, BJU Int. 2009
AUC for detection: 74% (95% CI: 72-76%)
Range across institutions: 68 to 89%

Variability in the Performance of Nuclear Matrix Protein 22 for the Detection of Bladder Cancer

**Question:** (How) can molecular markers support screening of patients at risk of having or developing bladder cancer?

**Statement:**
Feasibility of bladder cancer screening has been demonstrated in several prospective trials. The results from one study using dip-stick testing for hematuria suggests a survival benefit of individuals undergoing hematuria screening. Despite these encouraging reports validation of the results and improved definition of risk populations suited for screening is required.

**Recommendation:**

**Bladder cancer screening using urine for testing is promising but cannot be recommended at present.**

| LoE: 1b | Grade: B | Agreement: 100% |
**Question:** (How) can molecular markers support follow-up of patients with non-muscle invasive low risk bladder cancer?

**Statement:**
Marker-guided follow-up of patients with superficial low risk tumors appears feasible. However, studies proving the efficacy of this concept and demonstrating an added value for the patients or the health system are lacking.

**Recommendation:**
Marker-guided follow-up of patients with non-muscle invasive low grade bladder cancer appears attractive, however, based upon the current level of evidence this procedure cannot be recommended at present

| LoE: 1b | Grade: B | Agreement: 100% |
**Question:** (How) can molecular markers support follow-up of patients with non-muscle invasive high risk bladder cancer?

**Statement:**

Molecular markers detect high grade bladder cancer with high sensitivity. At this stage it remains unclear how molecular markers can support surveillance of patients with high grade bladder cancer.

**Recommendation:**

* A use of molecular markers in surveillance of patients with high grade bladder cancer cannot be recommended.

| LoE: 2b | Grade: B | Agreement: 100% |
**Question:** (How) can molecular markers be used in reflex testing for bladder cancer?

**Statement:**
At present experience with reflex testing is very limited (mostly restricted to FISH technique) and therefore does not permit a definite statement. Reflex testing should be exploited in more detail within prospective controlled studies.

**Recommendation:**
Reflex testing is considered experimental at present and should be investigated further.

| LoE: 2b | Grade: B | Agreement: 100% |
Summary I

- All test **sensitivities > cytology** (low grade!)
- All test **specificities < cytology**
- CIS sensitivities “surprisingly” low

**No single marker has demonstrated superior clinical utility over cytology and cystoscopy**

- There is no “ideal” marker
- We will have to **select appropriate markers according clinical needs**
  - Screening setting: high specificity
  - Follow-up setting: sensitivity
  - Diagnostic strategy affects selection of a marker
Despite numerous publications, the utility of markers in clinical decision-making remains limited.

“… meanwhile the first prospective trials on a marker-guided follow-up in bladder cancer patients are underway.

“In addition, several screening studies could demonstrate the feasibility of molecular markers in this setting.”

Probably no single assay will be sufficient because of the molecular heterogeneity of bladder cancer.
Clinical states of advanced UCB

- Determine prognosis
- Predict response to therapy
- Therapeutic target
- Monitor disease/treatment response

- Clinically Non-muscle Invasive Disease
- Local and/or Distant Recurrence
- Clinical Metastases
- Death from Disease
- Death from Other Causes
Clinical Needs

• Accuracies of prognostic models (i.e., nomograms) not perfect
  – there may be markers that help improve outcome prediction

• Molecular markers established as independent predictors of disease recurrence and survival in pts treated with bladder cancer

arrow Novel markers may identify patients with biologically and clinically aggressive BCa and thereby help improve current staging and prognostic models
Tumors are heterogeneous
Potential Role for Biomarkers

- Identify high risk patients (staging and prognosis)
  - Advanced disease at cystectomy
  - Recurrence after cystectomy
- Predict response to chemotherapy
- Identify pathways for targeted therapy
### PROMISING TISSUE-BASED PROGNOSTIC MOLECULAR MARKERS

<table>
<thead>
<tr>
<th>Category</th>
<th>Markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell cycle related markers</td>
<td>p53, pRB, p21, p27, cyclin E1, cyclin D1, Ki67</td>
</tr>
<tr>
<td>Apoptosis</td>
<td>Fas (CD95), Caspase-3, Survivin, Bcl-2</td>
</tr>
<tr>
<td>Angiogenesis</td>
<td>Microvessel density, Thrombospondin-1, VEGFR, bFGF</td>
</tr>
<tr>
<td>Signaling proteins</td>
<td>ERBB family receptors, RAS, PI3K pathway genes, FGFR3</td>
</tr>
<tr>
<td>Hormone receptors</td>
<td>Her2, AR, ER, PR</td>
</tr>
</tbody>
</table>

### PROMISING BLOOD-BASED PROGNOSTIC MOLECULAR MARKERS

<table>
<thead>
<tr>
<th>Markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma-insulin growth factor binding protein-1 and -3</td>
</tr>
<tr>
<td>Transforming growth factor-β₁</td>
</tr>
<tr>
<td>Interleukin-6 and its receptor</td>
</tr>
<tr>
<td>Soluble E-cadherin</td>
</tr>
<tr>
<td>Urokinase plasminogen activation axis (uPA, PAI-1, PAI-2, uPAR)</td>
</tr>
<tr>
<td>Matrix metalloproteinase</td>
</tr>
</tbody>
</table>

### HIGH-THROUGHPUT TUMOR PROFILING (DNA microarray, metabolomics, etc...)
Investigated pathways

**Cell Cycle regulation**
- p53: inhibits G1/S progression
- pRb: sequesters E2F, inhibits cell cycle progression
- p21/p16/p27: cyclin-dependent kinase inhibitors
- Cyclin D1/cyclin E: cell cycle control at G1/S transition
- KI-67: cell proliferation

**Apoptotic pathway**
- p53: induces apoptosis or DNA repair
- Bcl-2: inhibits caspase activation
- Bax: activates cytochrome C release and apoptosis
- Caspase 3: induces apoptosis
- Survivin: protects from apoptosis and regulates mitosis

**Angiogenesis pathway**
- TSP1: inhibits angiogenesis
- VEGF: promotes angiogenesis through NOS
- uPA: degrades extracellular matrix
- bFGF: growth factor stimulating angiogenesis
Is one marker optimal?

Combined cell-cycle biomarkers
Shariat et al., J Clin Oncol 2003

Combined apoptosis biomarkers
Karam et al., Lancet Oncol 2007
Nomograms

Recurrence

BCa-specific Death

Shariat et al., Cancer 2008
Competing-risk nomograms for prediction of clinical outcomes in patients with pT1-2 N0 UCB after radical cystectomy

Shariat et al., J Urol, 2011
Ongoing clinical trials at UT Southwestern Dallas, Texas

1. **Prospective staining of all TUR and cystectomy specimens for markers**

2. **Prospective, randomized single center study:** adjuvant chemotherapy after radical cystectomy in patients with pT1-3 N0 who have ≥ 3 markers altered

Shariat et al., Cancer 2008
UCB Molecular Pathways- Opportunities for **Targeted Therapies**

**Non Invasive LG UCB pathway:** HRAS or FGFR3 mutant proteins
- Inhibition of RTK-as signaling pathway
  - e.g. Receptor tyrosine kinase inhibitors: gefitinib, erlotinib
  - ErbB2 blocker: trastuzumab
  - EGFR blocker: cetuximab

**Invasive High Grade UCB pathway:**
- Restoration p53/RB function: gene therapy/small molecules
- Inhibition VEGF/VEGFR: Sorafenib, sunitinib, pazopanib, bevacizumab
- Inhibition of anti-apoptotic molecules (survivin)
Summary

• Currently NO prognostic marker is ready for integration into clinical decision-making

• Bladder cancer develops along multiple molecular pathways → multiple molecular markers to capture biological potential of tumor

• Molecular medicine holds the promise that clinical outcomes will be improved by directing therapy toward tumor mechanisms and targets

• The advent of high-throughput technologies is allowing comprehensive identification of molecular targets and molecular markers
The Future: integration of molecular panels

- **Improve prognosis** of heterogeneous disease (UCB)
  e.g. early cystectomy in pT1HG
- **Improve selection and thereby increase use of current chemotherapy**
- **Prediction of response to current chemoRx**
- **Therapeutic response indicator**
  e.g. select patients who achieve pT0 after neoadjuvant chemotherapy for bladder preservation
- **Target for therapy** (combination therapies)
Questions?
ICUD-EAU 2011
Recommendations of committee on LG Ta disease

Badrinath Konety (USA), Willem Oosterlinck (Belgium), Paul Sved (Aus), Raj Pruthi (USA), Sam Chang (USA), Eduardo Solsona (Spain), Sigurdur Gudjonsson (Sweden), Mark Soloway (USA)
# Levels of Evidence used

*(modified from Sackett et al. OCEBM 2001)*

<table>
<thead>
<tr>
<th>Level</th>
<th>Type of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Evidence obtained from meta-analysis of randomized trials</td>
</tr>
<tr>
<td>1b</td>
<td>Evidence obtained from at least one randomized trial</td>
</tr>
<tr>
<td>2a</td>
<td>Evidence obtained from one well designed, controlled study without randomization</td>
</tr>
<tr>
<td>2b</td>
<td>Evidence obtained from at least one other type of well designed, quasi-experimental study</td>
</tr>
<tr>
<td>3</td>
<td>Evidence obtained from well designed non-experimental studies such as comparison studies, correlation studies and case reports</td>
</tr>
<tr>
<td>4</td>
<td>Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities</td>
</tr>
<tr>
<td>Grade</td>
<td>Nature of recommendation</td>
</tr>
<tr>
<td>-------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>A</td>
<td>Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomized trial</td>
</tr>
<tr>
<td>B</td>
<td>Based on well conducted clinical studies but without randomized clinical trials</td>
</tr>
<tr>
<td>C</td>
<td>Made despite the absence of directly applicable clinical studies of good quality</td>
</tr>
</tbody>
</table>
Grade classification (WHO-ISUP)

• Papilloma
• PUNLMP
• Low grade

• High grade
## Incidence of LG Ta SEER-Medicare 2000-2005

<table>
<thead>
<tr>
<th>Year of Diagnosis</th>
<th>Stage I Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>807 (19.28)</td>
</tr>
<tr>
<td>2001</td>
<td>814 (19.28)</td>
</tr>
<tr>
<td>2002</td>
<td>797 (18.33)</td>
</tr>
<tr>
<td>2003</td>
<td>835 (17.37)</td>
</tr>
<tr>
<td>2004</td>
<td>930 (17.96)</td>
</tr>
<tr>
<td>2005</td>
<td>848 (18.06)</td>
</tr>
</tbody>
</table>
LG Ta

- Progression rates are low <20%
- Cancer specific survival is extremely high >95%
- PUNLMP – more likely to recur but progression extremely rare
- Lifelong risk of recurrence with late recurrence following years of no tumor
Overall survival LG Ta

Kaplan-Meier Estimate for Overall Survival

Survival Distribution Function

survival_months

STRATA: gradecat=High Grade Censored gradecat=High Grade gradecat=Low Grade Censored gradecat=Low Grade gradecat=Undifferentiated Grade Censored gradecat=Undifferentiated Grade gradecat=Unknown Grade Censored gradecat=Unknown Grade
Cancer specific survival LG Ta

Survival Distribution Function

Survival_months

STRATA:
- gradecat=High Grade
- gradecat=Low Grade
- gradecat=Undifferentiated Grade
- gradecat=Unknown Grade

Censored gradecat=High Grade
Censored gradecat=Low Grade
Censored gradecat=Undifferentiated Grade
Censored gradecat=Unknown Grade
Prior recommendations – Oosterlinck et al. 2005

- Lesions >0.5 cm, multiple (>5), papillonodular and positive cytology need further evaluation (B)
- Routine upper tract studies not recommended during follow up (B)
  - To be considered in symptomatic patients and those with positive cytology (A)
- Random biopsy for positive cytology (B)
Previous recommendations

• Immediate post TUR intravesical chemo recommended (A)
  – MMC (40mg or Epirubicin (50mg) (A)
  – Avoid chemo if perforation present (D)
  – Instillation same day as TUR (B)
  – Adjuvant intravesical chemo for multiple tumors (A)
• Intravesical chemo first line (B)
• BCG second line (A)
• Cysto at 3 months if negative next at 9 months (C)
• Office fulguration acceptable (C)
• Urine cytology or markers not needed at diagnosis (A) or follow up (B)
Literature review

- PubMed search conducted
- Search terms used
  - Bladder cancer; bladder neoplasm, low grade, low stage, diagnosis, intravesical therapy; cystoscopy, smoking, prevention, observation, expectant management, CT urography, intravenous pyelogram/IVP, cytology, urinary markers, fluorescent cystoscopy, transurethral resection, surveillance, BCG, Mitomycin.
  - Human, 25 years
  - Other association guidelines (AUA, EAU, BAUS, Int. Consultation on bladder tumors/SIU)
### Urinary Tumor Markers

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Level of evidence</th>
<th>Grade of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>• BTA has little role in diagnosis of LG Ta tumors</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>• NMP22 has better sensitivity than cytology but cannot replace cystoscopy</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>• ImmunoCyt has good sensitivity for LG Ta tumors and can be used to prolong intervals between cystoscopy</td>
<td>2a</td>
<td>B</td>
</tr>
<tr>
<td>• UroVysion/FISH has no role in diagnosis of LG Ta tumors</td>
<td>2b</td>
<td>B</td>
</tr>
</tbody>
</table>
# Performance characteristics of markers

<table>
<thead>
<tr>
<th>Marker</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>UroVysion®</td>
<td>30-72</td>
<td>63-95</td>
</tr>
<tr>
<td>Microsatellite analysis</td>
<td>58</td>
<td>73</td>
</tr>
<tr>
<td>Gene microarray</td>
<td>80-90</td>
<td>62-65</td>
</tr>
<tr>
<td>Immunocyt/ uCyt+</td>
<td>76-85</td>
<td>63-75</td>
</tr>
<tr>
<td>Nuclear matrix protein 22</td>
<td>49-68</td>
<td>85.8-87.5</td>
</tr>
<tr>
<td>BTA stat</td>
<td>57-83</td>
<td>68-85.7</td>
</tr>
<tr>
<td>BTA TRAK</td>
<td>53.8-91</td>
<td>28.3-83.9</td>
</tr>
<tr>
<td>Cytokeratins</td>
<td>12.1-85</td>
<td>75-97.4</td>
</tr>
<tr>
<td>Survivin</td>
<td>53-90.4</td>
<td>88-100</td>
</tr>
</tbody>
</table>
# Upper tract evaluation and surveillance

