Bladder Cancer, Version 3.2020

Thomas W. Flaig, MD[1,*]; Philippe E. Spiess, MD, MS[2,*]; Neeraj Agarwal, MD[3]; Rick Bangs, MBA[4]; Stephen A. Boorjian, MD[5,*]; Mark K. Buyyounouski, MD, MS[6]; Sam Chang, MD, MBA[7]; Tracy M. Downs, MD[8]; Jason A. Efstathiou, MD, DPhil[9]; Terence Friedlander, MD[10]; Richard E. Greenberg, MD[11,*]; Khurshid A. Guru, MD[12]; Thomas Guzzo, MD, MPH[13]; Harry W. Herr, MD[14,*]; Jean Hoffman-Censits, MD[15]; Christopher Hoimes, MD[16,*]; Brant A. Inman, MD, MSc[17,*]; Masahito Jimbo, MD, PhD, MPH[18]; A. Karim Kader, MD, PhD[19]; Subodh M. Lele, MD[20]; Jeff Michalski, MD, MBA[21]; Jeffrey S. Montgomery, MD, MHSA[18]; Lakshminarayanan Nandagopal, MD[22]; Lance C. Pagliaro, MD[5,*]; Sumanta K. Pal, MD[23]; Anthony Patterson, MD[24]; Elizabeth R. Plimack, MD, MS[11]; Kamal S. Pohar, MD[25]; Mark A. Preston, MD, MPH[26]; Wade J. Sexton, MD[2,*]; Arlene O. Siefker-Radtke, MD[27,*]; Jonathan Tward, MD, PhD[3]; Jonathan L. Wright, MD[28]; Lisa A. Gurski, PhD[29]; and Alyse Johnson-Chilla, MS[29]

ABSTRACT

This selection from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Bladder Cancer focuses on the clinical presentation and workup of suspected bladder cancer, treatment of non–muscle-invasive urothelial bladder cancer, and treatment of metastatic urothelial bladder cancer because important updates have recently been made to these sections. Some important updates include recommendations for optimal treatment of non–muscle-invasive bladder cancer in the event of a bacillus Calmette-Guérin (BCG) shortage and details about biomarker testing for advanced or metastatic disease. The systemic therapy recommendations for second-line or subsequent therapies have also been revised. Treatment and management of muscle-invasive, nonmetastatic disease is covered in the complete version of the NCCN Guidelines for Bladder Cancer available at NCCN.org. Additional topics covered in the complete version include treatment of nonurothelial histologies and recommendations for nonbladder urinary tract cancers such as upper tract urothelial carcinoma, urothelial carcinoma of the prostate, and primary carcinoma of the urethra.

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[1]University of Colorado Cancer Center; [2]Moffitt Cancer Center; [3]Huntsman Cancer Institute at the University of Utah; [4]Patient Advocate; [5]Mayo Clinic Cancer Center; [6]Stanford Cancer Institute; [7]Vanderbilt-Ingram Cancer Center; [8]University of Wisconsin Carbone Cancer Center; [9]Massachusetts General Hospital Cancer Center; [10]UCSF Helen Diller Family Comprehensive Cancer Center; [11]Fox Chase Cancer Center; [12]Roswell Park Comprehensive Cancer Center; [13]Abramson Cancer Center at the University of Pennsylvania; [14]Memorial Sloan Kettering Cancer Center; [15]The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins; [16]Case Comprehensive Cancer Center/University Hospitals Seidman Cancer Center and Cleveland Clinic Taussig Cancer Institute; [17]Duke Cancer Institute; [18]University of Michigan Rogel Cancer Center; [19]UC San Diego Moores Cancer Center; [20]Fred & Pamela Buffett Cancer Center; [21]Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine; [22]O'Neal Comprehensive Cancer Center at UAB; [23]City of Hope National Medical Center; [24]St. Jude Children's Research Hospital/The University of Tennessee Health Science Center; [25]The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute; [26]Dana-Farber/Brigham and Women's Cancer Center; [27]The University of Texas MD Anderson Cancer Center; [28]Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance; and [29]National Comprehensive Cancer Network

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Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

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All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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The complete NCCN Guidelines for Bladder Cancer are not printed in this issue of *JNCCN* but can be accessed online at NCCN.org.

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Individual disclosures for the NCCN Bladder Cancer Panel members can be found on page 354. (The most recent version of these guidelines and accompanying disclosures are available at NCCN.org.)

