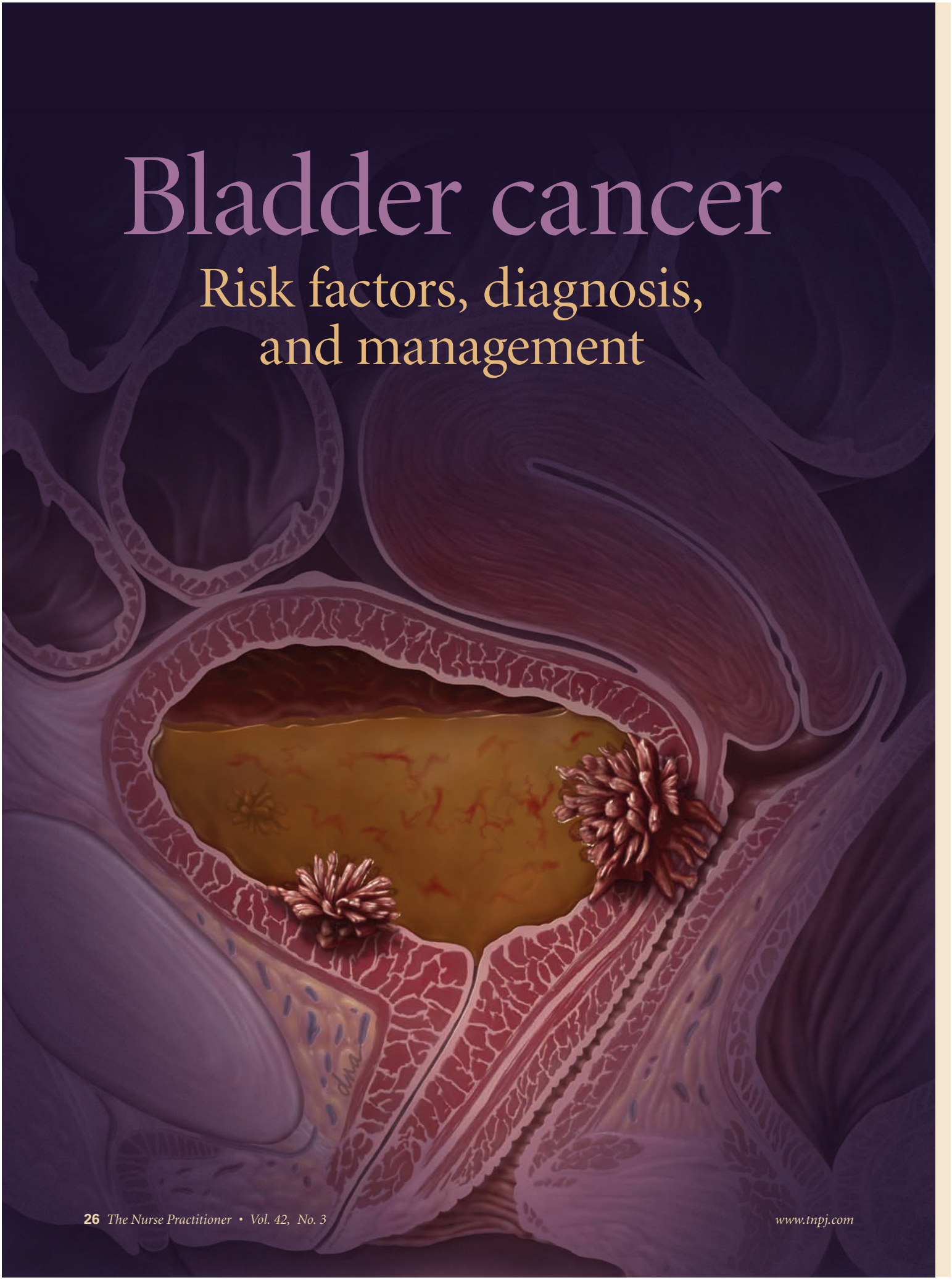
Bladder cancer

Risk factors, diagnosis, and management



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Abstract: Bladder cancer is the most common genitourinary cancer in the United States. Symptoms of bladder cancer mimic those of a urinary tract infection, which can delay timely diagnosis. Because of the high rate of bladder cancer, it is likely advanced practice registered nurses will be responsible for the care of patients with bladder cancer. This article reviews the signs and symptoms of bladder cancer along with management options to safely care for this patient population.

