Superficial Bladder Cancer: An Update on Etiology, Molecular Development, Classification, and Natural History

Erik Pasin, MD,* David Y. Josephson, MD,* Anirban P. Mitra, MBBS,†
Richard J. Cote, MD, FRCPath,*,† John P. Stein, MD, FACS*

Departments of *Urology and †Pathology, Norris Comprehensive Cancer Center,
University of Southern California Keck School of Medicine, Los Angeles, CA

Superficial "non–muscle-invasive" bladder tumors represent a heterogeneous group of cancers, including those that are (1) papillary in nature and limited to the mucosa, (2) high grade and flat and confined to the epithelium, and (3) invasive into the submucosa, or lamina propria. The goal of treatment is 2-fold: (1) to reduce tumor recurrence and the subsequent need for additional therapies and the morbidity associated with these treatments and (2) to prevent tumor progression and the subsequent need for more aggressive therapy. This update reviews important contemporary concepts in the etiology, molecular mechanisms, classification, and natural history of superficial bladder cancer.
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In 2007 it was estimated that 67,160 new patients would be diagnosed with bladder cancer, with 13,750 projected deaths from the disease. The incidence of bladder cancer is nearly 4 times higher in men than in women.[1] Histologically, more than 90% of bladder-cancer cases are transitional cell (urothelial) carcinoma, approximately 5% are squamous cell carcinoma, and less than 2% are adenocarcinoma.[2]

Transitional cell carcinoma (TCC) of the bladder is the second most common malignancy of the genitourinary tract and the third most common cause of death among people with genitourinary tumors.[1] Nearly 80% of patients who initially present with bladder TCC have tumors confined to the mucosa or submucosa—so-called superficial "non–muscle-invasive" bladder cancers.[2] Superficial bladder tumors represent a heterogeneous group of cancers that include those that are (1) papillary in nature and limited to the mucosa (Ta), (2) high grade and flat and confined to the epithelium (Tis), and (3) invasive into the submucosa, or lamina propria (T1).[3]

This article reviews the recent literature concerning important contemporary issues in the management of patients with superficial bladder TCC. A brief overview of all aspects of superficial bladder cancer including the etiology, molecular development, diagnosis, and treatment is presented with a focus on recent advances.

Etiology

Classically, bladder cancer has been associated with exogenous and environmental risk factors. The 2 best known risk factors for bladder cancer are smoking and occupational exposure. Compared with the general population, smokers are at 2 to 4 times greater risk of bladder cancer, and heavy smokers are at 5 times the risk.[4] The exact mechanism by which tobacco causes bladder cancer is not known, but urothelial carcinogens such as acrolein, 4-amino-biphenyl, arylamine, and oxygen-free radicals have been implicated.[5-8] Furthermore, increased duration and intensity of tobacco exposure and degree of inhalation contribute significantly to cancer development, whereas smoking cessation has been associated with an almost immediate decline in risk.[9] With established tobacco-associated superficial TCC of the bladder, those who continue to smoke after diagnosis have a worse recurrence-free survival rate than those who quit at the time of diagnosis.[10]

Occupational exposure to aniline dyes and aromatic amines such as 2-naphthylamine and benzidine has been implicated as the second most common risk factor for bladder cancer.[11,12] Benzidine, the most carcinogenic aromatic amine, has been primarily used in dye production and as a hardener in the rubber industry. The degree of carcinogenesis due to occupational exposure varies with the degree of industrialization, but in heavily industrialized nations, occupational exposure may account for up to one fourth of all urothelial cancers.[13] The latency period between exposure and tumor development is usually prolonged. Occupational bladder cancer has also been observed in gas workers, painters, and hairdressers.[14]

Other etiologic factors implicated in the development and progression of bladder cancer include analgesic use[15]; urinary tract infections,[16] including bacterial, parasitic,[17] fungal, and viral infections[18]; urinary lithiasis[19]; pelvic radiation[20]; and chemotherapeutic agents such as cyclophosphamide.[21] Although caffeine ingestion has been implicated as a risk factor for bladder cancer,[22,23] risk estimates for this association decrease after controlling for concomitant tobacco use.[24] Similarly, saccharin-containing artificial sweeteners have been shown to induce bladder neoplasms in the rat model,[25] but previous human epidemiological studies have failed to establish this relationship.[26,27] More recently, large case-control human studies have shown that a dosing association may exist, as "heavy" use of artificial sweeteners (> 1680 mg/day) was related to an increased relative risk of bladder cancer but "low" usage (< 1680 mg/day) was not.[28]

Molecular Pathogenesis

The large fund of molecular knowledge on carcinogenesis, which has expanded remarkably in recent years, has provided evidence and a better understanding of the genetic alterations that lead to the development of bladder cancer. Most superficial bladder tumors show a loss of heterozygosity (LOH) of chromosome 9.[29] In fact, deletions on chromosome 9 are the most common chromosomal abnormalities in TCC and are found in more than 50% of all grades and stages of TCC.[30] LOH of chromosome 9 is considered to be the least divergent event, indicating that this is likely to be an early genetic change, whereas subsequent events occur during independent evolution of different tumor subclones (Figure 1).

