BLADDER CANCER: OVERVIEW, TREATMENT CHALLENGES, AND TRENDS

Abstract

Bladder cancer is the most common malignancy of the genitourinary system and one of the ten most prevalent cancers worldwide. Its high propensity for recurrence often requires lengthy and costly treatment regimens to reduce both recurrence and progression. Non-muscle-invasive urothelial carcinoma accounts for more than 80% of cases, including the high-risk carcinoma in situ*. Intravesical chemotherapy and immunotherapy using bacille Calmette-Guerin (BCG) have been treatment mainstays for two decades, but in recent years newer therapies have been in development to help address both the global shortage of BCG and the issue of BCG-unresponsive disease.*

This article will provide background on bladder cancer, with a particular focus on current and in-development treatments for non-muscle-invasive disease.

Background

Bladder cancer, the most prevalent malignancy of the genitourinary system, is the sixth most common type of cancer in the U.S. and the tenth most common worldwide. Globally, an estimated 600,000 people are diagnosed with it each year, and more than 82,000 of these cases occur in the U.S. Additionally, approximately 200,000 bladder cancer-related deaths (17,000 in the U.S.) occur per year worldwide. Geographically, North America and Western Europe have the highest incidence rates of bladder cancer, while Central America and Middle and West Africa have the lowest.[1,2]

Categories and Types

Bladder cancer can be characterized as either epithelial or nonepithelial (mesenchymal) based on where the tumor originated. Epithelial neoplasms account for 99% of all bladder cancers (Figure 1). Urothelial carcinoma, a specific type of epithelial neoplasm, is the most common histologic type, present in up to 90% of cases in North America and Western Europe combined.

ABOUT THE AUTHOR

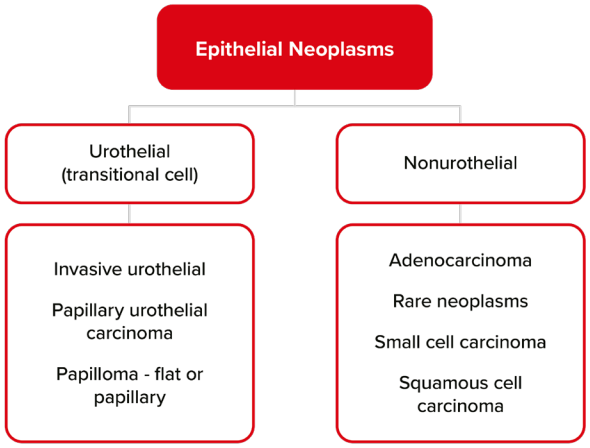
Megan Leivant, M.D.
Megan.Leivant@rgare.com

Dr. Megan Leivant, Vice President and Medical Director for RGA Reinsurance Company, assesses mortality risk for facultative life referrals, provides medical education and training for underwriters, and contributes to RGA underwriting manual development.

Prior to joining RGA in 2021, Megan was a medical director with General Re Life Corporation and OneAmerica. She also has a decade of experience in outpatient medical practice and has served as a physician reviewer for the Medical Review Institute of America.

Megan's Bachelor of Arts (B.A.) in biological sciences is from DePauw University, and her Doctor of Medicine (M.D.) is from Indiana University School of Medicine. She is a diplomate of the American Board of Internal Medicine, an Education Committee member of the American Academy of Insurance Medicine, and a member of the American College of Physicians.

Figure 1: Types of Epithelial Bladder Tumors

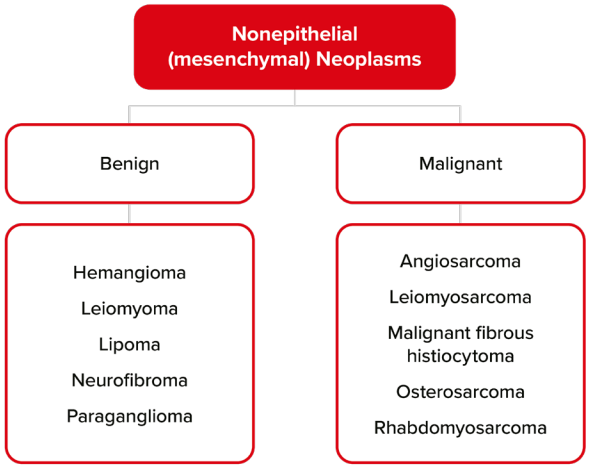


The urinary bladder and genitourinary tract are lined with urothelial cells, which are specialized transitional epithelial cells. These cells are constantly exposed to environmental toxins as the kidney filters them through the urine, making them prone to malignant transformation.[3]

Nonurothelial bladder tumors, which arise from cells other than the urothelium, make up the remaining proportion of epithelial neoplasms, including subtypes such as adenocarcinoma, small cell carcinoma, and squamous cell carcinoma. Squamous cell carcinoma is the most prevalent type in the Middle East and Africa due to its association with the parasitic disease schistosomiasis.

