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This document has been updated to reflect changes in availability of the chemotherapeutic agents epirubicin and valrubicin.

American Urological Association

Education and Research, Inc.

Bladder Cancer

Bladder Cancer Clinical Guideline Update Panel

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Guideline for the Management of Nonmuscle Invasive Bladder Cancer: (Stages Ta,T1, and Tis): 2007 Update

Guideline for the Management of Nonmuscle Invasive Bladder Cancer: (Stages Ta, T1 and Tis: Update (2007)

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Chapter 1: The Management of Bladder Cancer: Diagnosis and Treatment

Recommendations

Introduction

More than 60,000 new cases of bladder cancer are diagnosed each year in the United States accounting for approximately 13,000 deaths annually.[1] In recent decades the overall incidence of bladder cancer has appeared to be rising[2] and this may be due to the latent effects of tobacco abuse and industrial carcinogens, as well as the overall aging of our population.

When initially diagnosed, most bladder cancers are nonmuscle invasive (also referred to as "superficial") – i.e., either noninvasive and confined to the mucosa or invading the lamina propria but not yet invading the detrusor muscle. In 1999, the American Urological Association (AUA) published a report by Smith and associates on the *Bladder Cancer Clinical Guidelines Panel Summary Report on the Management of Nonmuscle Invasive Bladder Cancer (Stages Ta, T1 and Tis)* (AUA Guideline) produced by the AUA's Bladder Cancer Clinical Guideline Panel (Appendix 1).[3] That expert panel developed a practice guideline for three types of patients: (1) the patient who presents with an abnormal growth on the urothelium but not yet diagnosed with bladder cancer; (2) the patient with established bladder cancer of any grade, stage Ta or T1, with or without carcinoma in situ (Tis) who had not had prior intravesical therapies; and (3) the patient with Tis or high-grade T1 cancer who had at least one course of intravesical therapy. The report provided an evidence-based guideline for the patient with nonmuscle invasive bladder cancer and included management standards, guidelines, and options based on the strength of evidence and expected amount of variation in patient preferences.

Since 1999 the field of nonmuscle invasive bladder cancer has changed substantially with regard to the understanding of the molecular biology and clinical behavior of this heterogeneous disease. In addition, the growing body and quality of clinical research methodologies have improved during this period. The more recent publication of randomized controlled trials, the gold standard of treatment evaluation, has allowed the evaluation and comparison of various treatment modalities. For these reasons, the AUA Practice Guidelines Committee has elected to update the initial report by appointing a panel (Appendix 2) to develop a new guideline for the management of nonmuscle invasive bladder cancer founded on evidence-based outcomes in the literature as well as expert opinion. Only topics having sufficient evidence on which to base conclusions were addressed in this guideline.

Background

This section will provide a current overview of nonmuscle invasive urothelial carcinoma including a discussion of epidemiologic features and possible etiologic factors, and a review of the histology and tumor subtypes of this disease.

Epidemiology

In the United States in 2007 an estimated 67,160 new cases of bladder cancer are expected to be diagnosed (approximately 50,040 men and 17,120 women), with an overall-lifetime risk of developing bladder cancer of approximately 1 in 28.[1,4] During the last three decades, i.e., since 1975, there has been a gradual rising trend in bladder cancer incidence by approximately 40% according to the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) Registry.[2] There will be approximately 13,750 deaths from bladder cancer in the United States this year.[1,4] Despite the increasing incidence of this disease, the death rate from bladder cancer has been gradually declining. Currently there are approximately 500,000 survivors of bladder cancer in the United States.[5]

Bladder cancer is three times more common in men than women and is the fourth most common cancer (and second most common urologic cancer) found in men in the United States. Caucasian Americans have approximately a two-fold increase in risk of developing bladder cancer compared with African Americans. Latin Americans have an even lower risk of bladder cancer

development than African Americans.[5] The underlying reasons for differences in gender and racial incidence are currently not well understood. Bladder cancer is a disease of older individuals with greater than 90% of diagnoses in patients more than 55 years of age; although uncommon, bladder cancer can occur in young adults and even in children.[5]

Etiology

The etiology of bladder cancer appears to be multifactorial with exogenous environmental factors, as well as endogenous molecular factors, playing possible roles. First postulated by Rehn in 1895, the link between bladder cancer and environmental carcinogens has long been observed.[6] A large body of epidemiologic evidence linking bladder cancer to certain chemical agents, occupations, and industries has been generated since that time. As the bladder functions as a reservoir of urine, it is therefore possible that it is susceptible to the effects of a variety of potential environmental carcinogens in the process of waste elimination. Rising rates of bladder cancer in recent decades, the increased incidences observed in industrial countries, and the relatively long latency periods observed between exposure and cancer development suggest a potential cumulative effect of carcinogens on malignant transformation of the urothelial lining of the bladder.

Molecular Mechanisms of Urothelial Carcinogenesis

Abnormal metabolic pathways and molecular instabilities may likewise play a role in bladder cancer development and progression. These include: (1) altered metabolism/detoxification of carcinogens, and (2) inherent or acquired genetic abnormalities that may promote tumor development (oncogenes), inhibit tumor cell proliferation (tumor suppressor genes), or impair DNA repair (DNA repair enzymes). Pathways involved in altered chemical metabolism of exogenous carcinogens have included aberrant cytochrome P450 metabolism (associated genetic defects), glutathione-s-transferase abnormalities, and N-acetyltransferase genetic and metabolic derangements.[7-10] In addition, DNA abnormalities may be inherent or acquired secondarily to carcinogenic exposure. Genetic instability may result in abnormal activity of oncogenes (e.g., *ras* and *myc* families) resulting in aberrant protein expression (e.g., GDP/GTP binding proteins), cellular proliferation, and resistance to apoptosis.[10,11] Abnormalities in tumor suppressor genes associated with bladder cancer have also been well studied and include p53, p21, p16, and Rb

(retinoblastoma) tumor suppressor genes that may be mutated or inactivated, and such defects may thereby predispose to cell cycle dysregulation and tumor cell development and progression.[12-15] Alterations in DNA repair (e.g., *ner* genes, *ber* genes, and dsb repair genes) have likewise been associated with polymorphisms that may result in bladder urothelial carcinogenesis.[10,16,17] Other potential inherent and acquired pathways have also been identified and may also be involved including telomere dysfunction, apoptosis, and cellular inflammation.[18,19]

Major Pathologic Subtypes

Transitional cell carcinoma, the most common pathologic subtype of bladder cancer, is observed in over 90% of tumors.[20] Less common subtypes include squamous cell carcinoma observed in approximately 5% of bladder cancers in the United States and adenocarcinomas observed in approximately 1% of bladder cancers.[21,22] Not infrequently, bladder tumors that are predominantly transitional in histology may have areas of squamous and/or glandular differentiation. Recently recognized variants of transitional cell carcinoma (nested and micropapillary) may have prognostic and therapeutic significance. Squamous cell carcinoma accounts for up to 75% of bladder cancers in certain regions of the world in which schistosomiasis (also known as Bilharziasis) infection is endemic.[23,24] Other uncommon types of nonurothelial cancers of the bladder include small cell (neuroendocrine) carcinomas, mesenchymal tumors, lymphomas, lymphoepithelial variants, and secondary malignancies (either via direct extension or as a site of distant metastases).