Most superficial bladder tumors show a loss of heterozygosity of chromosome 9. In fact, deletions on chromosome 9 are the most common chromosomal abnormalities in transitional cell carcinoma (TCC) and are found in more than 50% of all grades and stages of TCC.

Critical regions of LOH have been mapped on both 9p and 9q. These include 1 region of loss on 9p (9p21) and 3 regions on 9q (9q22, 9q32-q33, and 9q34).[31,32] The region 9p21 contains the cyclin-dependent kinase inhibitors *CDKN2A* and *CDKN2B* loci, which contain the genes that encode for the p16, p14 (on *CDKN2A*), and p15 (on *CDKN2B*) proteins; 9q22 contains *PTCH* (Gorlin syndrome gene), 9q32-q33 contains *DBC1*, and 9q34 contains *TSC1* (tuberous sclerosis syndrome gene 1).

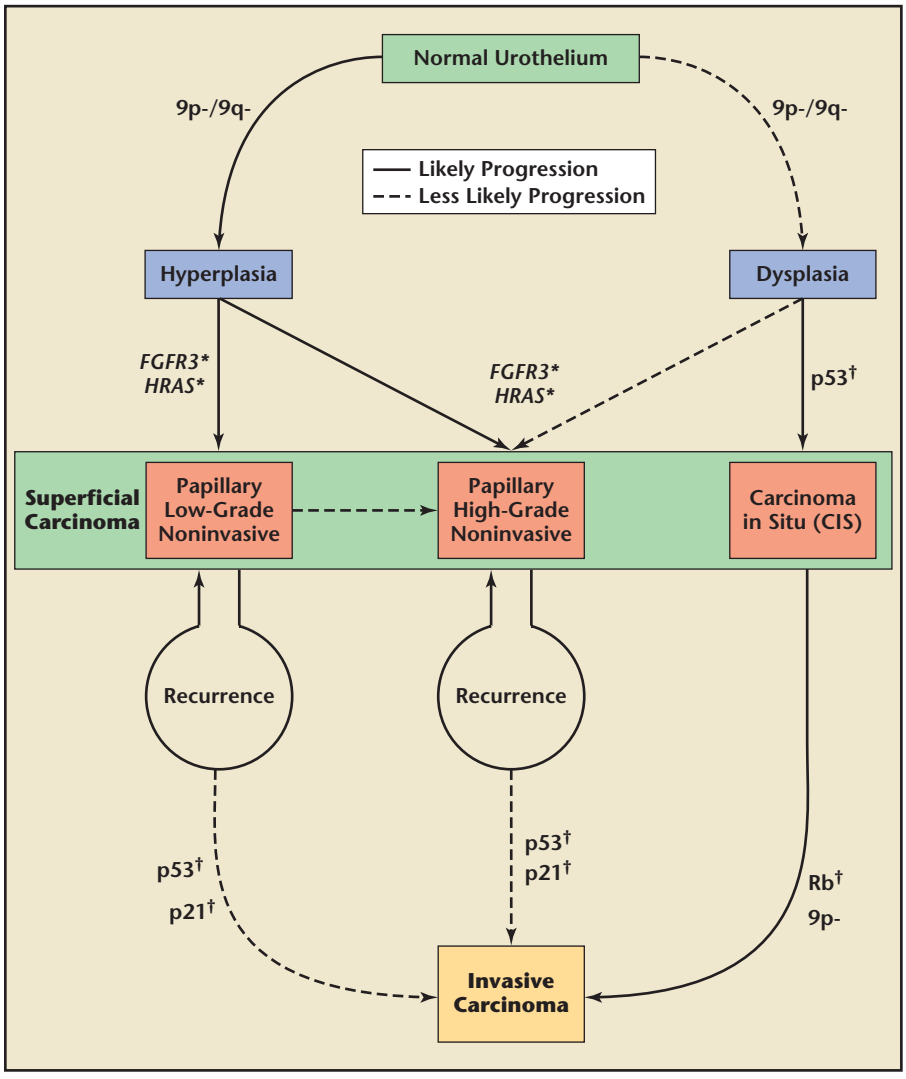

Figure 1. *Model depicting potential pathways for urothelial tumorigenesis and progression. This model includes some key molecular events that occur during bladder tumorigenesis and demonstrates how the less aggressive papillary carcinomas generally differ in their origin from the more aggressive carcinoma in situ. Most papillary noninvasive carcinomas do not progress to an invasive phenotype but are more prone to recurrences. Those that do, however, usually accumulate more genetic abnormalities. *Activating mutations; †Inactivating mutations; FGFR3, fibroblast growth factor receptor 3; HRAS, transforming protein p21/H-RAS-1 (Harvey murine sarcoma virus oncogene).*

p16 and p14 are key cell-cycle regulators. The former negatively regulates the retinoblastoma (Rb) pathway, whereas the latter negatively regulates the p53 pathway.[33,34] The genes for both proteins are commonly inactivated in bladder cancer by homozygous codeletion. LOH of 9p21 is seen in both low-grade Ta and invasive bladder cancer, and reduced copy number of 9p21 with or without LOH is present in approximately 45% of tumors,[35] indicating that haploinsufficiency of p16 and/or p14 may contribute to bladder tumor development. A significant correlation has been shown between the loss of p16 expression and progression in T1 tumors.[36]