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Level of evidence</th>
<th>Grade of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Routine upper tract studies are not recommended for patients with LG Ta</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>tumors at diagnosis of index tumor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Upper tract evaluation in patients with LG Ta UC is recommended in the</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>presence of:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>o gross hematuria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>o unexplained positive urine cytology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Routine upper tract studies surveillance is not recommended for patients</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>with LG Ta tumors during follow up</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Expectant management

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Level of evidence</th>
<th>Grade of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expectant management should be pursued only in patients with established history of LG Ta UC</td>
<td>3</td>
<td>B</td>
</tr>
<tr>
<td>Optimal tumor characteristics include low tumor burden</td>
<td>3</td>
<td>B</td>
</tr>
<tr>
<td>Particularly applicable to those with advanced age or co-morbidity but can be offered to younger patients after careful and thorough discussion</td>
<td>4</td>
<td>C</td>
</tr>
<tr>
<td>Surveillance includes periodic cystoscopy and cytology</td>
<td>3</td>
<td>B</td>
</tr>
<tr>
<td>Patients who demonstrate increase in size, number or appearance of tumor(s) or develop positive urine cytology should cease expectant management and undergo formal TUR and further evaluation</td>
<td>3</td>
<td>B</td>
</tr>
<tr>
<td>Office fulguration is a good option for patients with small LG Ta UC. This can be followed by post fulguration instillation of intravesical chemotherapy</td>
<td>3</td>
<td>B</td>
</tr>
</tbody>
</table>
Intravesical chemotherapy

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Level of evidence</th>
<th>Grade of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Initial step in management is complete TUR</td>
<td>2b</td>
<td>A</td>
</tr>
<tr>
<td>• Immediate post-TUR instillation of intravesical chemotherapy in the form of Mitomycin C or epirubicin is recommended to prevent recurrences</td>
<td>1a</td>
<td>A</td>
</tr>
<tr>
<td>• Induction chemotherapy with or without maintenance has unclear but potential benefit</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>• The risks of repeated courses of intravesical chemotherapy have to be weighed against the benefit</td>
<td>4</td>
<td>C</td>
</tr>
</tbody>
</table>
### Intravesical immunotherapies

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Level of evidence</th>
<th>Grade of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravesical BCG is not appropriate as initial intravesical therapy for patients with LG Ta UC</td>
<td>3</td>
<td>B</td>
</tr>
<tr>
<td>Intravesical BCG could potentially be used in patients with recurrent LG Ta UC who have not responded to courses of intravesical chemotherapy</td>
<td>3</td>
<td>B</td>
</tr>
<tr>
<td>Secondary immunomodulating therapies do not have a role in management of LG Ta UC at this time</td>
<td>3</td>
<td>C</td>
</tr>
</tbody>
</table>
High grade Ta, T1 and CIS

ICUD update session

dr. Max Burger, Regensburg
prof. Fred Witjes, Nijmegen

March 18, 2011
Members committee 4

- Marko Babjuk, Prague
- Maurizio Brausi, Modena
- Chris Cheng, Singapore
- Eva Comperat, Paris
- Jay Shah, Colin Dinney, Houston
- Joachim Thüroff, Wolfgang Jäger, Mainz
- Wolfgang Otto, Max Burger (co chair), Regensburg
- Fred Witjes (chair), Nijmegen
High grade Ta
Ta HG recommendation 1

• Ta HG should be suspected if
  – papillary tumour is seen in cystoscopy
  – urinary cytology is positive

• The assessment Ta HG should be based on
  – multiplicity
  – tumour size
  – early recurrence
  – concomitant CIS

• LOE 3, recommendation grade B
Ta HG recommendation 2

- Ta HG should be completely resected
  - photodynamic diagnostic may be considered
  - uncertain radicality should prompt re-TURB

- Ta HG should undergo instillation therapy
  - effect of early instillation uncertain
  - BCG should be given
  - duration of BCG should exceed one year

- LOE 2, recommendation grade A
CIS
CIS recommendation 1

• If CIS is suspected clinically
  – cytology, cystoscopy, upper tract imaging

• TURBT in CIS:
  – PDD considered in pos. cytology/ neg. cystoscopy

• LOE 1a, recommendation grade A
CIS recommendation 2

• Cystectomy in CIS:
  – provides excellent survival
  – however, overtreatment in 50%

• LOE 2, recommendation grade A
CIS recommendation 3

• Intravesical therapy
  – immediate instillation may be considered
  – should follow complete resection of pap. tumours
  – should be based on BCG

• LOE 1a, recommendation grade A

• Maintenance therapy
  – required, best schedule unkown, >1 year

• LOE 2, recommendation grade A
CIS recommendation 4

- Treatment response
  - should be assessed at 3 months
  - if no response: cystectomy or further BCG
  - BCG: another 6 wk. course or 3 wkly boosters
  - Unknown when best to abandon conservation

- LOE 2, recommendation grade B
CIS recommendation 5

- Follow up
  - white light cystoscopy and cytology
    - every 3 months for 2 years
    - every 4 months in 3rd year
    - every 6 months in 4th/ 5th year
    - once per year thereafter
  - imaging of upper tract yearly

- LOE NA, recommendation grade C
Q&A
T1 disease
T1 recommendation 1

• The assessment T1 BC should be based on
  – tumour grade and size
  – early recurrence
  – Multiplicity
  – concomitant CIS
  – UC involving the prostatic mucosa or ducts
  – depth of lamina propria invasion

• LOE1a, recommendation grade A
Prediction of prognosis impossible on an individual level
“Other” potential prognostic factors

- Response to intravesical therapy
  - Tumor at 3 months after BCG: up to 80% progression

- Insufficiently validated in clinical trials are:
  - LVI??
  - Markers
    - P53, p27, Ki67
T1 recommendation 2

- The use of one immediate postoperative instillation of chemotherapy is not supported by consistent data and therefore it should not be recommended as standard practice
- LOE1a, recommendation grade A
New literature on immediate instillation

- Hendricksen (2008):
  - course of epirubicin with or without one instillation
- Gudjonsson (2008), Berrum-Svennung (2008):
  - epi versus nothing
  - only effect in very low risk tumors
- Böhle (2009):
  - Gemcitabin versus placebo
  - 20 hrs contineous bladder irrigation
- Brausi (2010):
  - data in high risk very limited
In summary, one immediate instillation significantly reduces the risk of recurrence in TaT1 bladder tumours. Further studies are required, however, to determine the definitive role of immediate chemotherapy before BCG or further chemotherapy instillations in intermediate- and high-risk groups.
In summary, one immediate instillation significantly reduces the risk of recurrence in TaT1 bladder tumours. Further studies are required, however, to determine the definitive role of immediate chemotherapy before BCG or further chemotherapy instillations in intermediate- and high-risk groups.
T1 recommendation 3

- Patients with high risk and with recurrent or persistent disease after BCG immunotherapy should be offered cystectomy
- LOE2a, recommendation grade A
Who already *initial* cystectomy

- Especially consider immediate cystectomy in patients with 2 of the following factors:
  - Tumor multifocality
  - Size > 3 cm
  - Associated CIS

- Obviously non responders to BCG
  - 3 or 6 months
Why cystectomy

• No RCT’s, risk of overtreatment, but….

• Frequent understaging
  • Up to 30% in T1
  • Up to 50% in high grade T1

• Better survival after surgery

• QOL: pts seem to accept surgery and the consequences for better survival
Why cystectomy

• Prognosis in case of progression is bad
T1 recommendation 4

• If a bladder sparing approach is desired, a secondary TURB should be performed and followed by intravesical BCG therapy

• LOE3, recommendation grade B
BCG

- Some kind of maintenance schedule should be used
- Impact on progression unclear
- BCG has more toxicity
BCG failure
BCG failure recommendation 1

• In any BCG nonresponse or failure cystectomy is recommended
• LOE 2a, recommendation grade A.
BCG failure recommendation 2

- The threat of progression remains real but comfortably low enough within the first 6 months of beginning BCG to consider alternatives to cystectomy for those patients unfit or refusing this standard management option.

- LOE 2, recommendation grade B
Progression

• “comfortably low enough” means
  – <5% within 12 months
  – Usually exceeds 12 months
Know the different BCG failures

- **Refractory:**
  - disease free not achieved within 6 mths (persistence, recurrence, progression)

- **Resistant:**
  - recurrence of persistence at 3 months, free at 6 months

- **Relapsing:**
  - disease after 6 months and after CR

- **Intolerant:**
  - disease after less than adequate therapy
BCG failure recommendation 3a

• Alternative treatment options
  – repeat resection and repeat BCG (LOE 1a, Gr.A)
    • More than 2 cycles BCG seems ineffective
  – possibly combine with IFN-α (LOE 2, grC)
  – Gemcitabin has shown effectivity, but more studies are needed (2 recent trials)
  – Thermo-chemotherapy has shown effectivity, but more studies are
BCG failure recommendation 3b

**No** alternative treatment options

- There is no reported evidence of significant efficacy using
  - current intravesical chemotherapy
  - IFN-α monotherapy
  - photodynamic therapy
  - radiation therapy.
ICUD-EAU International Consultation on Bladder Cancer

Committee #6
Muscle-invasive bladder cancer

26th EAU Congress, Vienna, 2011
Committee Members

Joaquim Bellmunt
Michael S. Cookson
Georgios Gakis
Khurshid A. Guru
Axel Heidenreich
Seth P. Lerner
Edward M. Messing
David I. Quinn
Mark P. Schoenberg
William U. Shipley
Arlene O. Siefker-Radtke
Arnulf Stenzl (Chair)
Cora Sternberg
1. OVERVIEW
2. INDICATIONS AND ALGORITHM OF TREATMENT
3. RADICAL CYSTECTOMY
   1. Removal of the tumor bearing bladder
      1. Timing and delay of cystectomy
      2. Technique
      3. Lymphadenectomy
      4. Laparoscopic and robotic-assisted lap. cystectomy
   2. Surgical outcome: morbidity and mortality
   3. Oncological outcome of radical surgery according to TNM staging
4. PERIOPERATIVE CHEMOTHERAPY
   1. Neoadjuvant chemotherapy
   2. Adjuvant chemotherapy
5. PERIOPERATIVE RADIOTHERAPY

6. BLADDER-SPARING TREATMENT FOR LOCALISED DISEASE
   1. Transurethral monotherapy
   2. Partial Cystectomy
   3. External beam radiotherapy
   4. Multimodality treatment

7. TREATMENT OF MIXED HISTOLOGY UROTHELIAL CARCINOMA

8. FOLLOW-UP
   1. Site of recurrence
      1. Distant recurrences
      2. Follow-up and treatment of secondary ureteral and urethral tumors
Timing and delay of cystectomy

• Minimally invasive techniques including robotic assisted laparoscopic radical cystectomy have been reported in increasing numbers. Short-term outcomes, pathologic findings and assessments of morbidity compared to the open technique have been reported. Continued research with these techniques is required and specifically results of several randomized trials underway should be reported prior to accepting this as an equivalent option to open radical cystectomy (Level 2a Grade C).

• Cystectomy is also indicated as palliation for intractable pelvic pain and bleeding from locally advanced or metastatic bladder cancer (Level 4 Grade C)
Timing and delay of cystectomy

• Delay in cystectomy for muscle-invasive disease is associated with significantly reduced overall and cancer specific survival. (level of evidence: 3, grade of recommendation: B)

• Radical cystectomy in patients with muscle-invasive bladder cancer should be performed within 3 months after initial diagnosis of stage localized T2 -T4 disease. (level of evidence: 3 grade of recommendation: C)
Treatment of mixed histology urothelial carcinomas

• Nested variant and micropapilary urothelial cancers regardless of detected in non-muscle invading or muscle-invading stages should be treated with aggressive local extirpative therapy (Level of Evidence 3, Grade of recommendation B)

• Carcinosarcomas should be treated if possible with local extirpative surgery (Level of Evidence 3, Grad of recommendation B)

• Urothelial cancer with small cell components should be treated with neoadjuvant chemotherapy including cisplatin and etoposide neoadjuvantly followed by aggressive local treatment (Level of Evidence 3, Grade of recommendation B)
Radical Cystoprostatectomy

- Apex-sparing
- Seminal vesicle sparing
- Enucleation
Technique

• Preservation of the anterior and membranous urethra including parts of the prostate and seminal vesicles for reasons of fertility, potency and continence are technical variations to the nerve-sparing approach which may improve patients’ quality of life but must be attentively judged against possible oncological risks. (level of evidence 3, Grade C)
Cystectomy in Females -
Indications and extent

- T2-T4a, N0-NX, M0
- high-risk pTa-T1
- BCG Non-responder
- Transurethrally uncontrollable pTa-disease (GR B)

Urethra
Sphincter
Vagina
Nerve-sparing
Bladder
Pelvic Lymphadenectomy
Uterus
Adnexe

Eberhard-Karls University Tuebingen
Department of Urology
• In *female* patients standard anterior pelvic exenteration includes the entire urethra, adjacent vagina, uterus, distal ureters and respective lymph nodes (level of evidence: 3, Grade: C)

• The urethra + supplying autonomous nerves can be preserved in case of a planned orthotopic neobladder (level of evidence: 3, Grade: C)
Laparoscopic and robotic-assisted laparoscopic cystectomy (RALC)

- Minimally invasive approach to radical cystectomy has a significant role in management of locally advanced bladder cancer (level 3, grade C)

- Immediate oncologic results are acceptable and comparable to open radical cystectomy. Meanwhile long-term oncological data is still awaited and will define its permanent role in urologic oncology. (level 2b, grade B)
• Centers across the world with expertise in minimally invasive surgery especially surgical expertise should presently be offering these options for bladder cancer. (level 3, Grade C)

• High-volume centers with dedicated minimally invasive surgical teams have shown better and safe results. (level 3, Grade B)
Cystectomy:
Short/long costs of BCa/UUT Ca
Hospital/Surgeon Volume vs. costs

Konety et al., J Urol, 2004
Cystectomy: Hospital/Surgeon Volume vs. Mortality

Surgical complications associated with radical cystectomy and urinary diversion should be reported in a uniform grading system. The currently best adapted graded system for cystectomy is the Clavien grading system (level of evidence: 2, grade of recommendation B).

Surgical complications associated with radical cystectomy and urinary diversion should include the length of follow-up for the patient cohort, and a minimum of 30-day but preferable for 90-day reported outcome (level of evidence 3, grade of recommendation C).