Presentation and Diagnosis

Hematuria, occurring in the majority of patients with bladder cancer, is continuous or intermittent and either visible (gross) or microscopic. From microscopic hematuria screening studies, it has been estimated that approximately 1.3% of patients will have an underlying diagnosis of bladder cancer (range 0.4% to 6.5%), although this is more likely in patients with gross hematuria.[25-27] As such, the 2001 AUA Best Practice Policy on Asymptomatic Microscopic Hematuria[28] recommends that all patients with hematuria, particularly those without evidence of infections, stones, or other causative factors, should undergo cystoscopy and upper tract imaging.[3] Irritative

voiding symptoms including frequency, urgency, and dysuria are particularly associated with carcinoma in situ. Indeed, the diagnosis of bladder cancer is a consideration in patients with irritative voiding symptoms in the absence of infection.

The physical exam of patients with bladder cancer is often unremarkable especially in the case of nonmuscle invasive disease. A bimanual exam at the time of transurethral resection of the bladder tumor (TURBT) may help with clinical staging, especially for patients with muscle invasive disease. Cytology, either voided or upon barbotage, is an important adjunct in the diagnosis and surveillance of patients with urothelial carcinoma. The urinary tract and its unique epithelium (urothelium) are particularly suitable for cytologic sampling. Urinary cytology can be used to screen and evaluate patients at high risk for urothelial tumors (e.g., those with hematuria or irritative voiding symptoms) and to monitor recurrence, progression, or response to treatment in patients with a known history of transitional cell carcinoma. Sensitivity and positive predictive value of urinary cytology are particularly high in high-grade urothelial tumors as well as in cases of carcinoma in situ in which sensitivities can exceed 90%. Cytology is less effective for low-grade tumors and as a qualitative technique is subject to considerable variation in interpretation.[29-33] Radiologic imaging is often performed in conjunction with cystoscopy and is part of the hematuria evaluation in the patient undergoing assessment for urothelial cancer. In addition, in patients with a known history of bladder cancer, imaging can be useful in evaluating the presence of upper tract tumors that occur in less than 5% of patients with a known history of lower tract (i.e., bladder) cancer.[31,34] Common imaging techniques include intravenous urogram, retrograde pyelography, computerized tomography, and magnetic resonance imaging.

Urine-based Markers

Whereas the diagnosis and surveillance of patients with nonmuscle invasive urothelial cancers rely on cystoscopy, cytology, and biopsy when necessary, in recent years there has been an intense search for noninvasive adjunctive urine-based markers that could improve or perhaps replace cytology and cystoscopy. These may aid both in the diagnosis and the surveillance of patients with nonmuscle invasive urothelial cancers. Currently available Food and Drug Administration (FDA)-approved tests include the bladder tumor antigen STAT test (Bard Diagnostics, Redmond, WA, USA), the BTA TRAK test (Poly Med Co, Cortlandt Manor, NY, USA), the nuclear matrix protein (NMP) 22, and NMP22 BladderChek assays (Matritech,

Newton, MA, USA), ImmunoCyt test (Diagnocure Inc, Quebec City, Quebec, Canada), and fluorescence in situ hybridization (FISH) analysis (Urovysion Systems Vysis, Abbott Laboratories, Abbott Park, IL, USA). Other recently investigated tests and identified markers include Quanticyt (Gentian Scientific, Niawer, The Netherlands), BLCA-4, hyaluronic acid, telomerase, Lewis^{X} blood group antigens, microsatellite polymorphism analysis, cytokeratins, and survivin.[32,35] Despite their present and future potential, the critical evaluation and comparison of urine-based markers is beyond the scope of the current guideline involving the management of nonmuscle invasive bladder cancer.

Fluorescence Cystoscopy

In recent years, fluorescence cystoscopy, in contrast to conventional white light cystoscopy, has been investigated as a tool to enhance detection of occult papillary lesions and carcinoma in situ. Recent fluorescence photo detection strategies have used 5-aminolevulinic acid (5-ALA) – a precursor of heme biosynthesis. Intravesical installation of 5-ALA results in selective enhancement of protoporphyrin IX visualization through uptake by neoplastic cells. Upon excitation with blue light, protoporphyrin IX becomes readily visible with an appropriate observation filter on the cystoscope.[36] 5-Aminolevulinic acid-enhanced cystoscopy does appear to have improved sensitivities in detecting nonmuscle invasive bladder tumors such as carcinoma in situ.[36,37] Improved detection may enhance tumor identification and facilitate eradication thereby lowering recurrence rates.[38,39] Unfortunately, the specificity of fluorescence cystoscopy is limited; false-positive results may occur in patients with inflammatory lesions especially after use of intravesical therapies. Ongoing studies determining the effect of its use on disease free survival are accruing patients.

Diagnostic Transurethral Resection of Bladder Tumor

Ultimately, the diagnosis of urothelial carcinoma is made upon excision of the vesical lesion by TURBT.[40] Transurethral resection of bladder tumor provides essential histopathologic information for bladder tumor diagnosis as well as staging and grading of the cancer. At the time of TURBT, it is essential not only to resect the tumor itself but to provide a deep enough resection and biopsy to adequately assess the depth of invasion (i.e., sampling of the muscularis propria) for adequate staging information.[41] As outlined in subsequent text, repeat TURBT

(restaging TURBT) provides additional diagnostic and potentially prognostic information for patients with high-grade T1 tumors as well as select patients with high-grade Ta tumors.[42,43]

Tumor Characteristics

Staging

The staging for bladder cancer is divided into clinical and pathological stages. Clinical stage reflects the histologic findings at TURBT, the clinician's physical exam (including bimanual exam under anesthesia), and findings on radiologic imaging. Pathological staging (also known as surgical staging) is based on the extent of disease following surgical resection of the bladder (partial versus radical cystectomy) and of the adjacent pelvic lymph nodes. In the past, the Panel avoided using the term "superficial" in their report when categorizing the three nonmuscle invasive stages of bladder cancer, Ta, T1, and Tis. The Panel agrees with the International Society of Urological Pathology's recommendation that such use of the term should be discouraged[44] as Ta, T1, and Tis tumors behave differently from one another particularly with regard to tumor recurrence and progression.[44-46]

Currently, the staging system of the American Joint Committee on Cancer, also known as the Tumor-Node-Metastases (TNM) classification, is the most commonly used and universally accepted staging system for bladder cancer.[47] Under this system, nonmuscle invasive tumors include: (1) papillary tumors confined to the epithelial mucosa (stage Ta), (2) tumors invading the subepithelial tissue (i.e., lamina propria; T1), and (3) Tis (Table 1).