Investigators have shown decreased expression of *PTCH* mRNA in superficial tumors with LOH in the 9q22 region compared with normal urothelium, with marked fluctuations of levels in tumors without deletion.[37] *DBC1*, the ectopic expression of whose protein product is postulated to induce a type of cell death that does not follow the classical apoptotic pathway,[38] has been shown to be silenced by promoter hypermethylation in bladder cancer.[39] Located on 9q34, the *TSC1* gene encodes for hamartin, which complexes with the *TSC2* gene product tuberin in the PI3-kinase pathway to negatively regulate mTOR, a central molecule in the control of protein synthesis and cell growth.[40] Mutations of *TSC1* are found in approximately 12% of bladder tumors.[41] Interestingly, some of these mutations are in tumors that retain heterozygosity for *TSC1*, again indicating possible haploinsufficiency.[41] Thus, loss of 1 chromosome 9 homologue, a common event in superficial bladder tumors, could possibly affect haploinsufficient genes on both 9p and 9q.

In addition to LOH of chromosome 9, low-grade papillary tumors generally exhibit a constitutive activation of the receptor tyrosine kinase-Ras pathway, with activating mutations in the *HRAS* and fibroblast growth factor receptor 3 (*FGFR3*) genes, found in 30% to 40% and 60% to 70% of cases of the disease, respectively (Figure 1).[42] In a recent prospective study reporting the prevalence and distribution of *FGFR3* mutations and their association with outcome in 764 patients with non–muscle-invasive urothelial carcinoma, Hernandez and colleagues provided evidence that mutations of this gene are significantly more prevalent among tumors of low stage and grade and less prevalent among high-grade T1 tumors.[43] *FGFR3* mutations are confined to hot spots in exons 7, 10, and 15, and all are predicted to cause constitutive activation of the kinase activity of the receptor,[44] which in turn

can activate the mitogen-activated protein kinase (MAPK) pathway—a pathway shared with the Ras family of proteins.[42]

Interestingly, in a screen of 98 bladder tumors and 31 bladder cancer cell lines for mutations in *FGFR3* and the Ras genes (including *HRAS*), both mutations were found to be absolutely mutually exclusive, suggesting possible biological equivalence.[45] This mutual exclusion suggests that *FGFR3* and Ras gene mutations may represent alternative means to confer the same phenotype on bladder cancer cells wherein oncogenic activation of either *FGFR3* or *HRAS* results in stimulation of the MAPK pathway.

High-grade and high-stage cancers, on the other hand, are more commonly associated with p53 alterations.[46,47] Similarly, abnormal *RB* gene expression, as detected by immunohistochemical analysis of the Rb protein, has been seen in aggressive, higher stage/grade tumors.[48,49] Advanced bladder cancers have also been shown to have decreased expression of p21, a protein that inhibits cell-cycle progression downstream of p53.[50,51] In fact, a combined analysis of the expression of p53, p21, and Rb has suggested that with increasing number of alterations of these proteins, the final prognosis of the patient worsens considerably.[52]

Diagnosis

The diagnosis of superficial bladder cancer can be elusive. The presenting symptoms of bladder cancer may mimic those of other common urologic conditions such as urinary tract infection and general lower urinary tract symptoms. Approximately three fourths of patients with bladder cancer present with painless, intermittent hematuria.[53] It is estimated that approximately 20% of patients being evaluated for gross hematuria will subsequently be diagnosed with bladder cancer.[54,55] Similarly, of patients presenting with microscopic hematuria, up to 10% will be diagnosed with bladder cancer.[56] Microscopic hematuria in patients with bladder cancer tends to be unpredictable and inconsistent; therefore, a single negative urinalysis does not exclude the possibility of cancer.[57] The Best Policy Panel of the American Urological Association has accounted for this in its recommended definition of asymptomatic microscopic hematuria as "three or more red blood cells per high-power field on microscopic evaluation of urinary sediment from two of three properly collected urinalysis specimens."[58]

Approximately three fourths of patients with bladder cancer present with painless, intermittent hematuria. It is estimated that approximately 20% of patients being evaluated for gross hematuria will subsequently be diagnosed with bladder cancer.

The panel recommended that all patients without risk factors for primary renal disease should have a urologic evaluation including radiographic imaging of the upper urinary tract followed by cystoscopy. Although urine cytology is best utilized in patients with known bladder cancer, bladder washings should also be sent at the time of cystourethroscopy in patients with significant risk factors or a high index of suspicion for bladder cancer. Characteristic cytologic abnormalities that are highly specific for TCC include increased cell size and nuclear-cytoplasmic ratio, nuclear pleomorphism, and nucleolar prominence. It should be noted that irrigated bladder cytology is more sensitive than voided cytology in diagnosing bladder cancer.[59]