ASA score, age, previous treatment for bladder cancer or other pelvic diseases, surgeon and hospital volume of radical cystectomy, and type of urinary diversion influence surgical outcome (level of evidence: 3, grade of recommendation: C)

Reduction in blood loss and blood transfusion is afforded by meticulous technique, use of modern surgical devices, and improved understanding of pelvic anatomy. (level of evidence: 3, grade of recommendation C)
Follow-up and treatment of secondary ureteral tumours

• Ureterorenoscopy with biopsy is the diagnostic procedure of choice for the diagnosis of a metachronous upper tract recurrence after RC (Level 3, Grade C).

• The use of cytology and urine-based markers, i.e. fluorescence in-situ hybridization and immunocytology, cannot be recommended for routine follow-up of the upper tracts so far since their use has only been evaluated in patients with primary upper tract cancers (Level 3, Grade B).

• Routine upper tract imaging is only indicated in patients with clinical symptoms suspicious of a metachronous upper tract recurrence (Level 3, Grade B).
Follow-up and treatment of secondary ureteral and urethral tumours

- Nephroureterectomy is the treatment of choice for invasive upper tract recurrence providing prolonged survival. (Level 3, Grade B)

- A regional lymphadenectomy in patients undergoing radical nephroureterectomy is only of diagnostic value. (Level 3, Grade C).
Spare – for discussion only
Oncological outcome according to TNM staging

• The AJCC substratifications in node-negative pT2 and pT3 bladder cancer are of prognostic value (Level 3, Grade B)

• Nomograms provide improved prognostic information for oncological outcomes after radical surgery as compared to the pTNM staged predictions. However, its general applicability has not been established sufficiently by external validation so far (Level 3, Grade B)

• In patients older than 80 years, radical cystectomy is associated highest risk reduction on cancer-related and non-cancer related mortality (Level 3, Grade B).
Oncological outcome

- Radical cystectomy is the mainstay of treatment in muscle-invasive bladder cancer providing long-term survival (Level 2b, Grade B).

- The AJCC substratifications in node-negative pT2 and pT3 bladder cancer are of prognostic value (Level 2b, Grade B).

- In patients older than 80 years, radical cystectomy is associated with the highest risk reduction on cancer-related and non-cancer related mortality (Level 3, Grade B).

- Based on the scarce data available, the routine use of molecular markers for primary risk assessment in invasive bladder cannot be recommended so far (Level 3, Grade B).
• Surveillance regimens should be based on a risk-adapted strategy (Level 3, Grade C).

• The number of risk factors potentiates the risk of recurrence: (a) positive ureteral margin (b) carcinoma in situ of the bladder and ureter, (c) tumor multifocality, (d) urethral tumor involvement and (e) male gender (Level 3, Grade B).

• Patients with finally positive ureteral margins at surgery are at increased risk of ureteral recurrence. Frozen section analysis has a high sensitivity and specificity for the detection of malignant ureteral margins (Level 2b, Grade B).
Follow-up and treatment of secondary urethral tumours

- Risk factors for urethral recurrence in male patients are prostatic tumor involvement (either superficial or invasive) and bladder neck involvement in female patients (Level 3, Grade B).

- Intraoperative frozen section analysis has a high sensitivity and specificity for the detection of a malignant urethral margin for both male and female patients (Level 2b, Grade B).

- Patient with positive final urethral margins are at increased risk of urethral recurrence (Level 3, Grade B).

- Prophylactic urethrectomy is not justifiable in patients with carcinoma in situ at the urethral margin (Level 3, Grade C).
Follow-up and treatment of secondary urethral tumours

• The use of urinary cytology, urethral washings and diagnostic urethroscopy for follow-up has not proven to provide a survival benefit (Level 3, Grade B).

• Urethrectomy should be considered in patients with invasive carcinoma at the urethral margin at radical cystectomy or in case of invasive urethral recurrence (Level 3, Grade B).

• Local conservative treatment is an option in patients with non-invasive tumor(s) or carcinoma in situ of the urethra (Level 3, Grade C).

• In patients with urethral recurrence and concomitant distant recurrence outside the urinary tract systemic chemotherapy is indicated (Level 3, Grade C).
Committee 7: Urinary diversion

Richard E. Hautmann, Thomas Davidsson, Stefan H. Hautmann, Cheryl T. Lee, Stephan Madersbacher, Murugesan Manoharan, David F. Penson, Raimund Stein, Joachim W. Thueroff, Bjoern G. Volkmer

RCX AND URINARY DIVERSION

• **Highest** relative value in terms of **difficulty of the surgery** for any procedure **in urology**

• They are also the **most difficult laparoscopic or robotic procedures** and more so if the diversion is performed totally intracorporeally.

• **Risk of procedure is based not only on the technical challenges but also on the nature of the patients needing.**
RCX AND URINARY DIVERSION (UD) ARE 2 STEPS OF ONE OPERATION

- Literature uniformly reports the “complications of RCX”
- While ignoring that the majority of complications are diversion related (75%)!

This may seem semantic, but it is not

Hautmann, J Urol 2010
COMMON MEASURES FOR SURGICAL OUTCOMES OF RCX AND UD

- Estimated blood loss
- Operative time
- Analgesic use
- LOS
- Time to return to work
- Perioperative death
- Complication rates
- Hospital costs
FEW STUDIES ON RCX AND UD

REPORT ON

- Readmission rates
- Reoperation rates
- Intensive care stays
- Additional interventional radiologic procedures

DONAT, UROLOGY, 2007
THE MAJORITY OF RCX SERIES ON MORBIDITY HAD:

• NOT defined complications
• NOT utilized a grading system other than categorizing into “major versus minor”
• NOT accounted for comorbidities
• NOT employed a formal complication reporting system

Shabsigh EUR Urol 2009
CONCLUSIONS

• The lack of consistency in the method used to accrue, define, and report complication data makes it impossible to compare morbidity rates among different surgical techniques, surgeons or institutions.

• Improved surgical outcome reporting (f.i. Clavien system) will allow more meaningful comparisons when randomized trials are sparse and f.i. for comparison between open and minimaly invasive techniques.
EVIDENCE AND URINARY DIVERSION

• Not a single randomized study *
• Almost all studies used in this report are of Level 3 or Level 4 evidence including expert opinion based on „first principles“ research
• The grades of recommendations given are mostly of Grade C

* except studies on ureteroileostomy
Table 1: Numbers and Types of Urinary Diversions (%) performed by the Authors

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ICUD–EAU GUIDELINES ON BLADDER CANCER

UD AND RENAL FUNCTION

- Age related GFR decline: 1 ml /min/year ≥ age 50
- Serum creatinine remains normal until GFR < 50 %
- Ideal: Isotopic GFR ($^{51}$Cr-EDTA)
- Cut off for continent diversion:
  - Serum creatinine > 150 μmol/l
  - GFR < 50 %
- Upper tract dilatation: Does not equate to reduction of renal function
- Preexisting renal pathology: Greatest risk of postop renal deterioration
- Urinary diversion into bowel segments is not inherently damaging to the kidneys
Table 2: Secondary tumours after diversion using isolated gut segments

<table>
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<th>Ileum</th>
<th>Colon</th>
<th>Ileocecal</th>
<th>Stomach</th>
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<td>Total</td>
<td>60</td>
<td>42</td>
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From publications by Austen and Kälble (15,16), since 2004, and four Lund cases.

* This case was transferred from continent cutaneous diversion using colonic segment.

** Includes 2 Lund cases (described in this paper) but excludes a case (17) from Austen and Kälble, that is now transferred to the ileal conduit group.

Mansson 2011
<table>
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<tr>
<th>Procedure</th>
<th>no. secondary tumors</th>
<th>no. diversions</th>
<th>%</th>
<th>median latency period (years)</th>
<th>mean time: operation to analysis (years)</th>
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<td>4190</td>
<td>0,05 %</td>
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<td>239</td>
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<td>233</td>
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<td>620</td>
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Kälble 2011
Table 4: Tumor Risk in Continent and Incontinent Diversion

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<tr>
<td>Total</td>
<td>0.03%</td>
<td>0.27%</td>
<td>0.08%</td>
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|                  |          |              |        |
| Cystoplasty      | 1.71%    | 0.00%        | 1.58%  |

|                  |          |              |        |
| Ureterosigmoidostomy | 2.58%    |              |        |

Kälble 2011
CONCLUSIONS

• Ureterosigmoidostomy, cystoplasty and probably (ileo)colonic OBS bear a significantly increased tumor risk and require regular endoscopic evaluation beginning at the 5th postop year
• After OBS and conduits regular endoscopy is not mandatory
• In ileocecal pouches, it is recommended in the presence of symptoms such as hydronephrosis, chronic urinary infection, and hematuria
ORTHOTOPIC BLADDER SUBSTITUTION IN MEN (OBS)

INDICATION AND TUMOR STAGE

- Extent of pelvic disease: little bearing on appropriateness
- Pelvic recurrence: no impact on OBS function
- LN + patients: achieve good functional results

HAUTMANN, J UROL, 1999
OBS – INDICATION AND TUMOR STAGE

NO CONSENSUS

- **PREOPERATIVE DISTAL PROSTATIC BIOPSIES**
  - Paraffin-embedded biopsies more reliable
  - Discuss result with patient before surgery

- **FROZEN SECTION OF THE RESECTION MARGIN AT THE TIME OF SURGERY**
FUNCTION PRESERVING CANCER SURGERY OBS WITH NERVE SPARING RCX

- If tumor characteristics permit
- Chance of maintaining erectile function
- Preserved urethral sensation
- Improved resting pressure
- Better night time continence
OBS - AGE AND MOTIVATION

- **No age cut off** for OBS
- **In practice:** Many patients > 70 years will opt for a simpler conduit as the postoperative course is less arduous and incontinence is less likely.
- **Motivation** of the patient is the most important factor when considering suitability for an OBS, although it is difficult to assess this objectively.
- Patients must be prepared to commit to the long term follow up program necessary.
OBS - UPPER TRACT PRESERVATION

• Voding with OBS cannot produce reflux

• Antireflux nipple worse than isoperistaltic tubular segment
  2 RANDOMIZED SURGICAL TRIALS !

• Low anastomotic stricture rate (<2.7 %)

• Stented uretero-ileal anastomosis improves outcomes

WAIDELICH BJU 1998
STUDER J.UROL 2006
STUDER J.UROL 1996
SHAABAN BJU 2006
Active postoperative management and regular long term follow-up
Key issue is achieving a capacity of 400-500 ml
Residual free voiding of sterile urine
Treatment of any outlet obstruction
OBS IN FEMALES

PATIENT SELECTION: ONCOLOGIC FACTORS

- It is reasonable to advise against OBS for invasive bladder neck involvement or suspected invasion of the vaginal wall or cervix.

- Such patients may be considered for OBS if intraoperative frozen section of the urethral margin is negative.

- Overall 60-70% of women are reasonable candidates for OBS.
Prior to the 1990s the primary continence mechanism was located in the bladder neck itself.

The urethra alone could provide continence if the sphincter mechanism was carefully preserved.

The primary rhabdosphincter is an “OMEGA“ shaped structure surrounding the distal third of the urethra.

The main nerves supplying this sphincter are the somatic pudendal nerves which run under the endopelvic fascia. The autonomic nerves coursing through the pelvic plexus and along the lateral vagina supply the smooth muscle of the bladder neck and urethra.
NERVE SPARERS:

- Avoiding dissection below the endopelvic fascia surrounding the urethra helps insure that this muscle and its nerve supply are not disturbed.

- „Nerve sparing“ approach is crucial to maintaining urethral tone and may decrease the risk of retention due to spasticity of the denervated urethra.

MECHANICS:

- Routine dissection of presacral tissue as part of the node dissection without clear reduction of continence.

To date no randomized comparison of these two techniques has been performed.

References:
STENZL J.UROL 1995
TURNER J.UROL 1997
ALI-EL-DEIN J.UROL 2002
STEIN J.UROL 1997
<table>
<thead>
<tr>
<th>Author</th>
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# Anonymous validated questionnaire
CONTINENT CUTANEOUS DIVERSION (CCD)

Second choice after OBS

Indications in 2011

• Simultaneous urethrecomy
  TCC lower urinary tract
  TCC prostatic ducts (?)

• Patient preference
  Risk of leakage after OBS

• Patient refuses labor intensive rehabilitation

• Pediatric age group
ICUD-EAU GUIDELINES ON BLADDER CANCER

CCD – PRINCIPAL DISADVANTAGES

• No leak point (pop off)
• Need for antireflux mechanism

NO CONSENSUS

Pouch pioneers +
Pediatric urologists +

• Risk of complications
  Rupture 10 % <1%
  Stone formation 10-20 % <1%
  Bacterial colonization 100 % 15%
ICUD-EAU GUIDELINES ON BLADDER CANCER

CCD - OUTLET

- Nipples abandoned
- Appendix: Ready made
  - Availability, suitability
  - Stomal stenosis (10–20%)
- Tapered/plicated/stapled ileum: Simplicity
- Serous lined extramural valve (T-pouch)
  - Sophisticated
  - No general acceptance
CONDUIT
AND URETEROSIGMOIDOSTOMY

• No / very little new information
• Lack of hard data
• No standardized reporting
• Recent efforts to overcome this dilemma
### Table 6: Diversion specific (not RCX) long term complications *
using non-/ standardized reporting

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<th>Conduit</th>
<th>Neobladder</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bern</td>
<td>Mayo</td>
</tr>
<tr>
<td>f.u. median (years):</td>
<td>8.1</td>
<td>6.3</td>
</tr>
<tr>
<td>patients (n=):</td>
<td>131.0</td>
<td>1,057.0</td>
</tr>
<tr>
<td>complications (n=):</td>
<td>192.0</td>
<td>1453.0</td>
</tr>
<tr>
<td>patients with (n=):</td>
<td>87/131.0</td>
<td>642/1,057.0</td>
</tr>
<tr>
<td>patients with (%)</td>
<td>66.0</td>
<td>61.0</td>
</tr>
<tr>
<td>within years:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>45</td>
<td>50</td>
</tr>
<tr>
<td>10</td>
<td>50</td>
<td>68</td>
</tr>
<tr>
<td>15</td>
<td>54</td>
<td>70</td>
</tr>
<tr>
<td>20</td>
<td>94</td>
<td>80</td>
</tr>
<tr>
<td>Reoperation rate (%)</td>
<td>40%</td>
<td>6%</td>
</tr>
<tr>
<td>Complications (pts/%):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>bowel</td>
<td>32 (24%)</td>
<td>515 (39.3%)</td>
</tr>
<tr>
<td>UTI</td>
<td>30 (23%)</td>
<td>174 (16.5%)</td>
</tr>
<tr>
<td>stoma</td>
<td>32 (24%)</td>
<td>163 (15.2%)</td>
</tr>
<tr>
<td>anastomosis</td>
<td>40 (14%)</td>
<td>122 (11.5%)</td>
</tr>
<tr>
<td>urolithiasis</td>
<td>12 (9%)</td>
<td>162 (15.3%)</td>
</tr>
<tr>
<td>renal function</td>
<td>35 (27%)</td>
<td>213 (20.2%)</td>
</tr>
</tbody>
</table>