Table 1: Staging of primary tumors (T) in bladder cancer[47]

TX: Primary tumor cannot be assessed
Ta: Noninvasive papillary carcinoma Tis: Carcinoma in situ
T1: Tumor invades lamina propria
T2: Tumor invades muscularis propria
T2a: Invades superficial muscularis propria (inner half)
T2b: Invades deep muscularis propria (outer half)
T3: Tumor invades perivesical tissue/fat
T3a: Invades perivesical tissue/fat microscopically
T3b: Invades perivesical tissue fat macroscopically (extravesical mass)
T4: Tumor invades prostate, uterus, vagina, pelvic wall, or abdominal wall
T4a: Invades adjacent organs (uterus, ovaries, prostate stoma)
T4b: Invades pelvic wall and/or abdominal wall

Data gathered during the past few decades demonstrate that approximately 70% to 75% of bladder cancers present as nonmuscle invasive tumors.[31,48] Of these tumors, the majority (70% to 75%) are confined to the bladder mucosa (stage Ta).[20,31,48] Ta tumors are typically papillary in appearance and are often solitary lesions. The vast majority of lesions are categorized as low grade with only 2% to 4% categorized as high grade.[20,49,50] Recent studies, however, have reported a greater prevalence of high-grade tumors.[51] Ta tumors, like all bladder tumors, have a high rate of recurrence after TURBT but the risk of stage progression, particularly for low-grade papillary Ta tumors, remains low (less than 5%).[31,50]

Tumors that invade beyond the basement membrane into the subepithelial connective tissue (i.e., lamina propria) are stage T1 tumors and represent approximately 25% of all nonmuscle invasive tumors at initial presentation.[20,31,50] T1 tumors can be papillary or nodular in appearance. T1 bladder cancers have a worse prognosis than Ta tumors with a greater risk of progression to muscle invasive disease.[52-54] The lamina propria maintains abundant vascular and lymphatic channels that may predispose to tumor dissemination, and contains a variable layer of smooth muscle fascicles termed the muscularis mucosa.

Carcinoma in situ, a unique subtype of nonmuscle invasive transitional cell carcinoma, warrants its own unique stage and classification. Tis may appear as flat erythematous or "velvety" lesions of the mucosa or can be occult lesions not readily visualized on standard cystoscopy. Histologically, Tis are flat lesions in which surface epithelium-contained cells are cytologically malignant with severe cytological atypia and nuclear aplasia. The marked architectural and cytological abnormalities and disorderly appearance represent a process that is truly high grade. Tis is considered an ominous lesion due to its occult and multicentric nature that makes it difficult to readily identify and survey.[55] Furthermore, its propensity for progression to invasion in up to 83% of untreated cases is indicative of a potentially aggressive tumor.[56] The majority of Tis cases occur in association with high-grade nodular tumors; only 3% to 5% occur as isolated Tis disease.[57]

Grading

Tumor grade has long been recognized as one of the most important prognostic indicators with regard to the potential for disease recurrence and progression.[44,48,58] The most widely used classification for grading of nonmuscle invasive urothelial neoplasms has been the 1973 World Health Organization (WHO) classification. This system has designations for papilloma and Grades 1, 2, and 3 carcinomas. In 2004, members of the WHO and International Society of Urologic Pathologists published and recommended a revised consensus classification for papillary neoplasms (Table 2).[59] A new category of papillary urothelial neoplasm of low malignant potential was created to describe lesions with an increased number of urothelial layers when compared with papilloma but without cytologic features of malignancy.[59] The authors also categorized nonmuscle invasive papillary carcinomas as either low or high grade. This classification attempts to avoid the classification of intermediate grade (1973 WHO Grade 2), the grade that often represented the default grade diagnosis.[59,60] Indeed some reports have shown that Grade 2 tumors represent up to 65% of urothelial carcinoma diagnosed.[60,61] Under the new system, some Grade 2 lesions will be classified as low grade and others will now be categorized as high-grade tumors. This new system will potentially allow for enhanced prognostic significance but certainly will be greatly dependent on the pathologist for making these distinctions.

Table 2: 2004 World Health Organization/ International Society of Urologic Pathologists: Classification of Nonmuscle Invasive Urothelial Neoplasia[59]

Hyperplasia (flat and papillary)
Reactive atypia
Atypia of unknown significance
Urothelial dysplasia
Urothelial carcinoma in situ
Urothelial papilloma
Papillary urothelial neoplasm of low malignant potential
Nonmuscle invasive low-grade papillary urothelial carcinoma
Nonmuscle invasive high-grade papillary urothelial carcinoma

Other Prognostic Indicators

Although stage and grade represent perhaps the most important features of nonmuscle invasive urothelial neoplasm with regard to prognosis, other important clinical, histologic, and molecular features may also help predict prognosis and therapeutic response (Millan-Rodriquez European meta-analysis). Tumor multiplicity and tumor size represent two often used clinical features with prognostic significance in regard to disease recurrence.[62-66] Some authors have evaluated the potential prognostic value of substaging T1 tumors histologically to portend disease recurrence, response to therapy, and ultimately progression.[67-71]

A variety of other molecular markers in bladder cancer have been studied with regard to their ability to predict disease recurrence, response to therapy, and progression. These include flow cytometry, blood group antigens (e.g., Lewis^X), tumor suppressor genes (e.g., p53 and Rb), proliferative indices (Ki-67), urinary growth factors (e.g., epidermal growth factor, basic fibroblast growth factor, and CD44), matrix metalloproteinses (e.g., MMP-9), and urinary plasminogen activator (uPA).[35,72,73] In the future such indicators may prove to be valuable adjuncts to stage and grade in the management of nonmuscle invasive urothelial cancers.

Risk Stratification

Nonmuscle invasive bladder cancer represents a wide range of tumor biology and behavior. It is this heterogeneity that complicates the ability to compare therapeutic efficacy of different treatment modalities and thereby establish a common treatment guideline. For example, patients with the micropapillary variant of bladder cancer uniformly do poorly with bladder conservation.[74] This difficulty highlights the need to group or classify patients according to tumor behavior and prognosis. Such risk stratification could help classify patients with similar risk of stage progression and like prognoses. Index patients defined by the Panel below will assist in determining appropriate therapy for different risk categories. The European Association of Urology (EAU) has supported recent efforts in the development of risk stratification schemes and has included them in guidelines for nonmuscle invasive bladder cancer.[75]

Treatment Alternatives

In most cases of nonmuscle invasive bladder cancer, tumors are treated initially with TURBT. A careful cystoscopic examination of the entire urethra and all bladder surfaces precedes resection.[55] The position of tumors with reference to the bladder neck and ureteral orifices, the tumor configuration, whether tumors are papillary or sessile, and estimates of the number of tumors and their sizes should be noted to assist in future evaluation and follow-up. After resection of all visible tumors, adjuvant intravesical immunotherapy or chemotherapy can be used (Table 3).[31] Photodynamic therapy and laser ablation have been evaluated as secondary treatments in specific settings.