One fourth of patients with bladder cancer will present with irritative voiding symptoms of urgency, frequency, and dysuria.[60] In the primary care setting, these symptoms are frequently misinterpreted as signs of a urinary tract infection but may signify either trigone involvement with tumor or the presence of carcinoma in situ (CIS).[61] Although the incidence of metastatic bladder cancer with superficial disease is low,[62] patients may present with bone pain or flank pain due to retroperitoneal adenopathy or ureteric obstruction. Patients with ipsilateral hydronephrosis should be considered to have muscle-invasive disease.[63]

The initial evaluation and management of patients with suspected bladder cancer involves cystoscopic evaluation of the bladder, transurethral resection (TUR) of visible tumor, and assessment of the appearance of the uninvolved bladder and prostatic urethra. When urinary cytology is positive and no grossly visible tumor is apparent on cystoscopy, directed bladder biopsies, including cold-cup biopsies of the prostatic urethra, to evaluate for the presence of CIS are indicated on initial evaluation or during follow-up. Note that the upper urinary tracts must also be evaluated in this situation.

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In addition, directed bladder biopsies are indicated during TUR of any visible tumor associated with positive

cytology to map the bladder for concomitant CIS, the presence of which imparts a more aggressive pathology and may influence treatment decisions. Prostatic urethral resection biopsy may be indicated when visible abnormalities of the prostatic urothelium exist. Although physical examination rarely delineates any abnormalities, a bimanual examination should be performed at the time of cystoscopy, preferably under general anesthesia. Palpation of a mass is unusual, but a fixed mass typically represents more advanced disease. Small and/or flat lesions suspicious for CIS can be sampled with cold-cup biopsy forceps, and larger lesions should be completely resected, if possible, using loop electrocautery.

During TUR, attempts also should be made to obtain muscle in the specimen while avoiding bladder perforation. The fact that only 23% of patients classified as having high-grade Ta tumors on local pathology are confirmed by review pathology[64,65] and that approximately 30% of patients with T1 tumors are upstaged after repeat TUR and even higher if muscle is not present in the initial TUR specimen, argues that standard repeat TUR should be performed in patients with high-grade Ta or T1 tumors.[66,67]

A well-trained uropathologist may be an important component in the accurate histopathological diagnosis of patients with bladder cancer undergoing transurethral resection (TUR) for superficial disease. The presence of smooth muscle in the pathologic specimen is an important indicator for an adequately performed resection.

In addition, a well-trained uropathologist may be an important component in the accurate histopathological diagnosis of patients with bladder cancer undergoing TUR for superficial disease. The presence of smooth muscle in the pathologic specimen is an important indicator for an adequately performed resection. A small asymptomatic bladder perforation after TUR that is not apparent cystoscopically may occur more frequently than believed, but fortunately, these do not seem to impose a significant risk for extravesical tumor seeding.[68]

Radiographic evaluation of the upper urinary tract should also be performed if not done during the initial assessment of hematuria. Clearly, up to 4% of patients with superficial bladder cancer are at risk for synchronous and metachronous tumors of the upper urinary tract.[69-71] Patients with a history of CIS, tumors adjacent to the ureteral orifices, or persistently unexplained positive cytologies might be at increased risk for an upper tract tumor and prostatic urethral tumor involvement. Accurate clinical staging is important, because prognosis and therapy are directed by various clinical and histopathologic factors.

Classification

Normal Histology

The normal urothelium consists of 3 to 7 layers of transitional cells resting on a basement membrane composed of extracellular matrix. The most superficial layer consists of flat "umbrella" cells. The configuration of these cells varies from flat to cuboidal, depending on distention or contraction of the bladder. Below the basement membrane, the lamina propria, or submucosa, consists of loose connective tissue and can occasionally have scattered smooth muscle fibers (muscularis mucosae). The muscularis propria forms the next layer and comprises the (smooth) muscular wall of the bladder. Its muscle fibers are arranged in 3 bundled layers: middle circular, surrounded by inner and outer longitudinal fibers.

Dysplasia

The term *dysplasia* denotes architectural cell crowding and loss of polarity with sparse or absent mitotic figures. These features are usually limited to the basal and intermediate layers of the urothelium and are less pronounced than the changes seen in CIS. Dysplasia is a marker for cancer risk and progression and may be a precursor for invasion.[72,73] High-grade dysplasia should be considered CIS.

CIS

Urothelial CIS, or flat intraepithelial carcinoma, is characterized by flat, disordered proliferation of cells with marked cytologic abnormalities. On cystoscopy, it may appear as a velvety, reddish patch of urothelium in proximity to an exophytic lesion, as a focal lesion in a patient without macroscopic tumors, or be endoscopically invisible. Overall, 50% of patients with CIS have multifocal lesions with a predilection for the trigone, lateral wall, and dome.

By definition, CIS is a high-grade tumor and comprises about 10% of all cases of bladder cancer; 20% to 30% occur as an isolated lesion (primary CIS). Additionally, CIS can emerge during follow-up surveillance in the absence of grossly visible tumor (secondary CIS) or present initially or during follow-up associated with concurrent papillary tumors (concomitant CIS).[74-78] In general, concomitant CIS is much more difficult to treat than primary CIS.