*Bern: > complications 3 months; > 5 years follow up
Mayo: > 30 days of surgery
Ulm: > 3 months of surgery

Madersbacher J.Urol. 2003
Shimko J.Urol. 2011
Hautmann J.Urol. 2011
Table 6: Diversion specific (not RCX) long term complications * using non-/ standardized reporting

<table>
<thead>
<tr>
<th></th>
<th>Conduit</th>
<th>Neobladder</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bern</td>
<td>Mayo</td>
</tr>
<tr>
<td>f.u. median</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(years)</td>
<td>8.1</td>
<td>6.3</td>
</tr>
<tr>
<td>patients (n=)</td>
<td>131.0</td>
<td>1,057.0</td>
</tr>
<tr>
<td>complications (n=)</td>
<td>192.0</td>
<td>1453.0</td>
</tr>
<tr>
<td>patients with (n=):</td>
<td>87/131.0</td>
<td>643/1,057.0</td>
</tr>
<tr>
<td>patients with (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>within years:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5:</td>
<td>45</td>
<td>50</td>
</tr>
<tr>
<td>10:</td>
<td>50</td>
<td>68</td>
</tr>
<tr>
<td>15:</td>
<td>54</td>
<td>70</td>
</tr>
<tr>
<td>20:</td>
<td>94</td>
<td>80</td>
</tr>
<tr>
<td>Reoperation rate (%)</td>
<td>40%</td>
<td>6%</td>
</tr>
<tr>
<td>Complications (pts/%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>bowel</td>
<td>32 (24%)</td>
<td>215 (20.3%)</td>
</tr>
<tr>
<td>UTI</td>
<td>30 (23%)</td>
<td>174 (16.5%)</td>
</tr>
<tr>
<td>stoma</td>
<td>32 (24%)</td>
<td>163 (15.3%)</td>
</tr>
<tr>
<td>anastomosis</td>
<td>18 (14%)</td>
<td>122 (11.5%)</td>
</tr>
<tr>
<td>urolithiasis</td>
<td>12 (9%)</td>
<td>102 (15.3%)</td>
</tr>
<tr>
<td>renal function</td>
<td>35 (27%)</td>
<td>213 (20.2%)</td>
</tr>
</tbody>
</table>

*Bern: > complications 3 months; > 5 years follow up
Mayo: > 30 days of surgery
Ulm: > 3 months of surgery

Madersbacher J.Urol. 2003
Shimko J.Urol. 2011
Hautmann J.Urol. 2011
• Remains the most commonly used diversion in conjunction with RCX
• Technically easier than continent reconstruction
• Complications, early as well as late, are legion
• Incidence of upper tract complications increasing with length of follow up
• Comparisons with other techniques are difficult as surgical techniques have improved markedly over the last 25 years
• Few series report comparable long-term outcomes (>20 years) in patients with neobladders
ICUD-EAU GUIDELINES ON BLADDER CANCER

PEDIATRIC DIVERSION: INDICATIONS

• Neurogenic bladder
• Functional or anatomical loss of the lower urinary tract
• Failure of primary reconstruction of the lower urinary tract (bladder exstrophy)
• Radical surgery for malignancies
PEDIATRIC DIVERSION GOALS

• Urine storage at low pressures in an adequate capacity reservoir for preservation of the upper tract

• Achieving urinary continence
URINARY DIVERSION IN THE PEDIATRIC AGE GROUP
SPECIAL CONSIDERATIONS

• Options for continent diversion in patients with and without neurogenic deficits: Augmentation and CCD
• Anal diversion should be offered only to patients with competent anal sphincters
• Preferred solution for incontinent diversion: colonic conduit
Table 7: **Diversion specific long term complications (> 3 month post-op) at 10 years in 923 neobladder pts operated between 1986-2008 using the Kaplan-Meier method**

- Uretero-ileal stenosis: 13.80%
  - Refluxive anastomosis (Wallace): 6.40%
  - Non refluxive (Le Duc): 17.00%
- Urinary retention (female): 42.20%
- Subneovesical obstruction in men (correctable): 8.20%
- Functional obstruction in men (CIC): 5.10%
- Incisional hernia: 6.40%
  - (41 in 923 pts = 4.4%)

Hautmann, JUrol 2011
Table 5: Neobladder specific complications within 90 d of surgery by category in 1013 patients (modified CLAVIEN)

<table>
<thead>
<tr>
<th>category</th>
<th>no complication</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
<th>complications Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>infection</td>
<td>777 (76.7%)</td>
<td>38</td>
<td>146</td>
<td>35</td>
<td>5</td>
<td>12</td>
<td>236 (23.3%)</td>
</tr>
<tr>
<td>abscess</td>
<td>988</td>
<td>2</td>
<td>20</td>
<td>3</td>
<td>25</td>
<td></td>
<td>25</td>
</tr>
<tr>
<td>UTI</td>
<td>837</td>
<td>38</td>
<td>138</td>
<td></td>
<td>176</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>978</td>
<td>6</td>
<td>15</td>
<td>2</td>
<td>12</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>GU complications</td>
<td>843 (83.2%)</td>
<td>100</td>
<td>6</td>
<td>64</td>
<td>0</td>
<td>0</td>
<td>170 (16.8%)</td>
</tr>
<tr>
<td>renal failure</td>
<td>995</td>
<td>11</td>
<td>3</td>
<td>4</td>
<td></td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>ureteral obstruction</td>
<td>965</td>
<td>16</td>
<td>1</td>
<td>31</td>
<td></td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>urinary leak</td>
<td>948</td>
<td>44</td>
<td></td>
<td>21</td>
<td></td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>urinary fistula</td>
<td>1002</td>
<td>6</td>
<td></td>
<td>5</td>
<td></td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>urinary retention</td>
<td>985</td>
<td>23</td>
<td>2</td>
<td>3</td>
<td></td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>miscellaneous</td>
<td>918 (90.6%)</td>
<td>0</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>95 (9.4%)</td>
</tr>
<tr>
<td>metabol. Acidosis despite TX</td>
<td>1007</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>incisional hernia</td>
<td>1010</td>
<td></td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td>3</td>
</tr>
</tbody>
</table>

Grade 1: oral medications
Grade 2: intravenous medications
Grade 3: interventional radiology or operation
Grade 4: lasting disability or organ resection
Grade 5: death

Hautmann JUrol.2010
Conclusions:

- **Surgical morbidity** following UD is significant and, when strict reporting guidelines are incorporated, higher than previously published.
- Accurate reporting of postoperative complications after RCX is essential for:
  - Counseling patients
  - Combined modality treatment planning
  - Clinical trial design
  - Assessment of surgical success
Centralisation / regionalization

High volume surgeons / hospitals

Annual case load of ≥ 25 procedures

Not more than 2 surgeons
PROSTATE INVOLVEMENT BY UROTHELIAL CELL CARCINOMA

Joan Palou (Chair)
David Wood (co-chair)
Bernie Bochner
Henk van der Poel
H. Al-Ahmadie
Ofer yossepowitch
INCIDENCE

Primary bladder tumours: from 0.5 to 28 %
Depending on the population screened.

The incidence of prostatic UCC in patients with superficial or invasive bladder cancer oscillates between 12 and 48%, and between 7.6 and 16.6% of stromal invasion.

Palou et al, Urology 1995
INCIDENCE

CIS

First described by Melicow in 1952

Rarely present as an isolated lesion

In a series of 1529 patients with NMIBC it was 19% bladder CIS and 2.7% CIS in PU (Millan et al, J Urol 2000)

It may be detected from 15 to 40% in the followup of High grade NMIBC (Herr HW et al J Urol 1999; Davis JW et al, J Urol 2002)
PAPILLARY UROTHELIAL CELL CARCINOMA OF THE PROSTATIC URETHRA

INCIDENCE

Papillary lesions

Primary papillary lesions occur from 1-4 %

Bates HR, Jr, J Urol 1969

Multiplicity as a risk factor

Mungan MU et al, Eur Urol 2005
## INCIDENCE OF PROSTATIC UC IN CYSTECTOMY SPECIMENS

<table>
<thead>
<tr>
<th>Author</th>
<th>Publication</th>
<th>Year</th>
<th>Patients</th>
<th>TCC in prostate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schellhammer et al</td>
<td>J Urol</td>
<td>1977</td>
<td>300</td>
<td>12</td>
</tr>
<tr>
<td>Coutts et al</td>
<td>Brit J Urol</td>
<td>1985</td>
<td>43</td>
<td>36</td>
</tr>
<tr>
<td>Wood et al</td>
<td>J Urol</td>
<td>1989</td>
<td>84</td>
<td>23</td>
</tr>
<tr>
<td>Reese et al</td>
<td>J Urol</td>
<td>1992</td>
<td>115</td>
<td>29</td>
</tr>
<tr>
<td>Pagano et al</td>
<td>J Urol</td>
<td>1996</td>
<td>570</td>
<td>13</td>
</tr>
<tr>
<td>Esrig et al</td>
<td>J Urol</td>
<td>1996</td>
<td>489</td>
<td>29.2</td>
</tr>
<tr>
<td>Herr et al</td>
<td>J Urol</td>
<td>1999</td>
<td>186</td>
<td>39</td>
</tr>
<tr>
<td>Ngninkeu et al</td>
<td>J Urol</td>
<td>2003</td>
<td>283</td>
<td>27</td>
</tr>
<tr>
<td>Revelo et al</td>
<td>J Urol</td>
<td>2004</td>
<td>121</td>
<td>48</td>
</tr>
<tr>
<td>Nixon et al</td>
<td>J Urol</td>
<td>2002</td>
<td>192</td>
<td>15.6</td>
</tr>
</tbody>
</table>
STROMAL INVASION BY UROTHELIAL CELL CARCINOMA

INCIDENCE
Stromal invasion

Is present in 37-64% of men with prostate involvement at cystoprostatectomy.

The differences of incidence between the different studies are related to a careful pathologic assessment (whole mount section).

There is an increase risk of nodal metastases.
Pagano et al, J Urol 1996
## HISTOPATHOLOGY AND SURVIVAL

### Stromal invasion

<table>
<thead>
<tr>
<th>Stage</th>
<th>Patients (%)</th>
<th>Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contiguous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not contiguous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urethral mucosa</td>
<td>44 (61)</td>
<td>7</td>
</tr>
<tr>
<td>Acinal/ductal</td>
<td>28 (39)</td>
<td>46</td>
</tr>
<tr>
<td>Stromal</td>
<td>6</td>
<td>100</td>
</tr>
<tr>
<td>Extracapsular invasion</td>
<td>14</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>

*Pagano et al, J Urol 1996*
Coronal

Sagittal

## STAGING OF UCC OF THE PU

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>Tumour confined to the prostatic urothelium</td>
</tr>
<tr>
<td>Stage 2</td>
<td>Duct and acini invasion, but confined to the basal membrane</td>
</tr>
<tr>
<td>Stage 3</td>
<td>Stromal invasion</td>
</tr>
</tbody>
</table>

*Hardeman and Soloway, Worl J Urol 1988*
TNM BLADDER:  Pt4a (Stromal invasion)

TNM PROSTATIC URETHRA:

Tis pu CIS, affecting the prostatic urethra
Tis pd CIS, affecting the prostatic ducts
T1  Tumour invading the connective subepithelial tissue
T2  Tumour invading the prostatic stroma, the corpus spongiosum or the periurethral muscle
T3  Tumour invading the prostatic capsule of the corpus cavernosum or the bladder neck (extraprostatic extension)
T4  Tumour invading the neighbouring organs
ANATOMICAL AND HISTOPATHOLOGICAL HISTORY

RECOMMENDATION

TNM : pT4a only in cases of stromal invasion.
For the rest, the stage of the bladder tumour and of the PU should be indicated using suffix Tis pu or Tis pd, meaning extension towards prostatic urethra or towards prostatic ducts.

Extravesical invasion of the seminal vesicles is a sign of locally advanced disease.

Volkmer et al, J Urol 2003
Daneshmand et al, J Urol 2004
Macroscopic evidence of superficial bladder cancer of the prostatic urethra is highly specific.

*Nixon et al, J Urol 2002*

**CONSIDERATIONS:**
Correct sampling of the PU: extensive TUR not feasible in all the patients
Biopsy with the resectoscope loop from the lateral lobes distal to the bladder neck until the verum montanum
In any suspicious lesion and recurrent high grade or bladder CIS
Prostatic sampling plays an important role in the management of the urothelial cell cancer

Prostatic involvement may become a predictor of understaging in BCG failure in NMIBC.