Table 3. Current Treatment Alternatives

Treatment	Indication(s)
	Intravesical chemotherapy and immunotherapy
Transurethral resection of bladder tumor (TURBT)	

	urothelial carcinoma[40]
• Any suspected urothelial carcinoma; can be the sole treatment but only in nonmuscle invasive	• Perioperatively or postoperatively in an adjuvant fashion • To prevent recurrence following TURBT [76-84] • Adjunctive therapy in carcinoma in situ where diffuse tumor prevents complete resection [31,56,85]
Laser ablation therapy	• Treatment of select lower- and upper-tract cancer[55,86] • Treatment of low-grade papillary tumors • Not appropriate for new lesions prior to tumor staging/grading
Conservative management (office fulguration or cystoscopic surveillance)	• Low risk and recurrent nonmuscle invasive papillary bladder tumors • Well-documented history of low-grade Ta tumors[87-89]

Depending on patient and tumor characteristics, a number of patients may benefit from some form of intravesical therapy. The focus of this Panel's analyses was largely on the most commonly employed agents in the United States, bacillus Calmette-Guérin (BCG) and mitomycin C; however, interferon and other chemotherapeutic agents have been used as well (Table 4).

Table 4. Intravesical Immunotherapy and Chemotherapy

Agent	Mechanism of Action
Immunomodulatory Agents	
Bacillus Calmette-Guérin (BCG)	• Inflammatory host response; release of cytokines • May be combined with interferons[90-94]
Interferons	• Lymphocyte activation; cytokine release; phagocyte stimulation • Antiproliferative actions • Antiangiogenic[31,90]
Chemotherapeutic Agents	
Thiotepa	• Alkylating agent; cross-links nucleic acids[95]
Mitomycin C	• Antibiotic; inhibits DNA synthesis[76-78]
Doxorubicin, epirubicin, valrubicin	• Intercalating agents; inhibits DNA synthesis[75,96-98]

Gemcitabine	• Deoxycytidine analog; inhibits DNA synthesis[99-103]

Transurethral Resection of Bladder Tumor

Transitional resection of bladder tumor provides histologic assessment as to tumor type, grade, and depth of invasion (stage). In addition to potentially improving staging accuracy, repeat TURBT may also improve local control of disease.[42,43] Complete eradication of all visible tumors is accomplished by either resection or fulguration.

Intravesical Chemotherapy and Immunotherapy

Intravesical therapy can be administered in an adjuvant fashion, or as part of a maintenance regimen to prevent recurrence. Perioperative installation of chemotherapy immediately after TURBT has been advocated since the 1970s, and is becoming an increasingly common practice today.[76-78] The rationale for perioperative instillation includes the destruction of residual microscopic tumor at the site of TURBT and of circulating 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 provide long-term immunostimulation or chemotoxicity and thereby prevent disease recurrence.[79,80]

Bacillus Calmette-Guérin

Bacillus Calmette-Guérin, a live attenuated strain of *Mycobacterium bovis,* first indicated as a tuberculosis vaccine, has had widespread use in intravesical immunotherapy since the 1970s.[104]

It has since become a first-line treatment for carcinoma in situ and has been shown to be effective as prophylaxis to prevent bladder cancer recurrences following TURBT.[85,105-108]

Several products containing different substrains of BCG are available; the viability of BCG organisms per milligram of vaccine may vary with different substrains and from lot to lot within the same substrain.[31,109,110]

Initiation of intravesical BCG therapy is usually delayed for two to three weeks following TURBT to allow for healing of the urothelium and thereby decrease the risk of systemic side

effects. Most patients develop an inflammatory immunologic response to BCG during a typical induction course of six weekly instillations. Optimal dosing and instillation schedules have not yet been established but some recent trials have demonstrated that a reduced dosing regimen

(one-third dose) may be as effective as standard dosing but with fewer side effects.[111-113] Meta-analyses (including our own) suggest that maintenance BCG be administered,[84,114] although the optimal schedule and duration of therapy is unknown.

Interferon

Recombinant interferon alpha-2b has been the most commonly utilized interferon to treat nonmuscle invasive urothelial carcinoma. Intravesical interferon alpha-2b has been shown to have activity in nonmuscle invasive urothelial carcinoma both as monotherapy and most recently in combination with low-dose BCG therapy.[90-94] These phase II trials have suggested durable responses in both BCG-naïve and BCG-refractory patients but long-term randomized trials have yet to be conducted to validate these results.

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 lower dose appeared to be as effective as the higher one in a comparative study when the concentrations were the same.[95] The Medical Research Council Working Party on Urological Cancer Thiotepa, reported that the lower concentration of 30 mg in 50 mL was not effective.[115]

The usual regimen consists of six to eight weekly instillations followed by monthly instillations for one year. A low molecular weight of 189 kd allows partial absorption through the urothelium with possible systemic toxicity. Myelosuppression is a risk, especially with the 60 mg dose. Leukocyte and platelet counts are obtained before each instillation and treatment is delayed if necessary.

Mitomycin C

Because of its moderately high molecular weight of 329 kd, there are few problems with transurothelial absorption, and myelosuppression is therefore rare with mitomycin C. Dosage

varies from 20 to 60 mg per instillation; the most commonly used dose is 40 mg in 40 mL of saline or sterile water administered weekly for eight weeks followed by monthly instillations for one year. Although the optimal method of mitomycin C administration is uncertain, Au et al[116] have demonstrated improved recurrence free survival and a prolonged median time to recurrence using methods to enhance the concentration and activity of mitomycin C in the urine. In this phase III trial, a six-week intravesical course of 20 mL of mitomycin C at a concentration of 20 mg/mL was found to be inferior to an "optimized" six-week course of mitomycin C which consisted of a period of dehydration (no fluids for eight hours prior to treatment), urinary alkalinization (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 (postvoid residual <10 mL by ultrasound bladder scanner) and a higher mitomycin C concentration (40 mg in 20 mL of sterile water).[116]

Recently, mitomycin C has been commonly used in a perioperative fashion delivered intravesically immediately after TURBT (or in some studies within 24 hours postoperatively). Optimal timing post-TURBT has not yet been determined. Several randomized trials and recent meta-analyses (including our own) have demonstrated a relative-risk reduction with a single perioperative dose of mitomycin C in patients with nonmuscle invasive urothelial carcinoma with both low- and high-risk features.[76-78] 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.[117-119]

Intercalating Agents (Doxorubicin, Epirubicin, and Valrubicin)

Because its molecular weight of 580 kd is high, 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 three times a week to once a month. ~~At this time, epirubicin is not currently available in the United States for the treatment of bladder cancer.~~ Although epirubicin had not been commercially available in the U.S. preceding the publication of this guideline, it is now an available chemotherapeutic agent for this disease.

Valrubicin, a semisynthetic analog of doxorubicin, was approved by the U. S. 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, with modest efficacy observed in this setting.[98] ~~Although valrubicin has not been commercially available in the United States over the last few years, it is anticipated to again become an available chemotherapeutic agent for this disease.~~ Although valrubicin had not been commercially available in the U.S. preceding the publication of this guideline, it is now an available chemotherapeutic agent for this disease.