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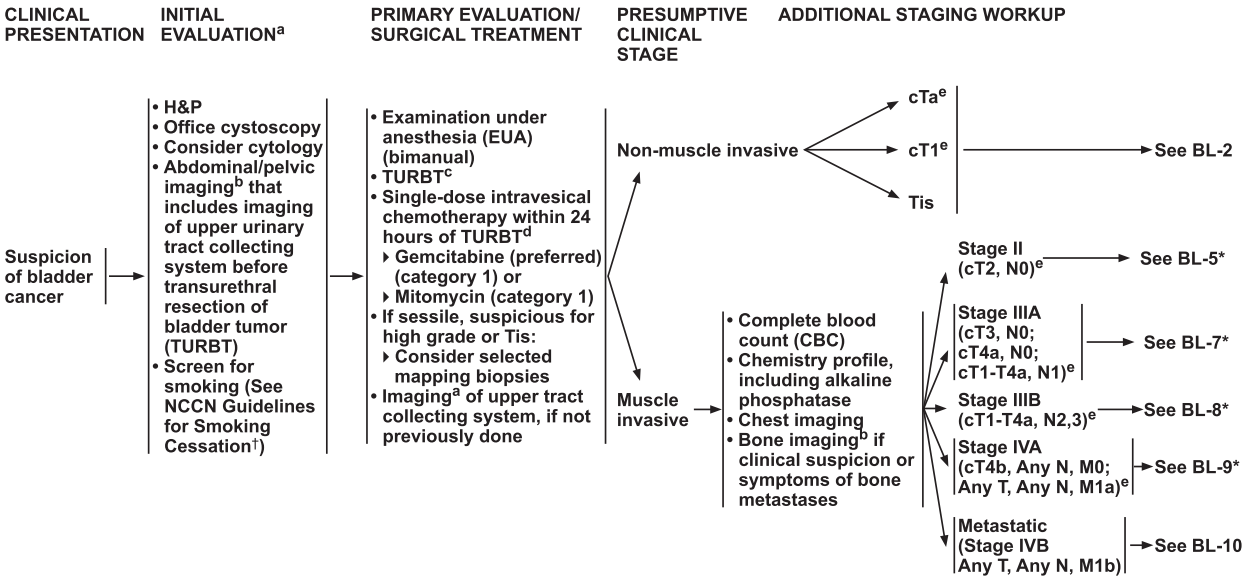

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[a] For tools to aid optimal assessment and management of older adults with cancer, see NCCN Guidelines for Older Adult Oncology.†
[b] See Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
[c] See Principles of Surgical Management (BL-B).
[d] Immediate intravesical chemotherapy reduces the recurrence rate by 35%. See Principles of Intravesical Treatment (BL-F).
[e] The modifier "c" refers to clinical staging based on bimanual examination under anesthesia, endoscopic surgery (biopsy or transurethral resection), and imaging studies. The modifier "p" refers to pathologic staging based on cystectomy and lymph node dissection.

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Overview

An estimated 80,470 new cases of urinary bladder cancer (61,700 men and 18,770 women) will be diagnosed in the United States in 2019 with approximately 17,670 deaths (12,870 men and 4,800 women) occurring during this same period.[1] Bladder cancer, the sixth most common cancer in the United States, is rarely diagnosed in individuals younger than 40 years of age. Given that the median age at diagnosis is 73 years,[2] medical comorbidities are a frequent consideration in patient management.

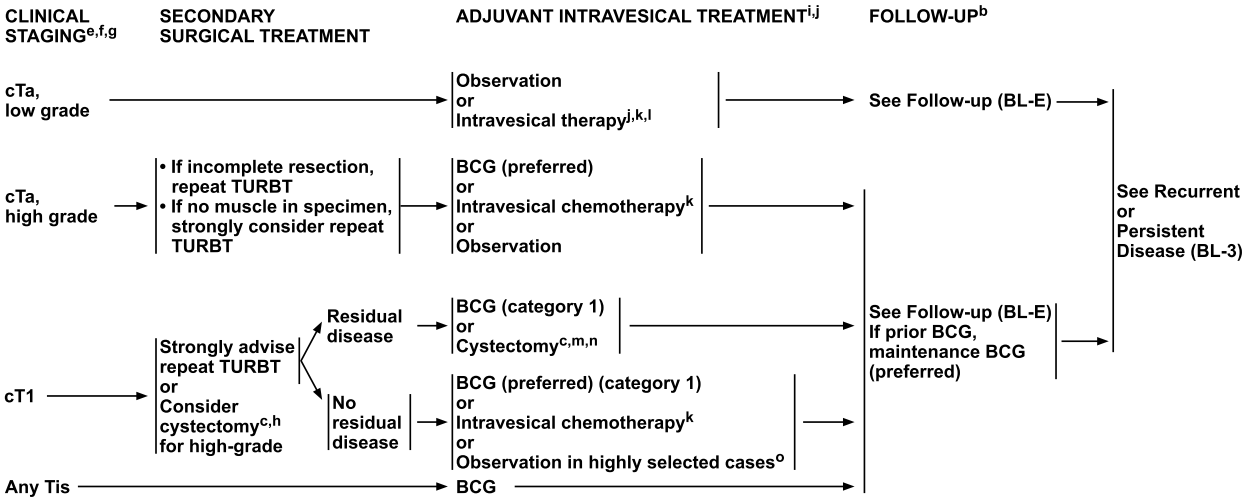
Risk factors for developing bladder cancer include male sex, white race, smoking, personal or family history of bladder cancer, pelvic radiation, environmental/occupational exposures, exposure to certain drugs, chronic infection or irritation of the urinary tract, and certain medical conditions including obesity and diabetes.[3–5] Although diabetes mellitus appears to be associated with an elevated risk of developing bladder cancer,[4] treatment with metformin may be associated with improved prognosis in patients with bladder cancer and diabetes.[6] Certain genetic syndromes, most notably Lynch syndrome, may also predispose an individual to urothelial carcinoma.[7]