Nonepithelial or mesenchymal neoplasms, which account for only 1% of all bladder tumors, arise within the bladder's connective tissue layers (Figure 2).

Figure 2: Types of Nonepithelial Bladder Tumors



Risk Factors

Approximately 80% of bladder cancer cases are attributable to identifiable and avoidable risk factors. The majority of these are environmental exposures such as cigarette smoking, the number one risk factor, which accounts for 50% to 65% of cases due to the presence of carcinogens such as polycyclic aromatic hydrocarbons and beta-naphthylamine[4] in cigarette smoke. Occupational exposure to aromatic amines, which are found in paints, metals, petroleum goods, rubber, and manufacturing dyes, account for another 10% to 20% of cases.

Additional risk factors include chronic bladder inflammation due to recurrent cystitis, hereditary factors, past pelvic radiation treatment, presence of arsenic in drinking water, certain medications, increased BMI, male gender, and advancing age. In the U.S. alone, more than 90% of bladder cancers occur in individuals ages 55 or older, with a median age of 73 at time of diagnosis.[5]

Symptoms and Diagnosis

Painless hematuria is the characteristic presenting sign or symptom associated with bladder cancer. It can be microscopic or grossly visible. Dysuria, urinary frequency, and urinary urgency are other common presentations. Diagnostic evaluation follows a risk-stratified approach that typically includes urinalysis demonstrating >3 RBC/HPF, renal ultrasound, and cystoscopy, the last of which is considered the gold standard test.

Urine cytology can be used as an adjunct to cystoscopy, but it has low sensitivity for diagnosing low-grade tumors. This low sensitivity has resulted in the development of tests that can detect multiple urine-based tumor biomarkers, which have numerous potential applications in the detection of urothelial bladder cancer. These tests target markers such as the differential expression of DNA, RNA, cellular markers, and tumor-related proteins.

Urine-based tumor markers have been found to have greater sensitivity than urine cytology for detection of low-grade tumors, but to be inferior to urine cytology with regard to specificity. False positive tests can also occur, especially in situations such as concomitant UTI,

renal calculi, or prior intravesical treatment. One study found that urinary biomarker tests miss 18% to 43% of patients with bladder cancer and yield false-positive results in 12% to 26% of individuals who do not have bladder cancer.[6]

Although this lack of specificity has limited the definitive clinical application of these biomarker tests, numerous potential applications still do exist.[7] For example, urine biomarkers could assist in the initial diagnosis of bladder cancer by risk-stratifying which individuals should undergo subsequent cystoscopy and imaging evaluation of the genitourinary tract. Similarly, biomarkers could aid in the surveillance of non-muscle-invasive bladder cancer (NMIBC) by serving as an adjunct to urine cytology to help detect the presence of low-grade tumors that might otherwise be missed, or cystoscopy to potentially serve in lieu of the procedure altogether.

Bladder cancer recurrence rate far surpasses that of all other cancers.

Staging

Bladder cancers can be divided into non-muscle-invasive and muscle-invasive disease. Pathologic staging of bladder cancer is contingent on the magnitude of tumor invasion into deep layers of the bladder. NMIBC accounts for 80% of newly diagnosed bladder cancers, including tumors in stage 0 subgroups Ta (70%-75%) and Tis (5%-10%), and the stage I subgroup T1 (20%-25%).[8]

NMIBC can be further stratified into low- and high-risk categories, with varying degrees of risk for progression and recurrence. According to the 2021 European Association of Urologists (EAU) guidelines, low-risk tumors are solitary, low-grade (Ta), less than three centimeters in diameter, and not carcinoma *in situ*. High-risk tumors include carcinoma *in situ* (Tis), high-grade disease, stage T1 lesions, and low-grade (Ta) tumors that are either multiple, recurrent, and/or large (more than 3 cm in diameter). Low-risk tumors have a 0%-4% risk of progression that increases to 30%-40% for high-risk lesions. It is estimated that 31%-78% of NMIBC cases recur within five years of diagnosis, a rate far surpassing that of all other cancers.[9]

Muscle-invasive disease, characterized by malignant extension into the detrusor muscle, includes tumors determined to be stages II through IV.