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According to the American Cancer Society, bladder cancer will be responsible for 5% of all cancer diagnosed in the United States in 2017, with 79,030 patients expected to be diagnosed with the disease and 16,870 expected patient deaths from bladder cancer.[1,2] The majority of newly diagnosed patients with bladder cancer are male, which is thought to be related to an increased rate of smoking and occupational exposure.[1] White Americans have a higher incidence of bladder cancer than Black Americans, and the average age of bladder cancer diagnosis is 73 years.[1,2]

Pathophysiology

The most common type of bladder cancer is urothelial cancer (also called transitional cell carcinoma), which is responsible for over 90% of bladder cancer tumors in the United States.[3] Squamous and adenocarcinoma, though less common (5% and 2%, respectively), are associated with an advanced stage and a higher mortality than urothelial cancer.[4] Patients at increased risk for developing squamous cell bladder cancer reside in areas known to house the schistosoma parasite, which includes Africa, the Middle East, South America, and the Caribbean.[5]

Bladder cancer can be categorized as nonmuscle-invasive bladder cancer (NMIBC) or muscle-invasive bladder cancer (MIBC), with the majority of newly diagnosed patients having NMIBC (70% to 85%).[6] This is an important distinction, as NMIBC allows the patient bladder-sparing options for cancer management. To help clarify between the two categories of bladder cancer, it is important to review the three histologic layers of the bladder.

The first layer of the bladder is the urothelium, the second layer is the lamina propria (suburethral loose connective tissue), and the third layer is the muscularis propria.[7] Cancers affecting the urothelium or lamina propria are NMIBC, and those invading the muscularis propria are MIBC.

In addition to distinguishing between NMIBC and MIBC, it is important to understand the staging and grade of bladder cancer. Staging of bladder cancer is determined by the TNM system.[8] The TNM identifies the primary tumor (T), presence of lymph node involvement (N), and if metastasis is present (M).[8]

The aggressiveness of bladder cancer is determined by the grade of the disease, with high-grade (poorly differentiated) most likely to progress and spread compared with low-grade (well-differentiated) bladder cancer.[9]

Patients with NMIBC are treated with bladder-sparing strategies, such as transurethral resection of bladder tumor (TURBT) followed by intravesical immunotherapy or chemotherapy; MIBC patients are treated with neoadjuvant chemotherapy and surgical removal of the bladder.[7]

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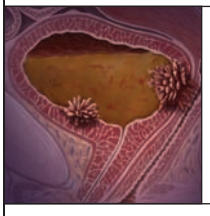
Keywords: bladder cancer, intravesical therapy, muscle-invasive bladder cancer, nonmuscle-invasive bladder cancer, transurethral resection of bladder tumor, urinary diversion for bladder cancer

Risk factors

Smoking. The most common risk factor for bladder cancer, smoking is responsible for approximately two-thirds of bladder cancers in men and one-third in women.[10] Smokers have a fourfold increased risk of bladder cancer compared with nonsmokers.[10] The number of cigarettes smoked, length of years smoked, and age when smoking began all increase an individual's bladder cancer risk.[10] Because the bladder's function is to store urine, there is ample time for carcinogens in the urine to affect the bladder.[11] The carcinogens associated with smoking remain in constant contact within the genitourinary system until eliminated, thus the high rate for urothelial cancers.[5]



Patients with chronic UTIs, chronic use of urinary catheters, and bladder stones are at an increased risk for bladder cancer.