The clinical spectrum of bladder cancer can be divided into 3 categories that differ in prognosis, management, and therapeutic aims. The first category consists of non–muscle-invasive disease, for which treatment is directed at reducing recurrences and preventing progression to a more advanced stage. The second group encompasses muscle-invasive disease. The goal of therapy is to determine whether the bladder should be removed or if it can be preserved without compromising survival, and to determine if the primary lesion can be managed independently or if patients are at high risk for distant spread requiring systemic approaches to improve the likelihood of cure. The critical concern for the third group, consisting of metastatic lesions, is how to prolong quantity and maintain quality of life. Numerous agents with different mechanisms of action have antitumor effects on this disease. The goal is using these agents to achieve the best possible outcome.

Clinical Presentation and Workup

The most common presenting symptom in patients with bladder cancer is microscopic or gross hematuria, although urinary frequency due to irritation or a reduced bladder capacity can also develop. Less commonly, the presenting symptom is a urinary tract infection. Upper tract obstruction or pain may occur in patients with a more advanced lesion. Patients presenting with these symptoms should be evaluated with office cystoscopy to determine if a lesion is present. If one is documented, the

Non-Muscle Invasive Bladder Cancer



[b] See Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
[c] See Principles of Surgical Management (BL-B).
[e] The modifier "c" refers to clinical staging based on bimanual examination under anesthesia, endoscopic surgery (biopsy or transurethral resection), and imaging studies. The modifier "p" refers to pathologic staging based on cystectomy and lymph node dissection.
[f] Montironi R, Lopez-Beltran A. The 2004 WHO classification of bladder tumors: A summary and commentary. Int J Surg Pathol 2005;13:143-153.
See Principles of Pathology Management (BL-C*).
[g] See Bladder Cancer: Non-Urothelial and Urothelial with Variant Histology (BL-D*).
[h] See Follow-Up (BL-E).
[i] Indications for adjuvant induction therapy: Based on probability of recurrence and progression to muscle-invasive disease, such as size, number, and grade.
[j] See Principles of Intravesical Treatment (BL-F).
[k] The most commonly used options for intravesical chemotherapy are gemcitabine (preferred) and mitomycin.
[l] Intravesical chemotherapy is preferred, although BCG may be considered when not in shortage.
[m] If not a cystectomy candidate, consider concurrent chemoradiotherapy (category 2B) or a clinical trial. See Principles of Systemic Therapy (BL-G 5 of 7*).
[n] Cystectomy is generally reserved for residual T1, high-grade, muscle-invasive disease at re-resection, and variant histology associated with adverse outcomes.
[o] Highly selected cases with low grade, small-volume tumors with limited lamina propria invasion and no CIS.