Table 1: Bladder Cancer TNM Staging	
Primary tumor (T)	
T category	**T criteria**
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Noninvasive papillary carcinoma
Tis	Urothelial carcinoma *in situ*: "Flat tumor"
T1	Tumor invades lamina propria (subepithelian connective tissue)
T2	Tumor invades muscularis propria
pT2a	Tumor invades superficial muscularis propria (inner half)
pT2b	Tumor invades deep muscularis propria (outer half)
T3	Tumor invades perivesical soft tissue
pT3a	Microscopically
pT3b	Macroscopically (extravesical mass)
T4	Extravesical tumor directly invades any of the following: Prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
T4a	Extravesical tumor invades directly into prostatic stroma, seminal vesicles, uterus, vagina
T4b	Extravesical tumor invades pelvic wall, abdominal wall
Regional Lymph Nodes (N)	
N category	**N criteria**
NX	Lymph nodes cannot be assessed
N0	No lymph node metastasis
N1	Single region lymph node metastasis in the true pelvis (perivesical, obdurator, internal and external iliac, or sacral lymph node)
N2	Multiple region lymph node metastasis in the true pelvis (perivesical, obdurator, internal and external iliac, or sacral lymph node metastasis)
N3	Lymph node metastasis to the common iliac lymph nodes
Distant Metastasis (M)	
M category	**M criteria**
M0	No distant metastasis
M1	Distant metastasis
M1a	Distant metastasis limited to lymph nodes beyond the common iliacs
M1b	Non-lymph-node distant metastases

Source: UpToDate[20]

Treatment

Management of each type of bladder cancer differs significantly and poses unique challenges. Radical cystectomy, with or without platinum-based neoadjuvant chemotherapy, is the treatment of choice for surgically amenable muscle-invasive disease but carries a high morbidity risk (60%) and a near 3% risk of mortality.[10] Conversely, transurethral resection of a bladder tumor (TURBT), with or without intravesical chemotherapy or immunotherapy, is preferred for non-muscle-invasive disease.

Tumors with low risk for recurrence benefit from a single immediate instillation of one of the two intravesical chemotherapeutics, gemcitabine or mitomycin C, following TURBT to help eradicate residual disease. High-risk NMIBC requires a restaging TURBT six weeks following the initial procedure (given the up to 50% risk of understaging), followed by adjuvant immunotherapy with intravesical bacille-Calmette Guerin (BCG). BCG, the live attenuated form of mycobacterium bovis, is the most widely used intravesical therapy for bladder cancer. Treatment courses often span one to three years for intermediate to high-risk tumors and involve a robust induction and maintenance schedule.[11]

For more than two decades, BCG immunotherapy has been the treatment of choice for individuals with high-risk NMIBC, especially carcinoma *in situ*, because it delays tumor progression, reduces the need for cystectomy, and improves survival. BCG does have limitations, however, as recurrence rates for cases where it is used approach 40% at two years, treatment failure occurs in 30% to 50% of cases, it can be poorly tolerated due to adverse side effects, and there may be diminished immunologic response over time.[12]

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Challenges and Advances

Since 2019, BCG has been in short supply worldwide due to an unforeseen reduction in the number of pharmaceutical manufacturers in the market, leaving affected individuals with suboptimal treatment options depending on the severity of disease.[13] Since then, the investigative focus has shifted to biomarkers to target responsiveness to therapy. In the past few years, such alternative regimens have been developed and successfully implemented, including the use of intravesical chemotherapies mitomycin C and gemcitabine, sequential gemcitabine/docetaxel, and even initial radical cystectomy in certain high-risk situations.

Therapeutic options for individuals with NMIBC are evolving to include gene therapy, immune checkpoint inhibitors, targeted therapy, and antibody-drug conjugates (ADCs), which are a monoclonal antibody chemically linked to a drug. Adstiladrin (nadofaragene firadenovec), one such ADC, is a recombinant nonreplicating adenovirus vector with complete response rates of up to 53%, and was approved by the U.S. Food and Drug Administration in early 2023 for BCG-unresponsive NMIBC.[14, 15]

Three immune checkpoint inhibitors have also been approved for individuals with locally or advanced metastatic bladder cancer. One of these treatments, Keytruda (pembrolizumab), approved in 2020, is a programmed cell-death protein 1 (PD-1) inhibitor that demonstrated a 41% response rate for BCG-unresponsive carcinoma *in situ* in the KEYNOTE-057 trial.[16, 17] There is a pending phase III evaluation of pembrolizumab plus CG0070, an oncolytic virus therapy, following phase II trial results showing complete response in 85% of individuals with BCG-unresponsive NMIBC.[18]

Molecular profiling is being performed to predict which subtypes of NMIBC respond to BCG, and multiple trials are also underway to investigate alternative therapies for BCG-unresponsive bladder cancer. A recent study uncovered three distinct BCG response subtypes, one of which had a lower recurrence-free and progression-free survival, thus allowing for more targeted treatment for people unlikely to respond to BCG.[19]

Conclusion

Bladder cancer is a disease recognized for its high propensity for recurrence. NMIBCs, the majority of cases, often require prolonged and costly treatment. Cystoscopy remains the gold standard for diagnosis, but the expanding availability of urine tumor biomarkers offers a potential adjunct in both the identification of bladder cancers as well as ongoing surveillance. The evolution of novel therapeutics, such as gene therapy or immune checkpoint inhibitors to address BCG-unresponsive disease and the ongoing BCG shortage, is also providing greater opportunities for individuals to achieve lasting treatment response while postponing or even avoiding radical cystectomy. Such responses could pose a more favorable underwriting outlook. RF

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