The fact that with CIS, the mucosa may appear entirely unremarkable cystoscopically reinforces the importance of urine cytology in diagnosing this entity.[60,79] In addition, fluorescence-guided cystoscopy using hexaminolevulinate (HAL) has been noted to

increase the detection rate of CIS.[80] In a prospectively controlled trial of 211 patients with superficial bladder cancer, HAL fluorescence detected approximately 30% more cases of CIS than standard white-light cystoscopy alone.

Unfortunately, the routine application of fluorescence cystoscopy has yet to gain wide clinical acceptance despite an improvement in the detection rate of CIS.[81] The routine clinical use may be limited in part because HAL fluorescence cystoscopy does suffer from the potential for false-positive results in the setting of inflammatory conditions. Nevertheless, directed bladder mapping of areas contiguous to and remote from the primary tumor areas remains important in the diagnosis and management of patients with CIS.

Histological Grading

Much controversy surrounds the grading of bladder tumors, and no uniformly accepted grading system exists at present. Arising from the need to develop a commonly accepted classification system that pathologists, urologists, and oncologists could use, a new classification of noninvasive urothelial tumors was proposed at the 1998 World Health Organization (WHO) and the International Society of Urological Pathology (ISUP) consensus meeting.[82] This new classification system for grading urothelial neoplasms was subsequently published by the WHO in 2004.[83] Unfortunately, the 2004 WHO grading system lacks validation based on long-term follow-up data. Even today, many published reports rely on the older WHO classification from 1973.[84,85] Therefore, a histological grading description based on both classification systems will be discussed here.

A papillary lesion with little or no variation in nuclear size, shape, or spacing when compared to normal urothelium is called a *papilloma* in both classification systems. The urothelium has an intact superficial umbrella layer with no mitotic activity. Patients with urothelial papillomas have a low incidence of recurrence and rarely progress to develop urothelial carcinoma.[86] It may be reasonable not to consider this entity as urothelial cancer.

Well-differentiated tumors, or grade 1 tumors based on the WHO 1973 classification, have an orderly arrangement of normal cells lining delicate papillae. They have minimal architectural abnormalities with minimal anaplasia or pleomorphism. Mitotic figures are rare or absent. Furthermore, WHO 1973 grade 1 lesions that show no cytologic atypia and merely thickened urothelium with, at most, nuclear enlargement are called *papillary urothelial neoplasms of low malignant potential* (PUNLMP) in the WHO/ISUP system. However, WHO 1973 grade 1 lesions with definite, yet slight cytologic atypia, would be diagnosed in the WHO/ISUP system as *low-grade urothelial carcinomas*.[83]

Moderately differentiated tumors, or WHO 1973 grade 2 lesions, retain some of the orderly appearance and maturation of grade 1 carcinoma but have some focal variation in nuclear appearance. The WHO 1973 grade 2 category is very broad, and most pathologists grade cases of urothelial cancer as WHO 1973 grade 2 by default. In an attempt to avoid using an intermediate category, the WHO/ISUP system classifies bladder papillary urothelial cancers into only 2 categories: *low-grade* or *high-grade papillary urothelial carcinoma*.

WHO 1973 grade 2 lesions that demonstrate an overall orderly appearance but have minimal variability in architecture and/or cytologic features and are easily recognizable at scanning magnification would be considered *low-grade urothelial carcinomas* in the WHO/ISUP system. When WHO 1973 grade 2 lesions display more of a disorderly appearance because of marked architectural and cytologic abnormalities, recognizable at low magnification, they are considered *high-grade urothelial carcinomas*. Poorly differentiated tumor lesions called WHO 1973 grade 3 are, by definition, *high-grade urothelial carcinomas* in the WHO/ISUP system. They demonstrate the most extreme nuclear abnormalities. There is an obvious disorder, loss of polarity, and frequent mitotic activity.

Pathologic Staging

Pathologic staging is most important regarding risk assessment and in dictating patient management. The current 2002 TNM classification of bladder cancer describes Ta tumors as noninvasive and papillary confined to the mucosa, Tis tumors as flat CIS confined to the mucosa, and T1 tumors as invasive tumors that invade the subepithelial connective tissue.[3] Overall, Ta tumors account for approximately 70% of superficial TCC. These tumors are composed of branching fibrovascular cores with more than 8 cell layers that display features of anaplasia. This arrangement provides their morphologic papillary appearance. In general, Ta tumors are low-grade cancers.

T1 tumors, by definition, invade the submucosa (also called lamina propria) and account for approximately 30% of all superficial bladder tumors. T1 lesions may have either a papillary or a broad-based appearance and are generally of higher grade than Ta tumors.[87] T2 and higher lesions, by definition, are muscle-invasive tumors. The management of muscle-invasive disease is beyond the scope of this manuscript, but it should be mentioned that these patients should be treated with more aggressive options

(ie, radical cystectomy) because they are at an increased risk of lymph-node and distant metastases, as well as death from bladder cancer.[88,89]