Huguet et al, Eur Urol 2005
**Cystectomy in Patients with High Risk Superficial Bladder Tumors Who Fail Intravesical BCG Therapy: Pre-Cystectomy Prostate Involvement as a Prognostic Factor**

J. Huguet\(^a\),* M. Crego\(^a\), S. Sabaté\(^b\), J. Salvador\(^a\), J. Palou\(^a\), H. Villavicencio\(^a\)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor in prostatic urethra</td>
<td>12.2</td>
<td>2.2–65.5</td>
<td>0.003</td>
</tr>
<tr>
<td>No tumor</td>
<td>0.4</td>
<td>0.07–2.5</td>
<td>0.3</td>
</tr>
<tr>
<td>Size</td>
<td>2.3</td>
<td>0.4–12.01</td>
<td>0.3</td>
</tr>
<tr>
<td>Grade</td>
<td>0.7</td>
<td>0.1–3.4</td>
<td>0.6</td>
</tr>
<tr>
<td>Presence of CIS</td>
<td>0.3</td>
<td>0.08–1.7</td>
<td>0.2</td>
</tr>
<tr>
<td>Sex</td>
<td>0.1</td>
<td>0.01–1.5</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Only the most significant variables in the bivariate analysis are included.
<table>
<thead>
<tr>
<th>TUR (n°)</th>
<th>BCG courses (n°)</th>
<th>Time BCG - cystectomy (months)</th>
<th>Clinical stage (TURB prior to cystectomy) Bladder/prostatic urethra (pu)</th>
<th>Pathological stage (cystectomy specimen)</th>
<th>Progress at follow up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>1</td>
<td>4</td>
<td>Cis</td>
<td>G3 pT3b + Cis</td>
<td>Alive (33)</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>20</td>
<td>Cis</td>
<td>G3 pT2b/pu: Cis</td>
<td>Alive (83)</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>27</td>
<td>G3 Tx</td>
<td>G3 pT2b + Cis</td>
<td>Alive (43)</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>110</td>
<td>G3 Ta + Cis</td>
<td>G3 pTa + Cis + N1</td>
<td>Dead (36)</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>9</td>
<td>G3 T1</td>
<td>G3 pT2b</td>
<td>Alive* (40)</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>18</td>
<td>G3 T1</td>
<td>G3 pT2b</td>
<td>Alive (24)</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>15</td>
<td>G3 T1 + Cis</td>
<td>G3 pT2a + Cis</td>
<td>Alive (36)</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>6</td>
<td>Cis</td>
<td>G3 stromal inv + Cis</td>
<td>Alive (35)</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>9</td>
<td>G3 T1</td>
<td>G3 stromal inv + Cis + N1</td>
<td>Dead (17)</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>6</td>
<td>G3 T1</td>
<td>G3 stromal inv</td>
<td>Alive (2)</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>50</td>
<td>pu: Cis</td>
<td>G3 stromal inv + Cis</td>
<td>Dead (70)</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>22</td>
<td>G3 Ta/pu: Cis</td>
<td>G3 stromal inv + Cis</td>
<td>Alive (16)</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>12</td>
<td>Cis/pu: G3 Ta</td>
<td>G3 stromal inv + Cis</td>
<td>Dead (9)</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>12</td>
<td>G3 T1/pu: G3 T1</td>
<td>G3 stromal inv + N1</td>
<td>Dead (6)</td>
</tr>
<tr>
<td>17</td>
<td>1</td>
<td>9</td>
<td>G2 T1/pu: G2 ducts</td>
<td>G2 stromal inv + N2</td>
<td>Dead (2)</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>40</td>
<td>G3 T1/pu: ducts</td>
<td>G3 stromal inv + Cis</td>
<td>Alive (44)</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>9</td>
<td>G3 Ta/pu: ducts</td>
<td>G3 stromal inv</td>
<td>Alive (31)</td>
</tr>
</tbody>
</table>

Tumors in clinical stages Tis, Ta, T1 that presented with infiltrating bladder tumor (>pT2) or with prostatic stromal invasion on the cystectomy specimen. TUR: Transurethral resection, Pu: prostatic urethra, Stromal inv: Prostatic stromal invasion.

* Alive with disease.
No understaged (n=45)

Understaged (n=17)

P = 0.006

Huguet et al, Eur Urol 2006
TREATMENT OF CIS OF THE PU (TIS PU)


Granulomas in the prostate up to 40 % after intravesical BCG
Mukamel et al, J Urol 1990

Increase of PSA after BCG in 41.6 % of the patients
Leibobici et al, J Urol 2000

Higher increase of PSA in BCG treated patients after TUR of the prostate.
Palou et al, BJU Int 2000
EFFECT OF BCG ON PSA SERUM LEVELS

TURp: Yes  No

Palou et al, BJU 2000
# Prostatic urothelial carcinoma: is transurethral prostatectomy necessary before bacillus Calmette-Guérin immunotherapy?

Ofer N. Gofrit, Dov Pode*, Galina Pizov†, Kevin C. Zorn, Ran Katz* and Amos Shapiro*

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of patients</th>
<th>Median follow-up, months</th>
<th>CR, n/N</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Prostatic-urethra</td>
</tr>
<tr>
<td><strong>BCG only</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Palou Redorta et al. [8]</td>
<td>10 (CIS)</td>
<td>27</td>
<td>8/10</td>
</tr>
<tr>
<td>Taylor et al. [9]</td>
<td>28</td>
<td>90</td>
<td>15/28</td>
</tr>
<tr>
<td>Palou et al. [11]</td>
<td>18 (all CIS)</td>
<td>31*</td>
<td>14/18</td>
</tr>
<tr>
<td>Mungan et al. [12]†</td>
<td>14 (CIS and exophytic)</td>
<td>66</td>
<td>9/14</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>70</td>
<td></td>
<td>46/70 (65.7%)</td>
</tr>
<tr>
<td><strong>TURP and BCG</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Bretton et al. [13]</td>
<td>23 (all CIS)</td>
<td>51.6</td>
<td>23/23</td>
</tr>
<tr>
<td>Present study</td>
<td>20 (CIS and exophytic)</td>
<td>58.5</td>
<td>18/20</td>
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<tr>
<td><strong>Total</strong></td>
<td>43</td>
<td></td>
<td>41/43 (95.3%)</td>
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</table>
MESSAGE:

High- and low-grade non-invasive UCC or CIS of the prostate should be treated with endovesical BCG.
The TUR seems to improve BCG contact with the PU.
It seems that TUR improves efficacy of BCG endovesical treatment.
SUPERFICIAL UCC OF THE PROSTATE
(mucosa involvement)

- LOW GRADE
  - BCG
    - No recurrence
    - Recurrence
      - LOW GRADE
        - 2nd COURSE OF BCG
      - HIGH GRADE or CIS
        - Progression
    - Recurrence
      - Consider CYSTOPROSTATECTOMY

- HIGH GRADE or CIS
  - BCG
    - No recurrence
    - Recurrence
TREATMENT OF CIS OF THE PROSTATIC URETHRA, WITH PROSTATIC DUCT INVOLVEMENT (TIS PD)

BCG ?
TREATMENT OF CIS OF THE PU WITH PROSTATIC DUCT INVOLVEMENT (TIS PD)

## TREATMENT PROSTATIC DUCTS

<table>
<thead>
<tr>
<th>Patients, n</th>
<th>Response, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bretton <em>et al.</em>, 1989&lt;sup&gt;19&lt;/sup&gt;</td>
<td>4</td>
</tr>
<tr>
<td>Schellhammer <em>et al.</em>, 1995&lt;sup&gt;17&lt;/sup&gt;</td>
<td>7</td>
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<tr>
<td>Hardeman and Soloway, 1988&lt;sup&gt;31&lt;/sup&gt;</td>
<td>7</td>
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</tbody>
</table>

- 4 radical surgery
- 3 conservative treatment

*Palou et al, Urology 2007*
<table>
<thead>
<tr>
<th>Pt no.</th>
<th>Prostatic urethra</th>
<th>Associated bladder tumor (p/r)</th>
<th>No. of instillations</th>
<th>Prostatic urethra post-BCG</th>
<th>Bladder post- BCG</th>
<th>Additional treatment</th>
<th>Follow up (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Normal</td>
<td>Tis pd</td>
<td>5</td>
<td>-</td>
<td>Tis</td>
<td>BCG</td>
<td>16</td>
</tr>
<tr>
<td>2</td>
<td>Normal</td>
<td>Tis pd</td>
<td>6</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>156</td>
</tr>
<tr>
<td>3</td>
<td>Normal</td>
<td>Tis pd</td>
<td>6</td>
<td>-</td>
<td>-</td>
<td>Chemo for metastatic disease</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>Tumoral</td>
<td>TaG3 + Tis pd</td>
<td>12</td>
<td>-</td>
<td>T1G2</td>
<td>-</td>
<td>27</td>
</tr>
<tr>
<td>5</td>
<td>Tumoral</td>
<td>TaG3 + Tis pd</td>
<td>5</td>
<td>Ductal +</td>
<td>-</td>
<td>Cystoprostatectomy (stromal invasion)</td>
<td>45</td>
</tr>
<tr>
<td>6</td>
<td>Tumoral</td>
<td>TaG3 + Tis pd</td>
<td>2</td>
<td>Ductal +</td>
<td>T1G3</td>
<td>Cystoprostatectomy (ductal +)</td>
<td>41</td>
</tr>
<tr>
<td>7</td>
<td>Tumoral</td>
<td>TaG2 + Tis pd</td>
<td>6</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>20</td>
</tr>
<tr>
<td>8</td>
<td>Tumoral</td>
<td>TaG1 + Tis pd</td>
<td>2</td>
<td>-</td>
<td>TaG1</td>
<td>TURB</td>
<td>32</td>
</tr>
<tr>
<td>9</td>
<td>Tumoral</td>
<td>TaG1 + Tis pd</td>
<td>6</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>36</td>
</tr>
<tr>
<td>10</td>
<td>Tumoral</td>
<td>Tis pd</td>
<td>6</td>
<td>-</td>
<td>-</td>
<td>- (14)</td>
<td>14</td>
</tr>
<tr>
<td>11</td>
<td>Tumoral</td>
<td>Tis pd</td>
<td>6</td>
<td>No urologic follow-up, nononcologic death 1.5 yr after BCG</td>
<td>-</td>
<td>-</td>
<td>18</td>
</tr>
</tbody>
</table>

p = primary; r = recurrent; TURB = transurethral resection of the bladder.
RESULTS

BCG is a feasible therapeutic option for this kind of patients with TCC affecting the prostatic ducts.

In this trial:
- 73% of the patients had bladder preservation
- Only one death by tumour was observed

It is obvious that these patients need to be strictly followed with cystoscopy and cytology to detect any recurrences and/or progression.

Palou et al, Eur Urol 2006
SUPERFICIAL UCC OF THE PROSTATE

Duct involvement

1. TUR + BCG
   - Re-TUR at 3 mos
     - NO TUMOUR
     - FOLLOW-UP

2. CYSTOPROSTATECTOMY
   - TUMOUR

FOLLOW-UP
Tumour incidence in the prostatic urethra when following-up superficial bladder carcinoma.

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Prostatic urethra tumour</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herr and Donat, 1999</td>
<td>186</td>
<td>39 %</td>
<td>15 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>62 % not invasive</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>38 % stromal inv.</td>
<td></td>
</tr>
<tr>
<td>Hardeman et al. 1988</td>
<td>63</td>
<td>16 %</td>
<td>43 months</td>
</tr>
<tr>
<td>Solsona et al. 1991</td>
<td>276</td>
<td>13.3 %</td>
<td>34.3 months</td>
</tr>
</tbody>
</table>
### Table: Intravesical instillations of BCG for Tis in prostatic urethra in patients with previous treatment(s) of BCG

<table>
<thead>
<tr>
<th>Pt n°</th>
<th>Initial tumor treated with BCG</th>
<th>Interval between BCG and Tis (up to) (months)</th>
<th>Tumor treated by second cycle of BCG</th>
<th>Result of second cycle of BCG</th>
<th>Additional treatment</th>
<th>Evolution</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Bladder</td>
<td>Prostatic urethra</td>
<td>Bladder</td>
<td>Prostatic urethra</td>
<td>Bladder</td>
<td>Prostatic urethra</td>
</tr>
<tr>
<td>1</td>
<td>T1G3 + Tis</td>
<td>-</td>
<td>50</td>
<td>-</td>
<td>Tis</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>T1G3 + Tis</td>
<td>Tis</td>
<td>3</td>
<td>Tis</td>
<td>Tis</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>TaG3 + Tis</td>
<td>Tis</td>
<td>78</td>
<td>Tis</td>
<td>Tis</td>
<td>Tis</td>
</tr>
<tr>
<td>4</td>
<td>T1G3 + Tis</td>
<td>Tis</td>
<td>3</td>
<td>TaG3</td>
<td>Tis</td>
<td>Tis</td>
</tr>
<tr>
<td>5</td>
<td>T1G3 + Tis</td>
<td>-</td>
<td>32</td>
<td>-</td>
<td>Tis</td>
<td>Tis</td>
</tr>
<tr>
<td>6</td>
<td>TaG3 + Tis</td>
<td>-</td>
<td>40</td>
<td>Tis</td>
<td>Tis</td>
<td>Tis</td>
</tr>
<tr>
<td>7</td>
<td>T1G3 + Tis</td>
<td>-</td>
<td>30</td>
<td>-</td>
<td>Tis</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>Tis</td>
<td>-</td>
<td>41</td>
<td>Tis</td>
<td>Tis</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>T1G3 + Tis</td>
<td>Tis</td>
<td>6</td>
<td>Tis</td>
<td>Tis</td>
<td>T4</td>
</tr>
</tbody>
</table>

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**Mean age:** 72 years (63-82)

**Mean follow up:** 47 months (12-84)
PROSTATIC URETHRA FOLLOW-UP

Secondary tumours: In high-risk superficial bladder cancer it occurs in some 10-15% at 5 years and some 20-40 % at 15 ys.

Herr et al, J Urol 1999

RECOMMENDATION

In patients with high-risk superficial bladder UCC and/or CIS, particularly with bladder neck involvement and multifocality, the prostatic urethra should be monitored.

Be careful with understaging
1. Macroscopic evidence of superficial bladder cancer in the prostatic urethra is highly specific. TUR of any macroscopic or suspicious lesion is required once a non-muscle invasive high-grade tumor or CIS, careful follow-up of the prostatic urethra is mandatory (grade C).

2. High- and low-grade non-invasive urothelial carcinoma and CIS of the prostate should be treated with intravesical BCG (grade C).

3. Evidence (level 3) shows that TUR may improve contact of BCG with the prostatic urethra and it looks that response rates to BCG are increased (grade C).
4. CIS or tumor in the prostatic ducts warrants further study. It is advisable for the clinician to perform radical surgery if there is any doubt, to avoid understaging (grade C).

5. Patients with non-invasive urothelial carcinoma in whom conservative therapy fails should be considered for cystoprostatectomy (grade C).

6. Patients with intermediate- to high-risk superficial urothelial carcinoma of the bladder or CIS, especially with involvement of the bladder neck and multifocality, require monitoring of the prostatic urethra (grade B or C).
Transurethral biopsies of the prostatic urethra have shown to be efficacious for identifying prostatic involvement, but they do not reliably determine the extension of such involvement, particularly regarding stromal invasion.

53 % sensitivity and 77 % specificity in the diagnosis of stromal invasion.

New methods are necessary to detect prostatic stromal invasion.

Wood et al, J Urol 1989
Donat et al, J Urol 2001
PROSTATIC STROMAL INVASION

PREDICTIVE FACTORS

CIS at the trigone

Tumor multifocacility

Location of the tumour at or below the trigone (or at the bladder neck)

Lymphovascular invasion

Pettus et al, Eur urol 2008
Richards et al, Urology 2010
Arce et al, Canad J urol 2011
ROLE OF CYSTECTOMY

RECOMMENDATION

Grade C

Radical cystoprostatectomy with lymphadenectomy, with or without urethrectomy, is the choice treatment for loco-regional control in patients with prostatic invasion.
ROLE OF LYMPHADENECTOMY

FACTS

There is a 40-50% incidence of positive nodes in a pT4a tumour.

Data exist that show lymphadenectomy’s potential impact on survival.

See: Invasive bladder cancer
1. The incidence of prostatic urothelial carcinoma in men with superficial or invasive bladder cancer ranges from 12% to 48%, and 7.6% to 16.6% have stromal invasion. The prostate is a site of relapse for patients with non-muscle invasive bladder cancer (grade C).