Occupational exposure. The second most common risk factor for bladder cancer is occupational exposure to aniline dyes, aromatic amines, and polycyclic aromatic hydrocarbons. These chemicals are often used in the textile, paint, plastic, printing, and rubber industries, which places these individuals at an increased risk for bladder cancer.[10]

Inflammation. Although the mechanism of action is unknown, patients with chronic urinary tract infections (UTIs), chronic use of urinary catheters, and bladder stones are at an increased risk for bladder cancer.[3] Patients infected with the parasite *Schistosoma haematobium* are at an increased risk for developing squamous cell cancer, a virulent and morbid form of bladder cancer.[3]

Radiation. Patients treated with pelvic radiation for genitourinary and gynecologic cancers, such as prostate and cervical cancer, have a higher rate of bladder cancer; however, with advancements in radiation therapy, this number is expected to decrease.[10]

Chemotherapy. Patients treated with cyclophosphamide for cancer and autoimmune diseases have a fourfold to ninefold increased risk of developing bladder cancer.[10] The risk is further increased with cumulative doses and length of treatment.[10]

Clinical presentation

The most common symptom of bladder cancer is gross, painless hematuria, occurring in 80% of patients with bladder cancer.[10] Hematuria can be either microscopic (blood visible under the microscope) or gross (blood visible in the urine). The degree of hematuria does not correlate to severity of disease.[10] Although patients may present with either continuous or intermittent hematuria, all patients with hematuria should be referred to a urologist to rule out bladder cancer, especially if they have a past or current history of smoking.[12]

It is important to note hematuria is not always caused by bladder cancer. It can also be caused by other conditions, including renal cancer, prostate cancer, interstitial cystitis, renal calculi, benign prostatic hyperplasia, and trauma, and can be exercise-induced, further warranting a referral to a urologist.[13]

Irritative urinary tract signs and symptoms, such as urinary frequency, urgency, hesitancy, and dysuria, are less common, affecting 30% of patients with bladder cancer.[12] Because irritative urinary signs and symptoms mimic those of a UTI, patients may be initially diagnosed with a UTI, delaying a bladder cancer diagnosis. Late signs and symptoms related to invasive or metastatic bladder cancer include flank pain, pelvic fullness, urinary retention, lower extremity edema, weight loss, and bone pain.[12]

Clinical exam

The advanced practice registered nurse (APRN) should perform a focused genitourinary exam to evaluate for kidney and bladder abnormalities, including flank tenderness and/or mass, abdominal mass, and suprapubic distension and/or mass.[14] The penis, urethral meatus, scrotum, rectum, and prostate should also be examined in male patients with gross or microhematuria.

If the penis is uncircumcised, a phimotic foreskin can be irritated and bleed, contributing to a false diagnosis of hematuria. Inspecting the urethral meatus for mass, meatal narrowing, or blood can help identify external sources of hematuria. Additionally, performing a digital rectal and prostate exam is done to assess for an enlarged prostate or prostate mass, both of which may contribute to hematuria.[14]

A genitourinary exam on a female patient should include inspecting the urethra for a mass, blood, or urethral caruncle, and inspecting the vagina for signs of genitourinary syndrome of menopause (vaginal stenosis or atrophic vaginal changes) as possible external causes for hematuria.[13] It is important to inspect the vagina for bloody discharge or mass, as this can help distinguish if hematuria is related to a gynecologic source. A catheterized urinalysis can be performed if any question remains as to a genitourinary or gynecologic source of bleeding.[14]

Diagnostic tests

Because bladder cancer signs and symptoms mimic those of a UTI, it is vital to rule this diagnosis out in any patient

complaining of gross or microhematuria and/or irritative voiding symptoms. A urine specimen should be sent for both a urinalysis (dipstick and microscopic) and urine culture to rule out an infection. If the urine culture rules out a UTI, it is important to review the microscopic (not dipstick) urinalysis for microhematuria.[15]

According to the American Urological Association's (AUA) *Guideline for the Diagnosis, Evaluation, and Follow-up of Asymptomatic Microhematuia in Adults*, a urinalysis with three or more red blood cells present per high-powered field (and without signs of a UTI, such as pyuria and bacteriuria) is defined as mircrohematuria and warrants further evaluation to rule out urothelial cancer.[15] The AUA further specifies a urologic evaluation is recommended once to rule out benign causes of microhematuria, such as menstruation, vigorous exercise, viral illness, and trauma.[15] In addition to submitting a urinalysis and urine culture, a urine specimen should also be sent for cytology. Urine cytology evaluates for the presence of abnormal cells, which may indicate urothelial cancer.[7] Urine cytology can aid in the initial diagnosis of bladder cancer and can also be used during routine surveillance monitoring of patients with bladder cancer.