Although the topic is not addressed in the current TNM staging system, several studies have proposed further substaging of T1 lesions.[90] Data suggest a significant difference in prognosis and survival based upon the depth of submucosal invasion, with a worse prognosis associated with increasing invasion of the submucosa.[91,92] A T1 substaging has been based on the following system: T1a, invasion of connective tissue superficial to the level of the muscularis mucosae; T1b, invasion to the level of the muscularis mucosae; T1c, invasion through the level of the muscularis mucosae but superficial to the muscularis propria. Opponents of this subclassification argue that it is often difficult to consistently and accurately assess the TUR tissue for the presence and actual depth of invasion because of orientation and artifactual changes. Similarly, it is argued that muscularis mucosae cannot be consistently identified with certainty in all TUR or biopsy specimens.[93,94]

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The precise definition and staging of prostatic involvement with bladder cancer is another topic of considerable debate. In the current TNM staging system, bladder tumors involving the prostate are considered T4a.[3] However, it is well documented that the survival rate of patients with superficial TCC of the prostate (urethra or ducts) in the context of superficial bladder cancer is much better than that of those with involvement of the prostatic stroma, either through direct extension through the bladder wall or through urethral extension beyond the ducts (T4a proper).[95,96] With this in mind, the 2002 TNM classification has recognized TCC of the prostatic urethra as a separate entity.[97]

Natural History

The natural history of superficial bladder cancer is difficult to predict because of tumor heterogeneity. The 2 features that characterize superficial bladder cancer are disease recurrence and disease progression. The risks for both recurrence and tumor progression are related to multiple histopathologic factors including histologic grade, depth of invasion, multiplicity, tumor size, tumor morphology, presence or absence of vascular or lymphatic invasion, and presence or absence of CIS. Although these conventional measures provide some prognostic information, they ultimately fail to clearly evaluate each individual tumor's malignant potential. These shortcomings with traditional clinical and histopathologic features have therefore led to significant efforts to better define a tumor's true biological potential on a molecular level.[98-100] Unfortunately, molecular markers do not have significant clinical application at present.

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Nearly 60% to 90% of patients with superficial disease will have a tumor recurrence if treated by TUR alone.[101] A retrospective analysis of 176 patients with superficial TCC from Sweden, who were followed up until death or for at least 20 years (with no adjuvant therapy), provides some insight into the natural history of this disease left untreated. An overall recurrence rate of 80% was reported, and 22% of patients (11% and 30% of Ta and T1 patients, respectively) died from the disease.[102] In this study, death was directly related to tumor grade, number of tumors, and volume of recurrences.

Grade

Several studies have investigated the role of tumor grade on tumor recurrence, progression, and mortality. Most reports have suggested that grade is a better prognostic indicator of progression and mortality than recurrence.[102-105] In a cohort analysis of 1529 patients with superficial bladder cancer from Barcelona (Spain), grade did not correlate with tumor recurrence. The main predictor of progression and mortality in this study, however, was the presence of grade 3 disease.[103] Similarly, Heney and associates reported tumor progression rates of 2%, 11%, and 45% for grade 1, 2, and 3 disease, respectively.[106] Furthermore, when stratified by stage of disease, tumor grade continued to correlate with patient mortality. In another study, Jakse and associates reported the following 10-year survival rates for patients with initial stage Ta or T1 disease: 95% for TaG1 compared with 84% for TaG3 and 78% for T1G2 compared with 50% for T1G3.[107]

Stage

Because Ta tumors are, by definition, confined to the basement membrane without access to lymphatics and vessels, these lesions tend to remain

localized. The National Bladder Cancer Cooperative Group studies of the 1970s have provided some insight into the natural course of superficial bladder cancer with regard to stage following TUR and no adjuvant intravesical therapy. Recurrence with progression to muscle invasion was found within 3 years in only 4% of patients with initial Ta tumors (without associated atypia or CIS) and 11% of patients with Ta tumor with associated atypia.[108]

Patients with low-grade Ta disease have a propensity for tumor recurrence despite low progression rates. In a long-term follow-up study of 255 patients with low-grade Ta disease, approximately 70% of patients had repeat resections for tumor recurrence, whereas only 2% of patients progressed to muscle-invasive disease.[109] When these patients were subclassified on the basis of the new WHO/ISUP classification system; 37% had PUNLMP and 63% had low-grade urothelial carcinomas. As expected, recurrence rates of PUNLMP were significantly lower than those of low-grade urothelial carcinoma: 35% versus 71%, respectively.

The incidence of high-grade Ta lesions is rare and varies between 2% and 9% of all cases of superficial bladder cancer.[106,107] Despite the relatively low malignant potential component of being Ta, it is the high-grade component that has significant impact on progression and poses a considerable problem for the clinician. Even with intravesical treatments, nearly 50% recur and 25% of these high-grade tumors progress to muscle-invasive disease.[110] A recent review showed that as many as 20% of patients with high-grade Ta lesions may die of bladder cancer.[111] Therefore, these lesions should be regarded as malignant and demand vigorous treatment and follow-up. Furthermore, there must be a high index for clinical understaging in patients reportedly having high-grade Ta tumors, and these patients should be considered for repeat TUR to ensure appropriate staging.