2. Transurethral biopsy of the prostatic urethra is effective in identifying prostatic involvement but does not accurately reveal the extent of stromal invasion (grade C).

3. Retrospective and prospective studies are needed to determine better prognostic factors for prostatic stromal invasion (grade C).
4. Radical cystoprostatectomy is the treatment of choice for locoregional control in patients with prostatic stromal invasion (grade B).

5. In patients with pT4 disease, the incidence of positive nodes ranges from 40% to 50%, and node mapping studies indicate that multiple sites are involved (grade C).

6. Data show that the extent of lymphadenectomy may have an impact on survival (grade C).
7. The number of patients with prostatic stromal invasion treated in radiation therapy trials is too small to allow definitive conclusions regarding survival outcome (grade C).

8. Although the data are limited and the number of patients with prostate stromal invasion cannot be determined from the literature, the use of radical cystectomy as a salvage procedure does not appear to diminish disease-specific or overall survival probability (grade C).
Chemotherapy for metastatic transitional cell carcinoma of the urothelium

Cora N. Sternberg, San Camillo Forlanini Hospital, Rome, Italy
Guru Sonpavde, US Oncology Baylor College, Webster
Walter M. Stadler, University of Chicago, Chicago
Dean Bajorin, Memorial Sloan Kettering Cancer Center, New York
Robert Dreicer, Cleveland Clinic, Cleveland
Daniel George, Duke University School of Medicine, Durham
Matthew Milowsky, Memorial Sloan Kettering Cancer Center New York
Dan Theodorescu, University of Colorado Cancer Center, Denver, Colorado
David Vaughn, University of Pennsylvania, Philadelphia
Matthew D. Galsky, Mount Sinai, New York
David Quinn, University of Southern California, Los Angeles

ICUD March, 2011
First line randomized trials in advanced transitional cell carcinoma

<table>
<thead>
<tr>
<th>Author</th>
<th>Treatment</th>
<th>N</th>
<th>RR (%)</th>
<th>MDS (mo)</th>
<th>Best arm</th>
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<tr>
<td>Loehrer</td>
<td>M-VAC</td>
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<td>M-VAC &gt; CDPP</td>
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<td>65</td>
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<td>CISCA</td>
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<td>46</td>
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<td>Von der Maase</td>
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<td>202</td>
<td>46</td>
<td>14.8</td>
<td>M-VAC ~ GC</td>
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<td>GC</td>
<td>203</td>
<td>49</td>
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<td>Sternberg</td>
<td>HD-M-VAC</td>
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<td>62</td>
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<td>HD-M-VAC &gt; M-VAC</td>
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<td>M-VAC</td>
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<td>Bamias</td>
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<td>54</td>
<td>14.2</td>
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<td></td>
<td>DC</td>
<td>111</td>
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<td>Bellmunt</td>
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<td>57.1</td>
<td>15.7</td>
<td>PCG ~ GC</td>
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<td>315</td>
<td>46.4</td>
<td>12.8</td>
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</tr>
</tbody>
</table>


Better patient selection, earlier diagnosis and screening, better supportive care (growth factors)
High Dose M-VAC vs M-VAC Study design (n=263)

Stratify
Who PS

Randomize

Classic M-VAC
MTX: 30mg/m2 DAYS 1, 15, 22
VLB: 3mg/m2 DAYS 2, 15, 22
ADM: 30mg/m2 DAY 2
CDDP: 70 mg/m2 DAY 2
Q 28 d

HD- M-VAC + G-CSF
MTX: 30mg/m2 DAY 1
VLB: 3mg/m2 DAY 2
ADM: 30mg/m2 DAY 2
CDDP: 70mg/m2 DAY 2
Q 14 d

Sternberg CN, J Clin Oncol 2001;19(10):2638-1646
High Dose M-VAC vs M-VAC
7 Year update of Overall Survival

Unadjusted p=0.0417
HR=0.76 (0.58 – 0.99)

M-VAC: median 14.9 months
HD-M-VAC: median 15.1 months

25% survival
35% survival

Number of patients at risk:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
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<td>HD M-VAC</td>
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<tr>
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<td>23</td>
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<td></td>
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<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Sternberg CN, Eur J Cancer 2006 Jan;42(1):50-4
M-VAC with G-CSF support

• Hellenic trial of M-VAC vs docetaxel and cisplatin: classic M-VAC with appropriate hematopoietic growth factor support is an effective treatment. (level of evidence 1b)

• EORTC trial of HD-MVAC vs M-VAC is another excellent option that may potentially lead to higher long term cure rates. (level of evidence 1b)
Doublet chemotherapy
GC vs M-VAC - 5 year update

Overall Survival

**GC**
14.0 months (12.3-15.5)

**M-VAC**
15.2 months (13.2-17.3)

HR: 1.09 (0.88-1.34)

Von der Maase H, J Clin Oncol 2005 Jul 20;23(21):4602-8
EORTC30987/Intergroup study design

Randomise

T4bN0M0 or TxCN2-3 or M1 TCC of urothelium
No prior chemotherapy

Opened in May 2001. Closed in June 2004
Centres activated: 107. Patients entered/required: 627/610
Treatment: until disease progression; a max. of 6 cycles

Gemcitabine: 1000 mg/m² days 1, 8 and 15
Cisplatin: 70 mg/m² day 1 or 2
Arm 1 is given as a 4 week cycle (28 days)
→ Every 21 days if d15 is withheld or missed

Paclitaxel 80 mg/m² on days 1 and 8
Cisplatin 70 mg/m² on day 1
Gemcitabine 1000 mg/m² on days 1 and 8
Arm 2 is given as a 3 week cycle (21 days)

Overall Duration of Survival

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number of patients at risk</th>
<th>Median Duration</th>
<th>14% r. reduction risk of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gem/Cis</td>
<td>247/315</td>
<td>12.8 mo</td>
<td></td>
</tr>
<tr>
<td>Pac/Cis/Gem</td>
<td>239/312</td>
<td>15.7 mo</td>
<td>0.86 (0.72-1.03)</td>
</tr>
</tbody>
</table>

Overall Logrank test: $p=0.10$

14% r. reduction risk of death (n.s.)

Median FU = 3.2 years
Maximum FU = 5.5 years
Survival for all patients grouped according to number of risk factors present at baseline

Risk factors:
0 = KPS > 80, no visceral mets
1 = KPS < 80 or visceral mets
2 = KPS < 80 and visceral mets

n=199

Proportion Surviving

Time in Months

0.0
0.2
0.4
0.6
0.8
1.0

No Risk Factors
13.4/13.6 m.
33.0 m.

One Risk Factor
9.3 m.

Two Risk Factors

First line chemotherapy for platinum eligible patients

• Recommended as first line therapy
  M-VAC, HD-MVAC and GC
  (level of evidence 1b)

• Triplet PCG not recommended as first line therapy (level of evidence 1b)
Cisplatin ineligible patients

• The majority of patients with advanced urothelial cancer are older (median age, 68 years)

• Renal function declines with age

• Alternative non-cisplatin based therapy is needed

• Approximately 40% of patients with advanced urothelial cancer are “cisplatin-ineligible” due to renal dysfunction alone

• The proportion of cisplatin-ineligible patients is much higher when including treatment-limiting factors such as poor performance status and comorbidities
Defining “cisplatin-ineligible” patients with metastatic bladder cancer

A large proportion of patients are “unfit” for cisplatin-based therapy

28% of all patients had CrCl < 60 ml/min
40% of patients > 70 had CrCl < 60 ml/min
EORTC 3098

At least one of the following:
• WHO PS 2
• CrCL > 30 mL/min and < 60 mL/min

Randomize

Gemcitabine
Carboplatin

Methotrexate
Carboplatin
Vinblastine

VINCENT

At least one of the following:
• NYHA Class III-IV CHF
• CrCL of ≤ 60 mL/min

Randomize

Vinflunine
Gemcitabine

Placebo
Gemcitabine
Hypothesis

- Tremendous variability exists in the definition of “unfit” patients
- A uniform definition of “unfit” patients will lead to:
  - more uniform clinical trials
  - a greater likelihood of developing a viable strategy for regulatory approval
Types of Definitions

“Pick and Choose”

At least one of the following:

• WHO PS 2
• Creatinine clearance of < 60 mL/min

Traditional inclusion/exclusion

All of the following:

• Karnofsky performance status ≥ 60%
• Creatinine clearance ≥ 30 mL/min
• Cardiac ejection fraction ≥ 40%
Survey of GU Medical Oncologists

• Survey sent on three occasions over 3 weeks

• 65/120 (54%) completed survey

• The majority (62%) cited prior involvement with clinical trials in “unfit” patients
What renal function threshold should be used?

- < 45 ml/min: 19%
- < 50 ml/min: 34%
- < 55 ml/min: 6%
- < 60 ml/min: 42%

N=65
How should renal function be measured?

- Any of these methods: 33%
- Measured GFR: 0%
- Calculated CrCl: 48%
- Measured CrCl: 19%

N=65
How should renal function be measured?

- Any of these methods: 33%
- Measured GFR: 0%
- Calculated CrCl: 48%
- Measured CrCl: 19%

N=65
What age threshold should be used?

- None: 82%
- > 65: 0%
- > 70: 5%
- > 75: 5%
- > 80: 8%
- Other: 2%

N=65
What PS threshold should be included?

- ECOG PS \( \geq 2 \): 42%
- ECOG PS 2: 32%
- ECOG PS \( \geq 1 \): 12%
- PS should not be used: 14%

N=65
What comorbidities should be included?

- Other: 20%
- Solitary kidney: 22%
- Hearing loss: 42%
- Heart failure: 46%
- None: 9%

N=65
Proposed eligibility criteria for clinical trials enrolling “unfit” patients

At least one of the following:

1. ECOG PS of 2 (KPS of 60-70)
2. Creatinine clearance < 60 ml/min
3. CTCAE v4 Grade ≥ 2 audiometric hearing loss
4. CTCAE v4 Grade ≥ 2 peripheral neuropathy
5. NYHA Class III heart failure
Conclusions

• Substantial heterogeneity exists among criteria defining “unfit” patients

• A simple and concise definition of “unfit” is proposed for use as eligibility criteria for clinical trials moving forward.
Randomized phase II/III study assessing gemcitabine/carboplatin (GC) and methotrexate/carboplatin/vinblastine (M-CAVI) in previously untreated patients (pts) with advanced urothelial cancer “unfit” for cisplatin based chemotherapy:

phase III results of EORTC study 30986

M. De Santis ¹, J. Bellmunt ², G. Mead ³, J.M. Kerst ⁴, M. Leahy ⁵, G. Daugaard ⁶, T. Gil ⁷, P. Maroto ⁸, S. Marreaud ⁹, R. Sylvester ⁹

¹ Kaiser Franz Josef - Spital and ACR-ITR VIEnna, Vienna; ² Hospital Vall d'Hebrón, Barcelona; ³ Royal South Hants Hospital, Southampton; ⁴ Netherlands Cancer Institute, Amsterdam; ⁵ St James Hospital, Leeds; ⁶ Rigshospitalet, Copenhagen; ⁷ Institut Jules Bordet, Brussels; ⁸ Hospital Santa Creu, Barcelona; ⁹ EORTC Data Center, Brussels
Phase II/III EORTC randomized trial in unfit metastatic bladder patients

- GCa; gemcitabine & carboplatin
- M-CAVI; methotrexate, carboplatin & vinblastine

- Performance status WHO 2 and/or
- Impaired renal function
  - (30 ml/ min GFR < 60 ml/min)

De Santis M et al, J Clin Oncol 2010 (suppl: abstr LBA 4519)
De Santis M et al, J Clin Oncol 2009, 27, no. 33, 5634-5639
Phase III results of EORTC study 30986

First valid PFS data in this patient population

HR=1.04 (95%CI: 0.80, 1.35)
p=0.78

4.2 months (95%CI: 3.7, 5.9)
5.8 months (95%CI: 4.8, 6.9)

De Santis M et al, J Clin Oncol 2010 (suppl: abstr LBA 4519)
Phase III results of EORTC study 30986

First valid OS data in this patient population

HR = 0.94 (95% CI: 0.72, 1.22)

p = 0.64

8.1 months (95% CI: 6.1, 10.3)
9.3 months (95% CI: 7.6, 11.3)

De Santis M et al, J Clin Oncol 2010 (suppl: abstr LBA 4519)
GCa vs M-CAVI in poor PS or CrCl< 60 ml/min

- The first randomized phase III trial comparing GCa and M-CAVI in cisplatin ineligible patients
- Patients ineligible for cisplatin, benefit from carboplatin based combination chemotherapy although toxicities were important
- Both combinations were active in this well defined group of unfit patients, although toxicity was higher on the M-CAVI arm
- Patients with CrCl 40-60 and those with poor PS could be evaluated separately

Sternberg CN, ASCO discussion 2010
This trial provides **level 1 evidence** for the use of GCa chemotherapy in patients deemed ineligible for cisplatin-based chemotherapy,

Adoption of a standard definition of “cisplatin-ineligible” and additional randomized studies of chemotherapy and novel agents in this patient population are desperately needed.
<table>
<thead>
<tr>
<th>Author and year of publication</th>
<th>Molecule</th>
<th>No. of patients evaluated</th>
<th>ORR (%)</th>
<th>Median survival time in months</th>
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<td>Blumenreich, 1982</td>
<td>Vinblastine</td>
<td>37</td>
<td>18</td>
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<td>Witte, 1997</td>
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<td>Mc Caffrey, 1997</td>
<td>Docetaxel</td>
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<td>Piritrexim</td>
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<td>Wulfing, 2009</td>
<td>Lapatininib</td>
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<td>Moore, 2003</td>
<td>Oxaliplatin</td>
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<td>Sridhar, 2005</td>
<td>Bortezomib</td>
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<td>Dreicer, 2007</td>
<td>Epothilone B</td>
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<td>Sweeney, 2006</td>
<td>Pemetrexed</td>
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<td>Gallagher, 2007</td>
<td>Sunitinib</td>
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<td>9</td>
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<td>Dreicer, 2009</td>
<td>Sorafenib</td>
<td>27</td>
<td>0</td>
<td>6.8</td>
</tr>
</tbody>
</table>
Phase III trial of Vinflunine plus Best Supportive Care vs BSC alone (n=370)

**Randomize**

- 2nd line
- T4bN0M0 or TxN2-3 or M1 Progression after 1st line Platinum treatment
- **Stratify**
- Center Refractory vs. non-refractory

**Randomize**

- VFL+BSC (PS 0: 320mg/m², q3w; PS 0 with previous pelvic irradiation and PS1: 280mg/m² (n=253)
- BSC with treatment upon progression permitted (n=117)

Primary endpoint: Overall survival
Secondary Endpoints: ORR, PFS, Disease control, QOL and Clinical Benefit

Bellmunt J, J Clin Oncol. 2009 Sep 20;27(27):4454-61
Phase III trial of Vinflunine plus Best Supportive Care vs BSC alone: OS

ITT population

N=370

Eligible patients

N=357

Bellmunt J, J Clin Oncol. 2009 Sep 20;27(27):4454-61
Overall Survival: Intent to Treat Population (N= 370)

7 month median survival is a benchmark in the second line setting!