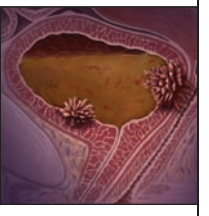
Although urine cytology is easy to obtain and highly sensitive and specific for high-grade lesions, it has a low sensitivity for low-grade lesions and a high rate of equivocal results.[16] Because of the low sensitivity for low-grade lesions, urine cytology should be used as an adjunct test to aid in the diagnosis of bladder cancer.[16]

Another urine test used to aid in the diagnosis and surveillance of bladder cancer is the fluorescence in situ hybridization (FISH) test.[17] FISH has the capabilities of detecting common chromosomal defects associated with urothelial cancer with a sensitivity and specificity of 72% and 83%.[17] FISH results, like cytology, are higher for high-grade than low-grade disease, but FISH has the capacity to foresee recurrent disease, unlike cytology.[17] This ability to "anticipate" recurrent bladder cancer is due to the FISH test's ability to recognize microscopic disease prior to being identified by cystoscopy.[18] Serum blood work, including a basic metabolic panel, should also be ordered to assess kidney function (serum creatinine) and if applicable, a prostate-specific antigen.[14]

In addition to the above-mentioned lab tests, radiologic imaging with computed tomography (CT) scan or magnetic resonance imaging (MRI) is used to assess the kidneys, ureters, and bladder for evidence of a mass or tumor.[19] A multiphasic CT urogram with precontrast, nephrographic, and excretory images is the radiologic test of choice for its high sensitivity and specificity for identifying upper tract lesions.[14]

Prior to obtaining a CT urogram, blood work, including a basic metabolic panel, is obtained to assess the patient's creatinine level before pursuing an I.V. contrast CT urogram. An abdominal pelvic MRI is an alternative in patients with a contraindication to a CT urogram, such as those with an elevated creatinine level or iodine contrast allergy.[14] Conversely, in patients who cannot tolerate an MRI due to the risk of nephrogenic systemic fibrosis (such as those with a glomerular filtration rate less than 30 mL/min/1.73 m^2), noncontrast CT scan or kidney ultrasound with retrograde pyelogram is a viable option.[14]

When obtaining tissue samples for biopsy, it is imperative that the biopsy or TURBT specimen include detrusor muscle.



Nephrogenic systemic fibrosis is a severe systemic fibrosing condition that occurs primarily when patients with advanced kidney disease are exposed to gadolinium-based contrast. Avoiding gadolinium-based contrast in this patient population has dramatically reduced the incidence of nephrogenic systemic fibrosis, thus the importance of appropriately screening patients prior to MRI.[20]

The urologist will perform an in-office cystoscopy to directly visualize the bladder for presence of a tumor. During a cystoscopy, the urologist inserts a flexible scope into the urethra with the assistance of topical anesthesia to inspect the urethra and bladder for bladder stones, tumors, or lesions.[19] (See *Cystoscopy.*) If a bladder tumor is identified, the patient is scheduled for either a bladder biopsy or a TURBT in the OR to remove the tumor and submit it for pathologic diagnosis.[19]

When obtaining tissue samples for biopsy, it is imperative that the biopsy or TURBT specimen include detrusor muscle, as this differentiates between NMIBC and MIBC.[19] Once the pathology results are available, the APRN can properly stage and grade the bladder cancer.

Treatment and management of bladder cancer

NMIBC. Previously referred to as superficial bladder cancer, urothelial tumors that have not invaded the bladder muscle (detrusor) are now called NMIBC.[13] NMIBC accounts for approximately 75% of bladder cancers, including those diagnosed with stage Ta, carcinoma in situ (CIS), or T1 invasive urothelial cancer involving the subepithelial lining/lamina propria.[9,12]

Although the treatment options for patients with NMIBC allow them to keep the bladder, they are at risk for recurrence and progression to MIBC.[6] The risk of recurrence is increased by the number of NMIBC tumors identified during cystoscopy, tumor size, concurrent CIS, tumor grade, and prior recurrence.[19] Based on the above-mentioned risk factors, the 5-year rate of recurrence can be as high as 78% and the rate of progression as high as 45%.[19]