Gemcitabine

Gemcitabine has a broad spectrum of antitumor activity and was first approved in the United States for the treatment of pancreatic cancer. In recent phase III trials of patients with metastatic bladder cancer, systemic gemcitabine in combination with cisplatin has been shown to result in similar survival rates compared to traditional systemic chemotherapeutic regimens, but with overall better patient tolerability and a better safety profile.[99] Recently, intravesical gemcitabine has been shown to have activity in nonmuscle invasive bladder cancer in intermediate risk and high risk patients.[100-103] Although early results are promising, the limited patient population evaluated supports the need for additional phase II and randomized phase III trials. Typical intravesical doses employed include 2 g in 50 to 100 mL of saline given weekly for six weeks with two-hour dwell times.

Other Therapies

Photodynamic Therapy

Several investigators have evaluated the efficacy of photodynamic therapy in the management of nonmuscle invasive urothelial carcinoma. The antitumor effects of photodynamic therapy primarily are due to the creation of reactive oxygen species that result from activation of a photosensitizing agent within the tissue. The agent is activated by absorbance of wavelengths of light specific for the spectrum of the agent.[120,121] The clinical trials of photodynamic therapy in the last 30 years have most commonly employed porfimer sodium as its sensitizing agent, but more recent studies have evaluated the therapeutic effects of 5-ALA. There are very few reports of the success of photodynamic therapy for bladder carcinoma with long-term follow-up.[122,123] Enthusiasm for its use is tempered by its side effects including skin photosensitivity similar to that in patients with porphyria. In addition, local symptoms including irritating voiding

symptoms, notable tissue sloughing, bladder contracture, and reflux have also been reported.[124,125] Photodynamic therapy is not readily available in the United States.

Laser Ablation Therapy

The neodymium-doped: yttrium aluminum garnet laser has so far proven to provide the most versatile wavelength for treating bladder cancer but other wavelengths also have been used.[55,86]

Lasers are not optimal for the treatment of new bladder lesions as tissue samples are requisite to determine depth of invasion (stage) and tumor grade. Appropriate patients for this therapy have papillary, low-grade tumors and a history of low-grade, low-stage tumors.[55]

Conservative Management

Certain patients with low risk and recurrent nonmuscle invasive bladder tumors may be managed conservatively with office fulguration of the lesions or even cystoscopic surveillance.[87-89] Only those patients with a well-documented history of low-grade Ta tumors have been considered for such an approach, in that the surgical and anesthetic risks of multiple repeated TURBTs in these patients may exceed the low risk of disease progression. Certainly, larger experiences and confirmatory trials are indicated to validate and support a conservative approach.

Follow-up

The high frequency of local recurrence and the potential for stage progression especially for high-risk disease highlights the importance of vigilant surveillance with cystoscopy for patients with nonmuscle invasive bladder cancer. Furthermore the potential for disease recurrence and progression even in the long term typically requires and necessitates lifelong follow-up.[31,88,126,127]

Although a variety of different follow-up strategies have been advocated, the most common approach has included patient assessment every three months in the first two years after initial diagnosis followed by every six months for the subsequent two to three years, and then annually thereafter.[31,128] Clinical follow-up involves an appropriate patient history including voiding symptoms and hematuria, urinalysis, cystoscopy, and urine cytology. Some studies have suggested that three-month post-TURBT clinical response as determined by follow-up cystoscopy is an important predictor of recurrence and progression.[64,129] At the present time, the

use and utility of urine-based molecular markers in the follow-up of patients remains uncertain. Surveillance often includes periodic upper tract imaging, especially for high-risk patients.[31,34]

Methodology

The methodology of this guideline update was similar to that used in the previous guideline. The intention was to determine the impact of the various available treatments on the outcomes of importance to patients. The efficacy outcomes examined were recurrence of bladder tumors and progression in stage or to cystectomy. The Panel also attempted to estimate the occurrence of side effects and complications of treatments and focused on post-TURBT treatments. It was assumed that all patients had TURBT eradication of all visible tumors. The Panel examined the efficacy of alternative follow-up treatments including repeat TURBT, intravesical immuno- and chemotherapies and photodynamic therapy. The impact of tumor stage, grade, multiplicity, and recurrence status on outcomes was also considered. Excluded were treatments that were not generally available in the United States and were not expected to be approved for general use by the time the guideline was published. The Panel also decided not to update outcomes for thiotepa and doxorubicin, treatments included in the previous guideline but deemed less effective than other agents by the previous panel, and as a result were not included in their analysis.

Literature Search and Data Extraction

The review of the evidence began with a literature search and data extraction. Articles included were identified on four MEDLINE searches beginning in October 2004 and concluding in February 2006, and supplemented with existing meta-analyses. Articles published between January 1, 1998 and December 31, 2005 were included in the analysis. The searches were limited to human subjects, English language, publication date from 1998 (the cutoff from the previous guideline) and contained the MeSH heading "bladder neoplasms." A total of 5,020 citations and abstracts were reviewed for relevance by the Panel chair and vice chair. In total, data from 322 articles were extracted by the Panel members. Inconsistencies in data recording were reconciled, extraction errors were corrected, and some articles were excluded by the Panel. A total of 158 articles were accepted for data analysis.

Evidence Combination

The analytic goals were expanded from the previous guideline. In addition to meta-analyzing the randomized controlled trials to determine if there were significant differences among the treatments, the Panel also decided to develop outcomes tables which actually provided estimates

of outcomes for the different treatment modalities. For this guideline, the Panel elected to use the confidence profile method,[130,131] which provides methods for analyzing data from studies that are not randomized controlled trials. Three different meta-analyses of the efficacy data were performed.

1. Meta-analysis of the comparable randomized controlled trials to determine the differences between pairs of available treatments. This analysis provides estimates of the absolute differences.

2. Meta-analysis of the individual arms of the randomized controlled trials to combine all the data from such trials for each treatment. This "single-arm" analysis provides an estimate of the actual rate of occurrence of each outcome.

3. Meta-analysis of the individual arms from all studies regardless of study design. For complications and side effects, only this method was used.

Hierarchical meta-analysis was used throughout due to the lack of homogeneity among the studies.

The outcomes analyzed for efficacy included recurrence and progression. For recurrence, only probability of recurrence (percentage of patients with recurrence) provided sufficient data for analysis. Time between recurrences, frequency of recurrences, and number of individual tumor recurrences could not be meta-analyzed. Similarly, the Panel decided that only probability of overall progression could be analyzed. Overall progression included progression in stage or to cystectomy. Grade progression could not be analyzed.

The way in which complications were grouped varied from study to study. Different names were also used for similar complications. The Panel attempted to group complications by including similar complications in a single group. Only studies that specifically reported data concerning occurrences of complications were included in the analysis.

The Panel attempted to evaluate outcomes based on a variety of patient characteristics including stage, grade, tumor multiplicity, and recurrence. However, in most cases, the outcomes data were not fully or consistently stratified by these conditions. Ultimately, the Panel elected to include all studies and analyze the data based on high and low risk as well as an analysis including all

studies. Low risk was defined as Grade 1 or low grade. High risk included groups that had no Grade 1 (low grade) patients or were entirely Tis and/or T1.