<table>
<thead>
<tr>
<th></th>
<th>VFL + BSC</th>
<th>BSC</th>
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<tbody>
<tr>
<td>N</td>
<td>253</td>
<td>117</td>
</tr>
<tr>
<td>No. of events</td>
<td>204</td>
<td>103</td>
</tr>
<tr>
<td>No. censored (%)</td>
<td>49 (19.4)</td>
<td>14 (12.0)</td>
</tr>
<tr>
<td>Median OS (months)</td>
<td><strong>6.9</strong> (5.7, 8.0)</td>
<td><strong>4.6</strong> (4.1, 7.0)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.88 (0.69, 1.12)</td>
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<tr>
<td>p value *</td>
<td>0.2868</td>
<td></td>
</tr>
</tbody>
</table>

* Stratified log rank test

Bellmunt J, J Clin Oncol. 2009 Sep 20;27(27):4454-61
Vinflunine - second line therapy

• Based on this study, vinflunine was approved by the European Medicine Agency (EMA)

• The only agent approved by a regulatory agency for this indication.

• A retrospective analysis of patients that received second-line vinflunine identified ECOG performance status >0, hemoglobin <10g/dL and liver metastasis as poor prognostic factors

Bellmunt J, J Clin Oncol 2010;28(11)1850-5
Combination therapy as second-line therapy

Paclitaxel and gemcitabine:

German randomized phase II trial of 102 patients compared 6 cycles of second-line gemcitabine-paclitaxel with continuation beyond 6 cycles until progression.

Italian trial of every 2 week gemcitabine-paclitaxel

Carboplatin-paclitaxel following prior cisplatin-based chemotherapy

Vaishampayan UN, Cancer 2005, 104(8):1627-32
Second-line chemotherapy

- Vinflunine: Level 2a and Grade B recommendation
- Clinical trials should remain the preferred option
## Novel agents: ongoing or planned phase II trials of salvage therapy for metastatic TCC

<table>
<thead>
<tr>
<th>Drug/Regimen</th>
<th>Molecular target</th>
<th>Institution</th>
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</thead>
<tbody>
<tr>
<td>Nab-paclitaxel</td>
<td>Tubulin</td>
<td>Canadian</td>
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<tr>
<td>AZD-4877</td>
<td>Kinesin spindle protein</td>
<td>Multicenter</td>
</tr>
<tr>
<td>Pralatrexate</td>
<td>Folate</td>
<td>Multicenter</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>VEGFR2, PDGFR</td>
<td>Italy, NCI (US)</td>
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<tr>
<td>Tamoxifen</td>
<td>Estrogen receptors</td>
<td>Baylor</td>
</tr>
<tr>
<td>Everolimus</td>
<td>mTOR</td>
<td>Belgian</td>
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<tr>
<td>Everolimus-Paclitaxel</td>
<td>mTOR and tubulins</td>
<td>SWOG</td>
</tr>
<tr>
<td>Aflibercept</td>
<td>VEGF, PIGF</td>
<td>NCI (US)</td>
</tr>
<tr>
<td>TKI-258 (Dovitinib)</td>
<td>VEGFR, PDGFR, FGFR</td>
<td>Multicenter</td>
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<tr>
<td>Vorinostat</td>
<td>HDAC</td>
<td>California</td>
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<tr>
<td>Docetaxel-ASA404</td>
<td>Tumor and endothelial tubulin</td>
<td>Mt. Sinai/HOG</td>
</tr>
<tr>
<td>BI-6727</td>
<td>Polo-like kinase</td>
<td>Multicenter (US)</td>
</tr>
<tr>
<td>Author</td>
<td>Regimen</td>
<td>Results</td>
</tr>
<tr>
<td>-------------------------</td>
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<td>------------------------</td>
</tr>
<tr>
<td>Petrylak 2003 (SWOG)</td>
<td>2nd line Gefitinib</td>
<td>N=29, 3%RR 4% PFS at 6 mos</td>
</tr>
<tr>
<td>Philips 2008 (CALGB)</td>
<td>Fixed Dose-Rate Gemcitabine, DDP + Gefitinib</td>
<td>N=25, 36% RR OS 11.1 mos</td>
</tr>
<tr>
<td>Hussain 2007</td>
<td>HER 2 positive Trastuzumab, Paclitaxel, Carbo + Gemcitabine</td>
<td>N=44/57 70% RR, OS 14.1 mos</td>
</tr>
<tr>
<td>Wülfing, 2009</td>
<td>2nd line Lapatananb</td>
<td>N=59, 1.7% OR, SD 31% med TTP 8.6 wks, OS 17.9 wks</td>
</tr>
</tbody>
</table>

Modified from Sternberg C, ASCO Education 2008
# Trials with HER 1/2 Inhibition

<table>
<thead>
<tr>
<th>Advanced Disease</th>
<th>Maintenance or Consolidation</th>
<th>Neo adjuvant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lapatinib + GC phase I (EORTC)</td>
<td>Lapatinib (Powles)</td>
<td>Erlotinib (Siefker-Radtke, MDACC)</td>
</tr>
<tr>
<td>GC +/- Cetuximab (Hussain)</td>
<td>Docetaxel +/- Gefitinib</td>
<td></td>
</tr>
<tr>
<td>Cetuximab +/- Paclitaxel (Fox Chase)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Modified from Sternberg C, ASCO Education 2008
Stage IV bladder cancer

4-8 cycles of 1st line chemotherapy

HER1/HER2 status

Positive

Response to chemo

CR/PR/SD

Randomisation

Lapatinib

Placebo

Progression free survival (primary end point)

Follow up for survival

Increase PFS from the time of completion of chemo. from 6 to 9 mos n=204

Response to chemo

PD

Exclusion criteria

Her1/Her2 positive

Responders

Randomized

Selected

(European Consortium) Maintenance
Targeting angiogenesis in urothelial cancer

- VEGF, bFGF and IL-8 levels correlate with stage and outcome
- MVD: predictor of progression, vascular inv, N+, recurrence, and S in invasive TCC
- ↑VEGF levels in the metastatic setting appears to correlate with poor DFS
- VEGF mRNA levels and MVD independent prognostic factors for recurrence and M1 in neoadjuvant M-VAC

Elfiky AA and Rosenberg JE, Curr Oncol Rep. 2009 May;11(3):244-9
# Single Agent Angiogenesis Inhibition in TCC

<table>
<thead>
<tr>
<th>Presented</th>
<th>Advanced</th>
<th>Ongoing</th>
<th>Advanced</th>
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<tbody>
<tr>
<td>Bellmunt ASCO GU 2008</td>
<td>1st line “Unfit” Sunitinib 14.3% PR, 78.6% benefit and 6 mos TTP</td>
<td>Necci ESMO 2010) Pili (ASCO GU)</td>
<td>2nd and 3° line Pazopanib (TKI)</td>
</tr>
<tr>
<td>Gallagher ASCO 2008/ 2009*</td>
<td>2nd line Sunitinib 7% PR, 24% Stab but 17% PFS &gt; 3 mos. Cont dose: less activity*</td>
<td>California Cancer Consortium</td>
<td>2nd line VEGF Trap (anti-VEGF antibody with broad activity)</td>
</tr>
<tr>
<td>Dreicer (ECOG) ASCO 2008</td>
<td>2nd line Sorafenib no significant activity</td>
<td></td>
<td></td>
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<tr>
<td>Hussain Consortium ASCO 2009</td>
<td><strong>Maintenance</strong> Randomized Phase II Sunitinib</td>
<td></td>
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</tbody>
</table>

Modified from Sternberg C, ASCO Education 2008
# Advanced Combination Chemotherapy and Anti-angiogenesis Trials

<table>
<thead>
<tr>
<th>Presented</th>
<th>Phase II</th>
<th>Ongoing</th>
<th>Phase II/III</th>
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<tbody>
<tr>
<td>Hahn (HOG) ASCO 2009</td>
<td>Cisplatin + Gemcitabine + Bevacizumab</td>
<td>Choueiri (DFCI)</td>
<td>2nd line Docetaxel +/- ZD6474 (Zactima)</td>
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<tr>
<td>Bajorin (MSKCC) ASCO 2009 (tox)</td>
<td>Carbo + Gem + Bevacizumab</td>
<td>Kelly (Jefferson)</td>
<td>Carboplatin + Gem+Sorafenib</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rosenberg (CALGB) Phase III</td>
<td>Cisplatin + Gemcitabine +/- Bevacizumab</td>
</tr>
</tbody>
</table>

Modified from Sternberg C, ASCO Education 2008
Personalized therapy using emerging technologies

- Pharmacogenomics (blood, tumor)
- Genomic profiling (molecular profiling)
- Genomic profiling/drug sensitivity: i.e. CO-XEN
- Mutational analysis (high-throughput)
- Proteomics – still in its infancy
- Micro RNA
- Circulating tumor cells
Pharmacogenomics in bladder cancer

- Differences in DNA repair capacity modify individual susceptibility to carcinogenesis, but also affect individual response to therapy

- Nucleotide excision repair (NER) is one of the major DNA repair pathways (ERCC1, BRCA1)

- The product of ERCC-1 gene functions in the NER pathway and is a molecular marker of platinum resistance
Predictive factors of response: ERCC1

Nucleotide excision repair

- Excision repair cross complementing 1 (ERCC1) predicts response and resistance to cisplatin.

- Significant correlation between relative gene expression levels > 7 and decrease in survival (p = 0.035).


57 patients with advanced TCC, Rx with GC or the triplet containing paclitaxel and GC.
Co-expression extrapolation (COXEN) algorithm

- Predicting clinical outcomes by using molecular signatures (i.e. breast cancer)
- Incorporates gene profiling with drug sensitivity
- Validates the clinical setting with patient outcomes
- Forecasts drug responses

Evaluation of COXEN treatment response biomarkers in human bladder cancer

Focus on the subset of probes that constitutes a signature of drug sensitivity!
Validation of new drug effectiveness in human bladder cancer cells: 45,545 compounds tested

**NSC 637993**

40 human bladder cancer cell lines (BLA-40)

Bladder Cancer Clinical Trial with C-1311

Log base 10 of molar concentration of NSC 637993

Courtesy of D. Theodorescu
Concordant Gene Expression Signatures Predict Clinical Outcomes of Cancer Patients Undergoing Systemic Therapy

Paul D. Williams,¹ Sooyoung Cheon,¹ Dmytro M. Havaleshko,² Hyeon Jeong,² Feng Cheng,³ Dan Theodorescu,²,⁴ and Jae K. Lee¹

[ Cancer Res 2009;69(21):8302–9 ]

Gene expression model
Genome-wide gene expression profiling
Predicting response to neoadjuvant M-VAC

**Fig. 1.** Expression patterns of the 50 genes that discriminated responders from nonresponders among 15 patients with bladder cancer. Horizontal rows represent individual genes; vertical columns represent individual samples. Each cell in the matrix represents the expression level of a single transcript in single sample, with red and green indicating transcript levels, respectively, above and below the median for that gene across all samples. Black represents unchanged expression or slight expression (intensities of both Cy3 and Cy5 under the cutoff value). Color saturation is proportional to the magnitude of the difference.

**Increased expression in non-responders**
(25 genes)

**Decreased expression in non-responders**
(25 genes)
Genetic signatures associated with aggressive behavior

High throughput DNA microarrays identify biomarkers for bladder cancer

Gene expression based or immunohistochemical detected biomarkers

- Promising biomarkers have not yet been extensively validated in sufficient numbers in prospective clinical trials
- Could become part of the diagnostic workup and management in the future
- Grade of recommendation: Not recommended outside a clinical trial or biomarker study (level of evidence 2b)
Conclusions for first line therapy

- First-line advanced urothelial cancer with adequate renal function: combination cisplatin regimens are the standard of care (Grade A recommendation).

- Use of triplet regimens adding paclitaxel to gemcitabine plus cisplatin is not recommended.

- Unfit patients: renal impairment, advanced age or poor performance status: carboplatin and gemcitabine (Grade A recommendation).

- Renal impairment only gemcitabine/carboplatin/paclitaxel can be considered (Grade C).
Conclusions for second line therapy

- For second line therapy after a platinum based treatment, vinflunine has been adopted as a standard in Europe but not in North America. (Grade B recommendation).

- Novel agents and approaches are urgently needed and clinical trial accrual needs to be actively encouraged.

- The standard of care for a majority of patients with advanced bladder cancer is the best clinical trial available.
Non-urothelial cancer of the Bladder

Bruce R. Kava (USA) – sub committee chair
Jack Baniel (Israel)- presentation
Hassan Abol-Enein (Egypt)
Alexandra J Colquhoun (USA)
William H Turner (UK)
Adrienne J. K. Carmack (USA)
Non-urothelial Bladder Cancer

- TCC is the most prevalent bladder tumor (superficial and invasive)
- The other end of bladder tumors:
  - Squamous Cell Carcinoma
  - Adenocarcinoma
  - Small cell carcinoma
  - Others

(Level 3 evidence)
Clinical Epidemiology of Nonurothelial Bladder Cancer: Analysis of The Netherlands Cancer Registry

Martine Ploeg, Katja K. Aben, Christina A. Hulsbergen-van de Kaa, Mark P. Schoenberg, Johannes A. Witjes and Lambertus A. Kiemeney*

From the Departments of Urology (MP, JAW, LAK), Epidemiology, Biostatistics and HTA (KKA, LAK), and Pathology (CAHvdK), Radboud University Nijmegen Medical Centre and Comprehensive Cancer Centre East (KKA, LAK), Nijmegen, The Netherlands, and Department of Urology, The Johns Hopkins Hospital (MPS), Baltimore, Maryland

<table>
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<tr>
<td>Overall</td>
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Worldwide Incidence
Urothelial and Nonurothelial Bladder Cancer

Squamous Cell Carcinoma (SCC)

Two main categories:

- SCC in western countries (non-bilharzial)
- SCC in the bilharzial bladder

(Rundle, 1982) (Level 3 evidence)
Non-bilharzial SCC of the Bladder

Epidemiology

- 2nd bladder malignancy
- age ≥ 70 years
- 2-5% in contemporary cystectomy series
- Black to white 2:1
- Male to female ratio 1.4:1
- Presents at advanced stage

(Serratta, 2000) (Level 3 evidence)
Non Bilharzial SCC of The Bladder
Gender Differences

In USA:
- incidence of urothelial ca in men >3x women
- incidence of non-urothelial ca in men =1.4x women

(Johansson SL and Cohen SM 1997: compiled data from 915 patients in 10 series)

Women present with more advanced stage tumors:

Data derived from the Netherlands Cancer Registry: Level 3)
Non Bilharzial SCC of The Bladder

Etiology

- Relation to cigarette smoking is not clear.
- *Chronic inflammatory disorders.
- *Calculi, diverticula, indwelling catheters.
- Spinal cord injury patients.
- Squamous metaplasia is common.