Recurrence of NMIBC can be managed successfully with transurethral surgery and intravesical therapy.[7] Instilling a single dose of intravesical chemotherapy (mitomycin C) immediately after TURBT can decrease the tumor recurrence rate from 48% to 37%.[5] Though not FDA approved for bladder cancer, mitomycin C is the most common perioperative intravesical chemotherapeutic agent recommended by the National Comprehensive Cancer Network (NCCN) guidelines.[21]

Because of the high rate of recurrence, patients with NMIBC require vigilant monitoring with cystoscopic exams and intravesical immunotherapy with bacillus Calmette-Guerin (BCG) or chemotherapy with mitomycin C to prevent or delay tumor recurrence and progression.[13] Although the mechanism of action is unknown, BCG is thought to stimulate an immune response against further tumor cell growth, and BCG immunotherapy is the most effective treatment for managing NMIBC.[22]

Pending the stage and grade of NMIBC, patients may be candidates for intravesical BCG therapy induction and/or maintenance. Although various guidelines exist, the AUA and the NCCN recommend the following:

- For multifocal and/or large low-grade Ta tumors: BCG induction once per week for 6 weeks, followed by maintenance (3 weeks of BCG at 3 and 6 months, then every 6 months for 12 months)
- For high-grade Ta, T1, and/or CIS tumors: BCG induction followed by maintenance for 36 months.[6,21-23]

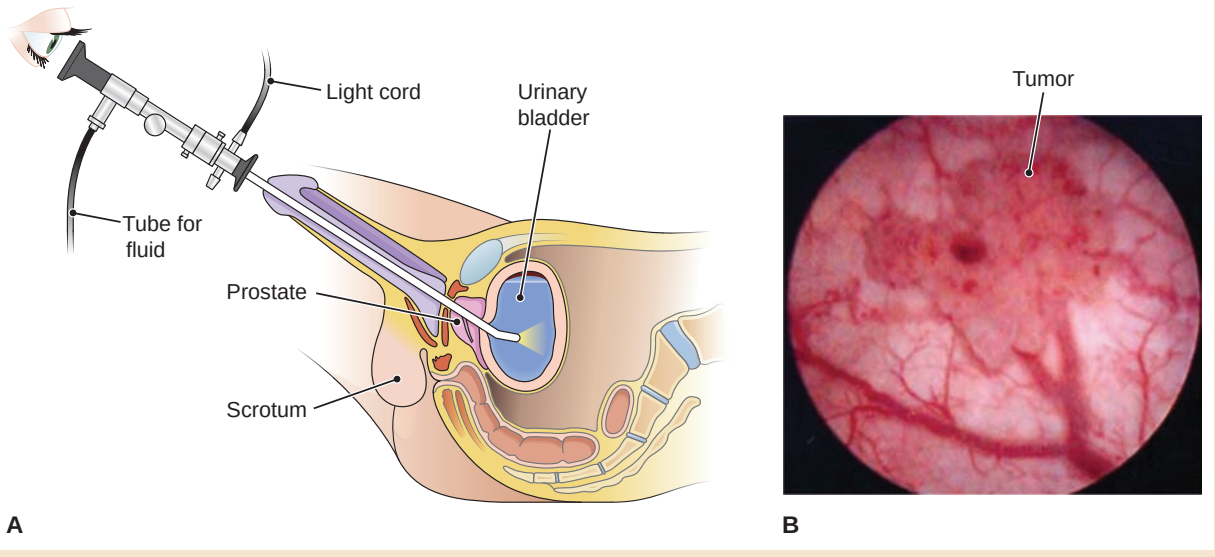
BCG induction begins approximately 4 to 6 weeks after TURBT when the patient returns to the urology office; a urethral catheter is used to instill BCG into the bladder. The patient is asked to hold his or her urine for 1 to 2 hours, allowing the BCG to remain in constant contact with the bladder epithelium prior to voiding.[5]

BCG adverse reactions

BCG is known to cause local adverse reactions, with 80% of patients reporting cystitis-like symptoms.[19] Because BCG has a cumulative effect, patients may notice an increase in adverse reactions further in the maintenance schedule.[19] Other common adverse reactions include dysuria, frequency of urination, and hematuria.[19] Systemic adverse reactions such as sepsis are less common, occurring in less than 5% of patients.[22] Systemic adverse reactions

Cystoscopy

(A) The lighted cystoscope is introduced through the urethra into the bladder of a male patient. Sterile fluid is used to inflate the bladder. The cystoscope is used to examine the bladder, remove specimens for biopsy, and remove tumors. (B) Cancer of the bladder, as viewed through a cystoscope.