Although the Panel originally considered a wide variety of treatments, limited data were available for many of those of interest. The Panel decided that it could not distinguish between the different types of TURBT, including repeat TURBT, so all forms of TURBT were considered the same. The Panel also considered maintenance therapy versus induction only. A wide variety of induction and maintenance schedules have been used and reported in the literature. Because the issues concerning the comparison of BCG with mitomycin C and of maintenance with induction were so important, the Panel elected to incorporate all randomized controlled trials of these agents in the analyses including those from the original guideline.

After the evidence was combined and outcome tables were produced, the Panel met to review the results and identify anomalies. From the evidence in the outcome tables and expert opinion, the Panel drafted the treatment guideline. As in the previous guideline, the guideline statements were graded with respect to the degree of flexibility in their application. Although the terminology has changed slightly, the current three levels are essentially the same as in the previous guideline. A "standard" has the least flexibility as a treatment policy; a "recommendation" has significantly more flexibility; and an "option" is even more flexible.

These three levels of flexibility are defined as follows:

1. **Standard**: A guideline statement is a standard if: (1) the health outcomes of the alternative interventions are sufficiently well known to permit meaningful decisions and (2) there is virtual unanimity about which intervention is preferred.

2. **Recommendation**: A guideline statement is a recommendation if: (1) the health outcomes of the alternative intervention are sufficiently well known to permit meaningful decisions, and (2) an appreciable but not unanimous majority agrees on which intervention is preferred.

3. **Option**: A guideline statement is an option if: (1) the health outcomes of the interventions are not sufficiently well known to permit meaningful decisions, or (2) preferences are unknown or equivocal. Options can exist because of insufficient evidence or because patient preferences are divided and may/should influence choices made.

The draft was sent to 88 peer reviewers; the Panel revised the document based on the comments received from 38. The guideline was submitted for approval to the Practice Guidelines Committee of the AUA and then to the Board of Directors for final approval.

The guideline is published on the AUA website (http://www.auanet.org). A summary will be published in *The Journal of Urology.*

Results of the Outcomes Analyses

Detailed findings of the efficacy and complications outcomes analyses are found in Chapter 3 of the guideline while a summary of the results of the complications analysis also is provided in this section. As mentioned previously, although the Panel considered a wide variety of treatments, data on the use of TURBT, BCG, and mitomycin C induction and maintenance regimens only were sufficient for analysis.

The Panel reviewed and analyzed treatment complications from both randomized controlled and nonrandomized trials. However, a number of limitations precluded meaningful combination and comparison among treatments, such as various undefined descriptors used among studies for the same complication. The degree of overlap between different complications was also impossible to glean from many reports. For example, within the category of lower urinary tract symptoms (LUTS), if "frequency" was noted in 20% of patients and "urgency" in 18%, it is likely that a large number of patients had both symptoms, but the exact number is unknown. In addition, few studies listed the total number of patients who experienced complications or how many had more than one complication.

Complications were combined into several large categories of bladder contracture, epididymitis/prostatitis/urethral infections, hematuria, LUTS, fever/chills/flu symptoms, and systemic infection (See Chapter 3). Lower urinary tract symptoms (including frequency, urgency, dysuria, etc.) were the most common side effects reported with all of the treatment options. Such symptoms were reported in 2% of patients treated with TURBT alone, or TURBT combined with single-dose post-TURBT mitomycin C. This is compared to a rate of 22% to 24% with multiple-dose mitomycin C with or without maintenance treatment, 38% with induction BCG, and 57% with induction plus maintenance BCG. Other local symptoms such as hematuria, bladder pain and prostatitis were also common, and were similar across all intravesical treatments. Bladder

contracture is a rare event for all intravesical therapies, including both immunotherapy and chemotherapy. Systemic complications including immunologic reactions (arthralgia, skin rash, and fever/chills/flu symptoms) and other systemic side effects (malaise/fatigue, nausea/vomiting, altered liver function tests, neurologic symptoms, cardiovascular or pulmonary problems, and sepsis) were also reported, and were more common with regimens containing BCG and/or interferon than those using intravesical chemotherapy or TURBT alone.

Only a few studies identified the number of patients who were unable to complete the initial course of therapy due to the side effects, a phenomenon that appeared to be relatively uncommon.[132] Additionally, no significant difference in complications has been reported between maintenance therapy versus an induction course. This contradicts the experience of the Panelists and other reports noting side effects do occur fairly frequently during maintenance regimens especially with immunotherapy regimens. In the Southwest Oncology Group (SWOG) trial, for example, only 17% of patients in the maintenance arm completed the treatment as planned largely because of side effects.[80] In general, Panel members felt that in patients with tumors that carry considerable risk of progression and ultimate death from bladder cancer, the potential benefits of intravesical treatments such as BCG seem to outweigh the risk of serious complications. On the other hand, the risk of possible serious side effects from intravesical immunotherapy may outweigh the potential benefit of therapy for those with low-risk lesions. Consequently, intravesical chemotherapy, especially single-dose chemotherapy, is an important alternative for low-risk patients.

Treatment Guideline Statements

The Panel based the majority of the following guideline statements on a careful analysis of comparative outcomes from randomized controlled trials. Included were data published after the previous guideline was completed as well as results from previous studies involving TURBT and intravesical therapies. These statements apply to the treatment of patients with nonmuscle invasive transitional cell carcinoma of the bladder including Tis as well as stages Ta and T1 tumors. Inherent in these guideline statements is the importance of individualizing patient diagnostic evaluation and therapy. Some of the treatment paradigms addressed below were not based on data but on Panel experience alone.

In an attempt to recognize commonly encountered clinical variations, the Panel has designated certain example settings as "index patients." In establishing these index patients, the Panel closely examined pressing questions involving the use of intravesical chemotherapy versus immunotherapy and the role of maintenance therapy. Each guideline statement addresses a specific index patient.

For All Index Patients

Standard: Physicians should discuss with the patient the treatment options and the benefits and harms, including side effects, of intravesical treatment.

[Based on Panel consensus.]

Although a variety of the adjuvant intravesical treatments studied decrease the probability of bladder cancer recurrence when compared with TURBT alone, published data do not support the conclusion that the rate of progression to muscle invasive disease is necessarily significantly altered, especially with low-risk tumors. Physicians should discuss these potential benefits as well as the possible complications with the patient. Currently, there is little evidence defining and/or verifying the optimal dose, number of doses, and timing of instillations for either induction or maintenance intravesical therapy. This lack of uniformity renders the establishment of a guideline statement regarding specific regimens impossible and increases the difficulty of comparing therapy types.

For Index Patient No. 1: ***A patient who presents with an abnormal growth on the urothelium but who has not yet been diagnosed with bladder cancer.***

Standard: If the patient does not have an established histologic diagnosis, a biopsy should be obtained for pathologic analysis.

[Based on Panel consensus.]

Although laboratory diagnoses can indicate the likelihood of bladder cancer, the definitive diagnosis is established by pathologic examination of tissue removed by TURBT or biopsy. Transitional cell carcinoma of the bladder often has a characteristic appearance, but other conditions can mimic the gross appearance of bladder cancer.

Standard: Under most circumstances, complete eradication of all visible tumors should be performed.