Most T1 bladder cancers are high-grade lesions with potential for recurrence, progression, and death. These lesions are frequently understaged or misclassified.[64,65] van der Meijden and colleagues assessed pathology results from 1400 patients treated in the European Organization for Research and Treatment of Cancer (EORTC) randomized trials, comparing various treatment strategies for superficial bladder cancer.[64] In this study, 10% of patients originally staged T1 by local pathologists were found to have evidence of muscle invasion simply on re-review. Furthermore, tumors that lack detrusor smooth muscle in the initial resected specimen are subsequently associated with residual tumor burden or muscle-invasive disease at repeat resection in up to 50% of cases.[66,112,113]

Importantly, a second TUR for T1 tumors is recommended because at least 30% of patients with T1 disease will be upstaged at the time of a second TUR. The percentage will be even higher if no muscle is present in the original TUR specimen. The risk of residual tumor on second TUR is also significant. Therefore, for patients with T1 disease, a second TUR should be performed within 1 to 4 weeks following the initial resection.

T1 bladder tumors have a high incidence of progression. Between 35% and 48% of patients with T1 tumors progress to muscle-invasive disease within 3 years when treated by TUR alone.[106,114,115] Furthermore, as mentioned earlier, the depth of submucosal invasion may be prognostically significant. The prognosis of high-grade T1 tumors is variable and multifactorial, based on additional tumor histopathologic characteristics. The presence of concomitant CIS confers a particularly worse prognosis, with up to 80% progressing to muscle-invasive disease.[106,116] Clearly, high-grade T1 disease represents a potentially lethal disease class that may warrant early radical cystectomy, particularly when conservative management with intravesical therapy fails.

CIS

The presence of associated CIS may be ominous, as patients are at increased risk for progression and death from bladder cancer with this pathologic entity. In 1 study, the presence of CIS significantly increased the 3-year risk of disease progression to 31% compared with only a 7% progression rate in patients without CIS.[73] Nearly one half of patients presenting with CIS that is either diffuse and symptomatic or associated with superficial papillary lesions of any grade progress to muscle-invasive disease.[117,118] Patients who present with marked urinary symptoms generally have a shorter interval preceding the development of muscle-invasive cancer.

Nearly one half of patients presenting with carcinoma in situ that is either diffuse and symptomatic or associated with superficial papillary lesions of any grade progress to muscle-invasive disease. Patients who present with marked urinary symptoms generally have a shorter interval preceding the development of muscle-invasive cancer.

Reliable prognostic factors that predict the course of CIS, unfortunately, do not exist. However, some studies have suggested that response

to intravesical chemotherapy or immunotherapy can be used to predict progression and death from the disease. With bacillus Calmette-Guérin therapy, a complete response rate of about 70% to 80% can be achieved.[119] Despite this complete response rate, however, as many as 20% of patients will ultimately die of metastatic disease, and a significant proportion will develop both intravesical and extravesical recurrences.[74] This implies that a durable and complete response is not always achieved and underscores the importance of lifelong surveillance in patients with this disease. Although the bladder remains the most common site for recurrence, the upper urinary tract and the prostatic urethra must be closely monitored in patients with CIS.

Number

The number of tumors is thought to be an important risk factor for recurrence.[106,120,121] Recurrences for solitary bladder tumors vary from 18% to 60%, whereas rates for multiple tumors range from 40% to 90%. In a multivariate analysis of prognostic variables, Herr reported in a series that the factor most predictive of recurrence is tumor multifocality, whereas tumor stage and grade correlated to a lesser degree.[122]

Size

Tumor size may be a prognostic factor for superficial bladder cancer. Heney and associates reported that progression to muscle invasion was seen in 35% of patients with superficial tumors larger than 5 cm, compared to only 9% of patients with small bladder tumors.[106] Others report that tumor size may influence tumor stage, but not progression.[123]

First Recurrence/Previous Recurrence Rate

The time for the first bladder-cancer recurrence may also be an important variable.[120,124] In a group of 414 people with Ta tumors, it was reported that if no recurrence occurred at the first follow-up cystoscopy, 79% of patients had no further recurrence for the remainder of the follow-up period. In patients with a follow-up recurrence at 3 months, however, only 10% were without any recurrence during the remainder of the follow-up period. Thus, in patients with a prior tumor history, previous recurrence rate predicts future recurrences. Specifically, for patients with low-grade Ta tumors, a previous recurrence rate of more than 1 per year imparts an increased risk of future recurrences.

Other Prognostic Factors

The patient's age at diagnosis is thought to be associated with prognosis, particularly in patients with primary CIS. In a study of 138 patients with primary CIS from the Mayo Clinic, patients' age of 65 years or less was a significant predictor for improved progression-free and overall survival.[125] In addition, the presence of vascular or lymphatic invasion has been identified as a poor prognostic sign.[106,126] Although lymphovascular invasion may be difficult to ascertain because of interobserver variability and the fact that it could be confused with retraction artifact, it has been shown to increase the risk of death to as high as 70% when present.[126,127]

Lastly, various laboratory parameters have also been evaluated for prognostic significance. Specifically, blood group antigens, tumor-associated antigens, proliferation antigens, oncogenes, peptide growth factors and their receptors, cell adhesion molecules, tumor angiogenesis and angiogenesis inhibitors, and cell cycle regulatory proteins have been identified recently.[99,128] Furthermore, an actual gene signature to predict clinical outcomes of superficial disease has also been identified through the use of full-genome expression analysis.[129]

The prognostic value of the most-studied molecular marker, p53, has been a topic of considerable discussion. Meta-analysis results of more than 3700 patients in 43 trials have shown that p53 correlates with tumor stage and grade, but it is unclear whether this molecular marker has independent prognostic information.[130] Despite these scientific advances, the potential application of molecular markers/genes is only beginning in clinical trials and, unfortunately, is not yet ready for clinical practice.