Source: Cohen BJ, Hull K. *Memmler's The Human Body in Health and Disease.* Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2014.

are minimized by not administering BCG in patients with acute UTI, gross hematuria, or after a traumatic catheterization.[22]

Muscle-invasive bladder cancer

Although the majority of patients with MIBC are diagnosed at the time of their first urology office visit, some patients with NMIBC will ultimately progress to MIBC.[24] MIBC has a high mortality rate, with 85% of patients dying within 2 years if left untreated.[24]

The gold standard treatment for MIBC is surgical removal of the bladder and pelvic lymph nodes with or without neoadjuvant chemotherapy.[24] In males, a radical cystectomy consists of removing the bladder, prostate, and seminal vesicles; in women, radical cystectomy consists of removing the bladder, ovaries, uterus with cervix, and the anterior vagina.[24] Following a radical cystectomy, a urinary diversion is required for elimination of urine.

Urinary diversions can be classified as either incontinent or continent. The most frequently used incontinent urinary diversion is the ileal conduit, and the most frequently used continent diversion is the orthotopic neobladder.[25]

Urinary diversions

Used since 1950, the ileal conduit remains the most common choice for urinary diversion due to the relative ease to perform, rapid recovery, and ease to maintain.[26] The ureters are implanted into a section of the small bowel (ileum), which is then attached to abdominal wall as a stoma.[5] Urine travels through the ileal conduit and is collected in an external storage pouch attached to the abdominal skin surrounding the stoma.[5]

For patients who do not want a stoma or external storage pouch, the continent orthotopic neobladder is another option. A section of bowel is used to create a reservoir that resembles the bladder and can attach to the urethra. The ureters are implanted in the neobladder, allowing urine to travel into the neobladder and out of the body via the urethra.[5] The neobladder does not have the same sensation as a native bladder and requires bladder retraining such as timed voiding and abdominal straining to empty the neobladder.[27]

Additionally, because the neobladder is constructed from the ileum, it is possible for the urine to contain mucus. Pending how much mucus the ileum produces, urinary retention may develop. In order to combat potential mucus production and urinary retention, patients are instructed on clean intermittent catheterization.[28]

For patients who want to avoid an external urinary storage pouch, another option is a continent catheterizable stoma or continent cutaneous diversion.[24] Commonly referred to as the Kock pouch, the Mainz pouch, or the Indiana pouch, a urinary reservoir is created using a section of ileum that patients catheterize throughout the day.[25,29] The location of the stoma is usually located near the umbilicus (see *Types of continent urinary diversions*).

Implications for advanced practice nursing

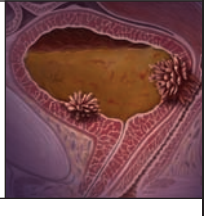
Patients with potential bladder cancer red flags, including gross or microhematuria, irritative voiding symptoms unresponsive to conservative medicinal therapy, and a history of smoking, should always be referred to urology. If the APRN identifies a patient as a current smoker, this opportunity can be used to educate the patient on the many adverse reactions of smoking, including bladder cancer.

Many patients are not aware of the association between smoking and bladder cancer, making this an important lifestyle modification recommendation.[30] Providing patients with smoking cessation support tools (such as the smoking cessation quitline 1-800-QUIT-NOW) can augment the teaching provided during the APRN office visit.

Patients with bladder cancer are under the care of not only their primary care APRN but their urologist; wound, ostomy, and continence nurse; and if applicable, a pelvic floor physical therapist. The urologist routinely monitors patients with bladder cancer during surveillance urology office appointments and cystoscopies.