[Based on Panel consensus.]

When feasible, surgeons should attempt to resect all tumors. The size and/or multiplicity of tumors or obvious deep muscle invasion may prevent complete resection. Also, comorbid conditions must be considered and may occasionally influence a decision about whether or not to attempt entire endoscopic removal of bladder tumors. Tumor resection can be accomplished with electrocautery resection, fulguration, or application of laser energy.

Adequate tissue should be available for determination of clinical stage, but in some cases endoscopic ablative techniques may not permit submission of all material for histologic evaluation.

Standard: If bladder cancer is confirmed, periodic surveillance cystoscopy should be performed.

[Based on Panel consensus.]

Neither the ideal interval nor the duration of follow-up cystoscopy has been defined. Given the variable risk of recurrence and progression, a risk-adapted approach should be considered. Patients with high-risk disease should undergo more intensive followup.

Option: An initial single dose of intravesical chemotherapy may be administered immediately postoperatively.

[Based on Panel consensus.]

The immediate use of intravesical chemotherapy was considered an option and not a standard by the Panel because of potential cost issues, uncertainty of pathology, side effects, and patient preference. In addition, the use of immediate intravesical chemotherapy would not be beneficial for bladder tumors that are most likely muscle invasive. In cases where the tumor appears to be papillary (Ta) by visual inspection and there are no contraindications to therapy, such as bladder perforation, immediate intravesical chemotherapy should be considered.

For Index Patient No. 2: ***A patient with small volume, low-grade Ta bladder cancer.***

Recommendation: An initial single dose of intravesical chemotherapy may be administered immediately postoperatively.

[Based on review of the data.]

Although outcomes data pertaining specifically to patients with low-grade, Ta bladder cancer are limited, the risk of recurrence and more importantly progression is relatively low. Meta- analyses including our own, do confirm, however, for nonmuscle invasive cancer, single postoperative instillation does decrease recurrence. In our comparison, the combination of TURBT and single-dose mitomycin C resulted in 17% (95% confidence interval [CI]: 8, 28) fewer recurrences than TURBT alone when all patient risk groups were considered. There is no evidence that multiple adjuvant instillations of either BCG or chemotherapy have additional benefit in patients at initial diagnosis of Ta Grade 1 bladder cancer.

For Index Patient No. 3: ***A patient with multifocal and/or large volume, histologically confirmed, low-grade Ta or a patient with recurrent low-grade Ta bladder cancer.***

Recommendation: An induction course of intravesical therapy with bacillus Calmette-Guérin or mitomycin C is recommended for the treatment of these patients with the goal of preventing or delaying recurrence.

[Based on review of the data.]

Adjuvant intravesical therapy is useful for nonmuscle invasive tumors. The Panel identified BCG and mitomycin C because they are the most widely available of the intravesical therapies and are used in the United States. The results of the analysis demonstrated a decreased probability of recurrence with either BCG or mitomycin C when compared to TURBT alone. In our meta-analysis of randomized controlled trials, regardless of patient risk, recurrences were reduced by 24% (95% CI: 3, 47) with the combination of TURBT and BGG induction only and by 3% (95% CI: -10, 16) with TURBT and mitomycin C induction only compared with TURBT alone. While it may appear from these data that BCG is superior to mitomycin C, the wide confidence intervals do not permit this conclusion.

Option: Maintenance bacillus Calmette-Guérin or mitomycin C may be considered.

[Based on review of the data.]

Maintenance therapy with BCG or mitomycin C is more effective in decreasing recurrences, when compared to induction alone. However, when considering cost, possible side effects, lack of a uniform and accepted dosing schedule and, importantly, the low risk of progression in this index patient, the Panel believes that routine maintenance therapy is an option. The Panel's meta-analysis of randomized controlled trials published between 1990 and 2006 demonstrated that compared to TURBT alone, recurrences are decreased by 31% (95% CI: 18, 42) with TURBT and BGG maintenance and by 18% (95% CI: 6, 30) with TURBT and mitomycin C maintenance. It is unclear whether any intravesical therapy affects the ultimate rate of progression to muscle invasive disease in these low-risk patients. The progression rate estimate in all patient risk groups was 8% (95% CI: 0, 15) with TURBT and BCG maintenance and 4% (95% CI: -26, 32) with TURBT and mitomycin C maintenance. Although maintenance therapy reduces recurrence and may reduce progression, the side effects and discomfort of the treatment and possibly the costs of the treatment may outweigh the benefits for some patients. Thus, discussion of the tradeoffs and consideration of patient preferences are important before beginning or continuing maintenance therapy. The optimal maintenance schedule and duration has yet to be determined.

However, the best available evidence supports the use of the SWOG regimen [80,133] a six-week induction course of BCG followed by a three-week maintenance course at 3, 6, 12, 18, 24, 30, and 36 months (if tolerated by the patient). This regimen was used in, by far, the largest trial that demonstrated the benefit of maintenance BCG therapy.

For Index Patient No. 4: ***A patient with initial histologically confirmed high-grade Ta, T1, and/or carcinoma in situ bladder cancer.***

Standard: For patients with lamina propria invasion (T1) but without muscularis propria in the specimen, repeat resection should be performed prior to additional intravesical therapy.

[Based on review of the data and Panel consensus.]

Disease-appropriate therapy is predicated on accurate staging. Despite continued attempts to

improve clinical staging, however, a significant percentage of patients are understaged. In the absence of muscularis propria in the specimen, data suggests that 20% to 40% of patients will have either residual tumor and/or unrecognized muscle invasive disease.[134-136] With the lack of accurate noninvasive clinical staging modalities, efforts should be focused on acquiring a definitive tissue diagnosis. Repeat resection may also be appropriate for patients with high-grade Ta tumors as well as patients with T1 tumors and muscularis propria in the specimen to increase the accuracy of clinical staging.

Recommendation: An induction course of bacillus Calmette-Guérin followed by maintenance therapy is recommended for treatment of these patients.

[Based on review of the data.]

As with Index Patient No. 3, both BCG and mitomycin C are intravesical therapies that can favorably prolong recurrence-free rates. However, in this high-risk group, maintenance BCG is superior to mitomycin C with or without maintenance. In our single-arm meta-analysis of randomized controlled trials of high-risk patients, the estimated five-year recurrence rate was 34% in patients receiving TURBT and BCG maintenance and 62% with mitomycin C maintenance. The meta-analysis of all risk groups found that, compared with TURBT and mitomycin C maintenance, TURBT and BCG maintenance therapy reduced recurrence by 17% (95% CI: 7, 26). In addition, there are limited data suggesting a trend to preventing progression with maintenance BCG. The progression in one study of 380 patients was reduced by 5% (95% CI: -1, 11) with TURBT plus BCG maintenance when compared with TURBT plus mitomycin C maintenance.[84] Although maintenance therapy reduces recurrence and may reduce progression, the side effects and discomfort of the treatment and possibly the costs of the treatment may outweigh the benefits for some patients. Thus, discussion of the tradeoffs and consideration of patient preferences is important before beginning or continuing maintenance therapy.