(Thorn, 1997) *(Level 3 evidence)*

(- *Level 4 evidence)*
Non Bilharzial SCC of The Bladder Association with Spinal Cord Injury

Incidence of SCC in Spinal Cord Injured patients:
2.3- 10% in early, small retrospective reports

West et al (Urology 1999): US Dept of Veteran’s Affairs Admissions Data:
33,560 patients with SCI identified
130 (0.39%) patients with Bladder cancer identified
of: 42 records available for review:
23 (55%) Urothelial ca
13 (33%) SCC
4 (10%) Adenoca

May reflect: increase in cigarette smoking and reduced indwelling catheters
Non Bilharzial SCC of The Bladder Association with Spinal Cord Injury


8/2900 (0.32%) SCI patients developed bladder cancer
2/8 SCC, 6/8 Urothelial ca

Pannek J (2002): by questionnaire sent to Urology Depts in Eastern Europe

43,561 SCI patients identified

Only 7% of patients had indwelling catheters
48 (0.11%) patients developed bladder cancer
19% of the patients with bladder cancer were SCC
SCC of the Bladder in Spinal Cord Injury

Recommendations: (Grade B)

- The incidence is less than 1%
- Monitoring of patients with indwelling catheters is important
- Hematuria should be evaluated
- Frequency of surveillance and diagnostic work up can not be determined
Non-bilharzial SCC of the Bladder

Pure SCC (Clinico-pathologic features):

- Usually present with hematuria
- 30-90% have associated infection – irritative symptoms
- Latent period from symptoms to diagnosis
- Superficial SCC is rare, majority are muscle-invasive

(Jones, 1980; Rundle, 1982; Quilty, 1986) (Level 3 evidence)
Non-bilharzial SCC of the Bladder

Pure SCC (Clinico-pathological features):
- Solitary large tumor
- Sessile lesion with ulceration surrounded with metaplasia
- Trigone, but can occur in other areas
- May develop in diverticula, associated with stones
- Imaging and work-up the same as for TCC

(Costello, 1984; Sereta, 2000)
(Level 3, 4 evidence)
Non-bilharzial SCC of the Bladder: Treatment

- Prognosis is generally poor (most die 1-3 years after dg.)
- Radical surgery is the most effective treatment
- 5-year survival rates range from (16-48%)
- Treatment failure is usually due to local pelvic recurrence
- Incidence of distant mets 8-10%  

(Jones, 1980)  
(Level 3 evidence)
Non-bilharzial SCC of the Bladder: Treatment

Radiotherapy Alone:

- 5-year survival 16-26%
- The response was more in $T_2$ disease.
- $T_3$ disease (4.8%) 5 years.

(Quilty, 1986; Johnson, 1976; Rundle, 1982)

(Level 3 evidence)
Non-bilharzial SCC of the Bladder: Treatment

Preoperative radiotherapy?

- Some improvement – 5 years 48% (many patients had been excluded).
- No reliable randomized studies to draw a conclusion.

(Richie, 1976)

(Level 3 evidence)
Non-bilharzicial SCC of the Bladder: Treatment

Chemotherapy?

- Role is uncertain
- Effective chemotherapy protocol has not been found
- Neoadjuvant M-VAC no response

*(Khaled, 2000)*
*(Level 3 evidence)*

- The results of new combination regimens (paclitaxel-gemcitabine-cisplatin) are awaited.

*(Level 4 evidence)*
Bilharzial SCC of The Bladder

Pathogenesis

- Latent period up to 30 years.
- Locally produced chemical carcinogen
- DNA changes
- Bacterial infections (Nitrosamines)
- Metaplasia (Mechanical irritation)

Level 4
Changing Patterns of Egyptian Bladder Cancer
Data abstracted from NCI- Cairo

Bilharzial SCC of The Bladder

Clinical presentation

- Latency period of approx 30 years between infestation and development of cancer
- Similar symptoms between bilharzial cystitis and malignant cystitis. Painful and frequent voiding, with hematuria
- Many cases have advanced disease when first seen
- Diagnostic work-up is the same as TCC (CK in the urine)
Retrospective Egyptian Cystectomy Series
Pathologic Stage and Prognosis

Tumor grade:
- GI: 50%
- GII: 32%
- GIII: 18%

Understaged in 33%

Bilharzial SCC of The Bladder
Clinico-pathological features:

- Most of the tumors are located in posterior or lateral walls
- 5 types based upon gross appearance
  - Nodular fungating: 60%
  - Ulcerative 23%
  - Verrucous 7%
  - Papillary 7%
  - Diffuse 3%
- Atypical changes - Metaplasia, dysplasia, leukoplakia are common but CIS is rarely seen.
- Very rare to invade the ureters or the urethra
Bilharzial SCC of The Bladder EUA/Endoscopic Resection

- In many cases, limited to biopsy
- Not a known tool for treatment because of bulky disease.
- In case of complete endoscopic excision, follow up cystoscopy and deep biopsy is required

Level 4
Bilharzial SCC of The Bladder
Partial cystectomy

Indications limited:

- Low grade, solitary lesion
- Small tumor allows good safety margin
- Away from the trigone.

These criteria were present in 19/190 pat. (10%).
Augmentation cystoplasty needed in 25%.
5 year survival in 26.5%.
Local recurrence was high.

*El-Hammady, (1975): Level 3*
Bilharzial SCC of The Bladder
Radical Cystectomy

- 608 patients with SCC.
- 5 year survival = 50.3%.
- Tumor stage, grade and LN involvement were independent prognostic factors.
- Cystectomy as single modality is inadequate.

Ghoneim (1997): Level 3
Bilharzial SCC of The Bladder
Neoadjuvant Radiation Therapy

- 20 cGy prior to cystectomy vs cystectomy alone
- Prospective, randomized trial evaluating 90 patients.
- 60 months follow-up
- Trend in favor of irradiation but not statistically significant.

Bilharzial SCC of The Bladder
Radiation Therapy alone:

- Few studies
- Poor response
  - Tumor bulk with hypoxic cells
  - Bilharzial cystitis (intolerance)

\textit{cystectomy vs. 20 rad + cystectomy vs. 20 rad + misonidazole + cystectomy} - Addition of misonidazole as a radiosensitizer did not alter survival advantage. \textit{Ghoneim 1985}
Bilharzial SCC of The Bladder
Chemotherapy

Phase II studies showed some activity of epirubicin.

*Level 4*

Neoadjuvant epirubicin showed an initial promising results in one study but was not reproducible.

*Level 2*

In recent multicenter trial using neoadjuvant cisplatin + gemcitabine, patients with SCC did not show survival advantage.  *Level 2*

New chemotherapy protocol has to be identified.
Squamous Cell Carcinoma
Grade B: Recommendations

**Non-Bilharzial SCC:**
Predominantly single center, retrospective series
Radical Cystectomy appears to offer the best survival in localized disease

**Bilharzial SCC:**
Predominantly single center, retrospective series
Radical Cystectomy appears to offer the best survival in localized disease
Adenocarcinoma of the bladder
Adenocarcinoma of The Bladder

- Primary
- Urachal
- Metastatic
Adenocarcinoma of the Bladder

Incidence

- 0.5-2% Western series
  (Bennet, 1984) (Level 3 evidence)

- 8-11% In Endemic Bilharzial areas
  (El-Mekresh, 1998) (Level 3 evidence)

- Exstrophy – 4% life time risk

- Male to female: 2.7:1
  (Level 3 evidence)
Adenocarcinoma of The Bladder

Uracchal Carcinoma:

- Rare tumor (1 in 1400)
- Younger age (49 years vs. 58 nonurachal)
- Male to female 4:3

(Dandeker, 1997)

(Level 3 evidence)
Adenocarcinoma of The Bladder

Urachal Carcinoma:
- Location (bladder dome)
- Extravesical extension
- Sharp demarcation
- Not associated with cystitis glandularis
- Indistinguishable from enteric adenocarcinoma

(Johnson, 1985)

(Level 4 evidence)
Urachal Carcinoma:

Staging (Sheldon, 1984)

I: Urachal mucosa

II: Invasion to the urachus

III: Invasion to the bladder, abdominal wall, local viscera

IV: regional nodes or distant metastases
Adenocarcinoma of The Bladder

Uracchal Carcinoma:

- **Treatment:** Wide excision of the umbilicus, urachus, and partial cystectomy

- **Survival:** 40% at 5 years (MD Anderson)

- **Prognosis:**
  - Lymph node involvement
  - Positive surgical margin

*(Level 3 evidence)*
Adenocarcinoma of The Bladder

Urachal Carcinoma:

systemic treatment:

Chemotherapy

- 5-fluorouracil and cisplatin
- No benefit (Level 3 evidence)

Radiotherapy

- Not enough trials – seems poor (Level 4 evidence)
Adenocarcinoma of The Bladder

Adenocarcinoma in bladder extrophy:
- The most common malignancy in the retained bladder
- More in males (McIntoch and Woly 1955) (Level 3 evidence)
- 4/102 patients followed for more than 35 years
- 700 times risk > normal population (Smeulder, 2001) (Level 3 evidence)
- Metaplasia of the urothelium d/t defunctionalised bladder and bowel augmentation (Level 4 evidence)
Adenocarcinoma of The Bladder

- Primary adenocarcinoma
  - Chronic vesical irritation, metaplastic changes
  - Virtually always invasive  \textit{(Dandekar, 1997)}
  - Mucin or non-mucin producing
  - Stage, Grade, LNs are the prognostic factors  \textit{(El-Mekresh, 1998)}  (Level 3 evidence)
## Adenocarcinoma of The Bladder

### Primary adenocarcinoma

#### Treatment

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>TUR</td>
<td>(19% -5 years)</td>
<td>(Kramer, 1979)</td>
</tr>
<tr>
<td>Partial cystectomy</td>
<td>(dismal ~25%)</td>
<td>(Abenoza, 1987)</td>
</tr>
<tr>
<td>Radical cystectomy</td>
<td>(0-80%)</td>
<td>(El-Mekresh, 1998)</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>(&lt;20%)</td>
<td>(Thomas, 1971)</td>
</tr>
<tr>
<td>Preoperative irradiation</td>
<td>(No benefit)</td>
<td>(Anderstrom, 1983)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>(Dismal)</td>
<td>(Hatch, 1989)</td>
</tr>
</tbody>
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*(Level 3 evidence)*
Adenocarcinoma of The Bladder

- Secondary adenocarcinoma
  - Direct extension
  - Lymphohematogeneous spread

- Colon 21%
- Prostate 19%
- Rectum 12%
- Cervix 11%

(Bates and Baithun, 2000) (Level 3 evidence)

- Deleted in Colon Cancer protein (DCC) immunostain +ve may differentiate primary from 2° (Yossepowitch, urology 2004) level 3
Adenocarcinoma of the Bladder

Secondary adenocarcinoma

**Treatment:**
- Wide excision with a wide safety margin is required (20% recurrence)
- Bladder-sparing surgery (100% recurrence)
- The treatment failure depends on the stage of the primary disease

*(Carne, 2004) (Level 3 evidence)*
Small Cell Carcinoma

- Rare tumor (neuroendocrine tumor in the lungs)
- +/- 300 cases reported
- 0.4 – 0.7% of all bladder tumors
- Age above 60, 80% are males
- Pathological diagnosis is difficult
- Usual appearance at stage $\geq T2$
- Metastatic disease in 67% (LN, liver, bone, lung and brain).

(Sved et al., 2004) (Level 3 evidence)
Small Cell Carcinoma

Treatment: multimodal therapy

Lung small cell – chemotx. – cis+etoposide/ifos+doxo, median survival – 10-14 months

MDA experience (JUrol,2004) – 46 pts. 5-year survival:
- cystectomy + post-op chemo – 36%
- neoadjuvant chemo + cystectomy -78% (chemo directed to small cell and not MVAC/gemzar+cis)

2009, 2 studies (UK+North Africa) survival – 7-33 months

(Siefker-Radtke et al.,2004) (Level 3 evidence)
Small Cell Carcinoma

GRADE B RECOMMENDATION:
Cure is most likely with a combined multimodality approach including neoadjuvant chemotherapy and local therapy
Bladder Sarcoma

- Leiomyosarcoma (50%)
- Hematuria → early diagnosis
- Radical cystectomy in early cases (80% survival) 
  (Rosso, 1992) (Level 3 evidence)
- Multimodal treatment in metastatic disease 
  (Level 4 evidence)
Rare Bladder Malignancies

**Carcinosarcoma**
- Aggressive disease (41 cases)
- Poor outcome following cystectomy alone
  
  *(Lopenz-Beltran, 1998) (Level 3 evidence)*

- Multimodal treatment  
  *(Froehner, 2001) (Level 4 evidence)*

**Paraganglioma, pheochromocytoma**
- Paroxysmal symptoms with micturition
- Cystoscopy under precaution (Biopsy !!!)
- Local excision with lymphadenectomy
- May be difficult to distinguish (benign or malig)
  
  *(Klingler, 2001) (Level 3 evidence)*
Rare Bladder Malignancies

**Melanoma:**
- Primary is rare
- Secondary from the skin is more prevalent
- Clinical picture and biopsy are diagnostic – urethra and not so much in the bladder
- Treatment is radical surgery
- Prognosis is poor

*(De Torres, 1995) (Level 3 evidence)*
Rare Bladder Malignancies

Lymphoma:

- Part of metastatic spread
- More in women
- Localized disease has good prognosis
- Local irradiation is satisfactory

(Kempton, 1997) (Level 3 evidence)
Bladder Pseudotumors

- Rare
- Resemble malignancy
- Postoperative spindle cell tumors
- Can mimic leiomyosarcoma
- Absence of mitotic figures
- TUR or partial resection is enough
- Cystectomy if the diagnosis is difficult

(Jones, 1993) (Level 3 evidence)