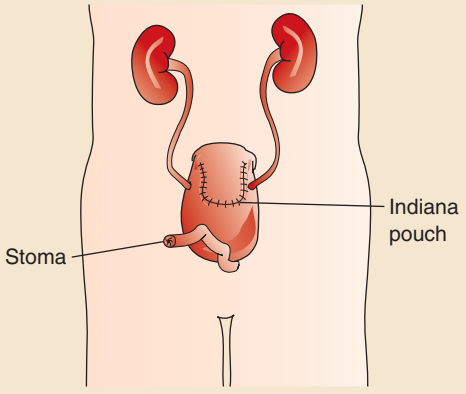
In addition to surveillance urology appointments, many MIBC patients have to learn to coexist with an ileal conduit or learn to void with a neobladder. Collaborating or referring MIBC patients who have an ileal conduit to a wound, ostomy, and continence nurse can help facilitate the patient's ostomy care along with providing an opportunity for the patient to experiment with various ostomy appliances. Conversely, patients with a neobladder may have a difficulty using their new bladder, and a pelvic floor physical therapist is instrumental to help educate patients.

For patients who do not want a stoma or external storage pouch, the continent orthotopic neobladder is an option.

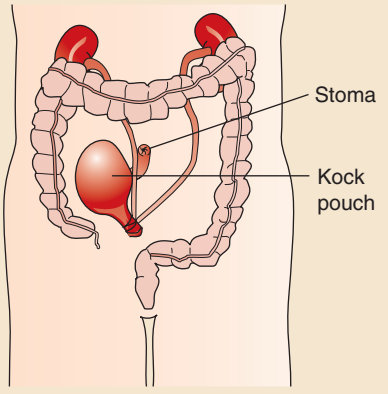


As both patients with NMIBC or MIBC require long-term follow-up, the APRN is in a position to forge meaningful connections with patients with bladder cancer and family members along with members of the patients'

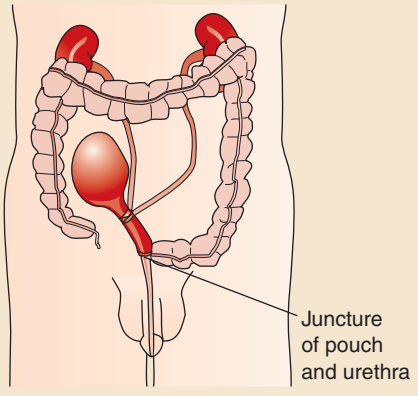
Types of continent urinary diversions



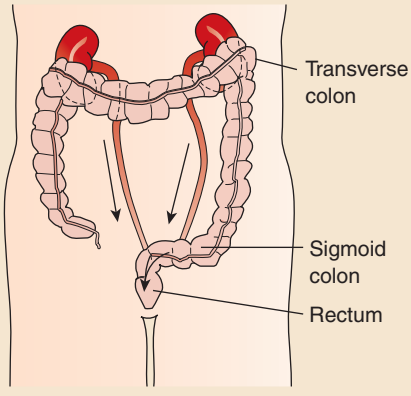
A
Indiana pouch. The surgeon introduces the ureters into a segment of ileum and cecum. Urine is drained periodically by inserting a catheter into the stoma.



B
Continent ileal urinary diversion (Kock pouch). The surgeon transplants the ureters to an isolated segment of small bowel, ascending colon, or ileocolonic segment and develops an effective continence mechanism or valve. Urine is drained by inserting a catheter into the stoma.



C
In male patients, the *Kock pouch* can be modified by attaching one end of the pouch to the urethra, allowing more normal voiding. The female urethra is too short for this modification.



D
Ureterosigmoidostomy. The surgeon introduces the ureters into the sigmoid, thereby allowing urine to flow through the colon and out of the rectum.

Source: Smeltzer SC, Bare BG, Hinkle JL, Cheever KH. *Brunner & Suddarth's Textbook of Medical-Surgical Nursing.* 12th ed. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2010.

interprofessional team. Connecting patients with bladder cancer to their local Bladder Cancer Advocacy Network (www.bcan.org) can help foster a sense of community in those affected by bladder cancer. NP

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