Option: Cystectomy should be considered for initial therapy in select patients.

[Based on review of the data and Panel consensus.]

Because there is risk of initially understaged muscle invasive disease or progression to muscle invasive disease even after intravesical therapy, cystectomy may be considered as an initial

treatment option in certain cases.[137,138] It is not certain whether intravesical therapy alters this risk of progression. In addition, the high cure rate associated with patients undergoing cystectomy further justifies this decision choice.[139-141] Among factors associated with increased risk of progression are large tumor size, high-grade, tumor location in a site poorly accessible to complete resection, diffuse disease, the presence of carcinoma in situ, infiltration of lymphatic or vascular spaces, and prostatic urethral involvement.[64,66,129,142] Cystectomy, however, is not without its possible complications and morbidity. Physicians should present specific information about the risks of cystectomy and methods for urinary reconstruction to patients who are contemplating bladder removal.

For Index Patient No. 5: ***A patient with high- grade Ta, T1, and/or carcinoma in situ bladder cancer which has recurred after prior intravesical therapy.***

Standard: For patients with lamina propria invasion (T1) but without muscularis propria in the specimen, repeat resection should be performed prior to additional intravesical therapy.

[Based on review of the data and Panel consensus.]

This guideline statement is the same for Index Patient 4. In this setting, accurate clinical staging is crucial for appropriate therapy.

Recommendation: Cystectomy should be considered as a therapeutic alternative for these patients.

[Based on review of the data.]

Even more so than patients who initially present with high-risk disease, those who fail initial intravesical therapy should be considered for cystectomy.[137] There is a substantial risk of progression to muscle invasive cancer in these patients. The high likelihood of intravesical treatment failure and adverse consequences of delaying cystectomy make cystectomy the preferred treatment for these patients.

Option: Further intravesical therapy may be considered for these patients.

[Based on review of the data and Panel consensus.]

There is some evidence that select patients will respond to second induction regimens, particularly with BCG.[80,143,144] Repeat intravesical therapy may be appropriate in patients who develop a late recurrence after previous complete response to an intravesical agent. However, in patients at high risk for progression, further intravesical therapy puts the patient at risk for muscle invasion and/or metastasis.[137] Data are insufficient, however, to support conclusions about the role of drug combination regimens or the beneficial effect of alternating therapies.

Future Research Needs

As illustrated in this evidence-based review, large, often multicenter, randomized, controlled trials have helped define the role of TURBT and the added benefits and risks of intravesical immunotherapy and chemotherapy for the treatment of bladder cancer. To date, most studies have focused primarily on the risk of recurrence and if recurrence can be decreased with intravesical therapy. However, progression is a more important outcome with lethal implications, and yet, the reduction of progression to muscle invasion remains definitively unproven and the endpoint of disease-specific survival is often unexamined.

Although many published studies have tested a variety of drugs and delivery regimens, they have failed to separate outcomes based on initial patient tumor characteristics such as number, size, stage, and grade. This lack of uniformity makes it very difficult to compare results between different observational or randomized trials. Although meta-analyses have been performed, it is difficult not to include discordant groups and thus compare groups of patients with inherently different risks of recurrence and progression or who receive different treatments. Many newer treatments and combinations of treatments have not yet been tested in large phase III trials. The clinician who today is faced with a patient who presents with a specific clinical picture is still often uncertain as to which treatment to recommend. This guideline attempts to provide a rational approach to these complex patients.

While tumor grade and the stage of nonmuscle invasive tumors can stratify risk for progression to muscle invasion, clinical understaging remains a difficult treatment situation and only contributes to the importance of better determining a patient's real prognosis. Profiling of tissue

and urine promise to provide better risk assignment and optimally to direct targeted treatment so as to increase efficacy and minimize toxicity.

The risk and significance of urothelial carcinoma outside the bladder must be further determined. Especially in patients with carcinoma in situ, urothelial cancers within the ureter or intrarenal collecting system may also occur at a frequency far exceeding the 5% previously accepted incidence. Periodic monitoring of the upper urinary tract is of value, and studies are needed to better determine the efficacy of administration of chemotherapy or immunotherapy to the upper urinary tract. Prostatic urethral involvement may occur, especially in patients with carcinoma in situ, even in the absence of identifiable disease within the bladder.

Historically, cystoscopic bladder surveillance for patients with nonmuscle invasive bladder cancer has been performed every three months for at least a year and with a progressively declining frequency after that point. Advances in molecular biology hold the promise of some day accurately predicting in advance which therapy is most likely to succeed and which tumors will not respond to intravesical therapy. With that knowledge, cystectomy can be offered early to those most likely to benefit.

Reporting of Bladder Cancer Data

The discoveries that will improve diagnosis and predict the biologic activity of urothelial cancer and response to various therapies are forthcoming. One strategy that is immediately available to improve the database of information and therefore the validity of conclusions regarding diagnosis, therapy, and outcomes is the construction of and adherence to a uniform system of reporting. The extraordinary individual variability of both observational and randomized controlled trials makes it very difficult to consolidate data in a meaningful fashion to permit robust conclusions despite the large number of patients that might be involved in the trial. The Panel suggests that authors refer to the CONSORT guidelines[145] and also proposes the following suggestions for authors to follow in their reporting of randomized controlled trials or observational cohort studies. This template does not in any way attempt to compromise or marginalize current data but provides an organization that will allow future guidelines to be more informative.

To allow optimal comparison between treatment outcomes, the Panel proposes that future

research in Ta and T1 bladder cancer include the following standard parameters for either observational studies or prospective clinical trials:

1. A table delineating outcomes stratified by stage (Ta, T1, Tis, or Ta, T1 with or without Tis) and grade, as the risk associated with these tumor categories is different.

2. A table delineating outcomes stratified by whether tumors are primary or recurrent and solitary or multiple. This would allow comparison of individual patient situations.

3. Reporting of endpoints, including recurrence and/or progression, using Kaplan-Meier methodology for graphic and tabular data at defined 12-month intervals and specifying the number of patients followed at each interval.

4. Separate reporting of grade or stage of progression with emphasis on progression from nonmuscle involvement to muscle invasion.

5. The specific total number of complications that occurred and the number of patients reporting each complication.

Similarly, it has been almost impossible to compare complications associated with various treatments because of the tremendous variability in reporting methods. Ideally, we would develop a standardized system of reporting similar to that of the National Institutes of Health

Common Toxicity Assessment system which would allow us to compare the type and severity of complications experienced by patients treated in different studies. However, until that is

available and accepted, we would propose that the following minimum reporting information on complications be included with each study report:

1. The number of patients for whom complications either resulted in a delay in therapy or withdrawal from therapy. In addition, it is important to report when this occurred (i.e., at what point during therapy).

2. The total number of patients who experienced local or systemic side effects or both.

3. Combination of specific lower urinary tract symptoms (frequency, urgency, dysuria) into a "LUTS" category.

4. The number of patients who developed severe side effects such as debilitating bladder contracture or complications requiring surgery or hospitalization.

If clinical studies of new treatments follow these reporting criteria, we will have powerful tools to compare treatment outcomes in the future.

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