Combined Risk Factors

On the basis of previously established data, a risk group classification system combining the aforementioned prognostic factors has been suggested. In a multivariate analysis of 1529 patients with superficial bladder cancer, risk groups were assessed by combining stage and grade. Risk groups were classified as low (grade 1 stage Ta disease and a single grade 1 stage T1 tumor), intermediate (multiple grade 1 stage T1 tumors, grade 2 stage Ta disease, or a single grade 2 stage T1 tumor), and high (multiple grade 2 stage T1 tumors, grade 3 stages Ta or T1 disease, and any stage disease associated with CIS). Recurrence, progression, and overall survival were significantly different among the 3 groups.[131] Low-risk and intermediate-risk patients demonstrated 37% and 45% risk of recurrence, respectively, without significant risk for progression or death from bladder cancer. On the contrary, in the high-risk category, the incidence of recurrence, progression, and mortality was 54%, 15%, and 9.5%, respectively (Table 1). Similarly, a combined analysis of about 2600 patients from

Table 1
Recurrence, Progression, and Mortality 40 Months After TUR in Patients With Primary, Superficial TCC of the Bladder

Risk Group	Recurrence (%)	Progression (%)	Mortality (%)
Low risk			
• Grade 1 stage Ta • Grade 1 stage T1, single tumor	37	0	0
Intermediate risk			
• Grade 1 stage T1, multiple tumors • Grade 2 stage Ta • Grade 2 stage T1, single tumor	45	1.8	0.7
High risk			
• Grade 2 stage T1, multiple tumors • Grade 3 stage Ta • Grade 3 stage T1 • CIS association	54	15	9.5
Overall	48	7.5	4.6

TUR, transurethral resection; TCC, transitional cell carcinoma. Adapted from Millan-Rodriguez F et al.[131]

7 EORTC trials has allowed Sylvester and colleagues to calculate short- and long-term risks of recurrence and progression based on multiple factors including stage, grade, presence of CIS, multifocality, size, and history of prior recurrence.[116] It is hoped that these tables will afford the urologist accurate prognostic information based on routinely assessed clinical and pathologic variables in an effort to focus on adjuvant therapy and optimize follow-up protocols.

Conclusion

In this article we have discussed the etiology, molecular mechanisms, classification, and natural history of non–muscle-invasive TCC of the bladder. The natural history of superficial bladder cancer is difficult to predict because of tumor heterogeneity.

Main Points

- Transitional cell carcinoma (TCC) of the bladder is the second most common malignancy of the genitourinary tract. More than 90% of bladder cancer cases are TCC.
- The 2 best established risk factors for development of TCC of the bladder are tobacco use and occupational exposure to aniline dyes and aromatic amines.
- Superficial "non-muscle-invasive" bladder tumors represent a heterogeneous group of cancers that include those that are (1) papillary and limited to the mucosa (Ta, approximately 70% of all tumors), (2) high grade and flat and confined to the epithelium (Tis, 5% to 10%), and (3) invasive into the submucosa, or lamina propria (T1, 20% to 25%).
- Most superficial bladder tumors exhibit a loss of heterozygosity of chromosome 9 and activating mutations in the *HRAS* and *FGFR3* genes.
- Initial evaluation and management for patients with suspected bladder cancer involves cystoscopic evaluation of the bladder, transurethral resection (TUR) of visible tumor, and assessment of the appearance of the uninvolved bladder and prostatic urethra.
- Directed bladder biopsies, including cold-cup biopsies of the prostatic urethra, to evaluate for the presence of carcinoma in situ (CIS) are indicated when urinary cytology is positive and no grossly visible tumor is apparent on cystoscopy. The upper urinary tracts must also be evaluated in this situation.
- The risks for both recurrence and tumor progression are related to multiple histopathologic factors including grade, depth of invasion, multiplicity, tumor size, tumor morphology, presence or absence of vascular or lymphatic invasion, and presence or absence of CIS.
- Between 35% and 48% of patients with T1 bladder tumors progress to muscle-invasive disease within 3 years when treated by TUR alone. Patients with T1 bladder tumors mandate repeat TUR to assure accurate staging and removal of any residual tumor burden.
- Molecular markers as a means of predicting a tumor's true biologic potential do not have significant clinical application at present but hold potential to identify more aggressive tumors and influence therapeutic decisions in the future.

Traditional clinical and histopathologic features gathered from biopsy or TUR are not without shortcomings and have thus led to significant efforts to better define a tumor's true biological potential on a molecular level. Although molecular markers do not have significant clinical application at present, their utilization to predict more aggressive tumors and influence therapeutic decision making is likely to be realized in the near future. ■

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