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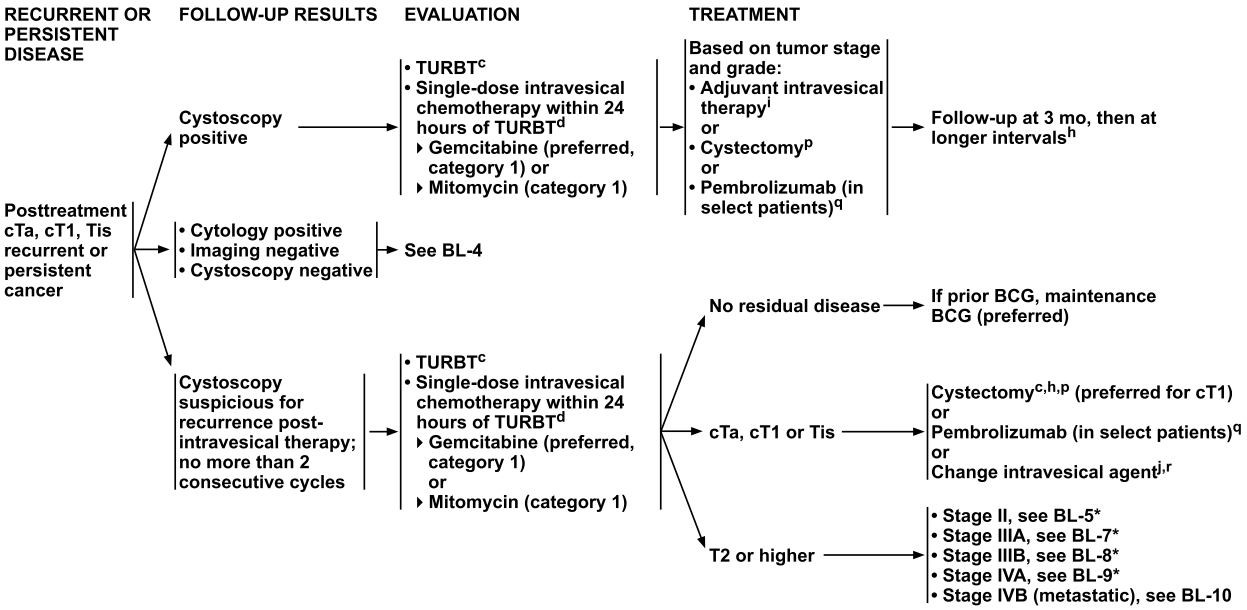
patient should be scheduled for a transurethral resection of the bladder tumor (TURBT) to confirm the diagnosis and determine the extent of disease within the bladder. Urine cytology may also be obtained around the time of cystoscopy. Being that smoking is a major risk factor for bladder cancer,[8] screening for smoking and initiation of treatment for smoking cessation, if appropriate, is recommended during the initial evaluation (see NCCN Guidelines for Smoking Cessation, available at NCCN.org).

A CT scan or MRI of the abdomen and pelvis is recommended before TURBT, as long as it is logistically feasible, to allow for better anatomic characterization of the lesion and possible delineation of suspected depth of invasion. Additional workup for all patients should include consideration of urine cytology, if not already tested, and evaluation of the upper tracts with a CT or MR urography; a renal ultrasound or CT without contrast with retrograde ureteropyelography; a ureteroscopy; or a combination of techniques. CT urography is generally the preferred approach to upper tract imaging in patients who can safely receive intravenous contrast agents.

TURBT with a bimanual examination under anesthesia is performed to resect visible tumor and to sample muscle within the area of the tumor to assess invasion. The goal of TURBT is to correctly identify the clinical stage and grade of disease while completely resecting all visible tumor. Therefore, an adequate sample that includes bladder muscle (ie, muscularis propria) preferentially should be obtained in the resection specimen, most notably in the setting of high-grade disease. A small fragment of tumor with few muscle fibers is inadequate for assessing the depth of invasion and guiding treatment recommendations. When a large papillary lesion is noted, more than one session may be needed to completely resect the tumor. With carcinoma in situ (CIS), biopsy of sites adjacent to the tumor and multiple random biopsies may be performed to assess for a field change. Single-dose intravesical gemcitabine or mitomycin (both category 1, although gemcitabine is preferred due to better tolerability and lower cost) within 24 hours of TURBT is recommended if non–muscle-invasive disease is suspected (see "Intravesical Therapy" [BL-F 1 of 3], page 339). Existing data support this approach largely for low-volume, low-grade disease.[9–11]

Although selected mapping biopsies may be indicated in specific situations for lesions that are solid (sessile) or

Non-Muscle Invasive Bladder Cancer



[c] See Principles of Surgical Management (BL-B).
[d] Most efficacious in patients with low grade, low-volume Ta urothelial cancer. See Principles of Intravesical Treatment (BL-F).
[h] See Follow-Up (BL-E).
[i] Indications for adjuvant induction therapy: Based on probability of recurrence and progression to muscle-invasive disease, such as size, number, and grade.
[j] See Principles of Intravesical Treatment (BL-F).
[p] If not a cystectomy candidate, and recurrence is cTa or cT1, consider concurrent chemoradiotherapy (category 2B for cTa, category 2A for cT1) or a clinical trial. See Principles of Systemic Therapy (BL-G 5 of 7*).
[q] Pembrolizumab is indicated for the treatment of patients with BCG-unresponsive, high-risk, non-muscle invasive bladder cancer with Tis with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy.
[r] Valrubicin is approved for BCG-refractory carcinoma in situ.

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if Tis or high-grade disease is suspected (eg, planned partial cystectomy, definitive chemoradiotherapy, evaluation of an unexplained positive urine cytology, certain clinical trials), random biopsies rarely yield positive results, especially for low-risk tumors.[12] Therefore, mapping biopsies of normal-appearing urothelium are not necessary for most patients.

Positive urinary cytology may indicate urothelial tumor anywhere in the urinary tract. In the presence of a positive cytology and a normal cystoscopy, the upper tracts and the prostate (prostatic urethra) in men must be evaluated and ureteroscopy may be considered.

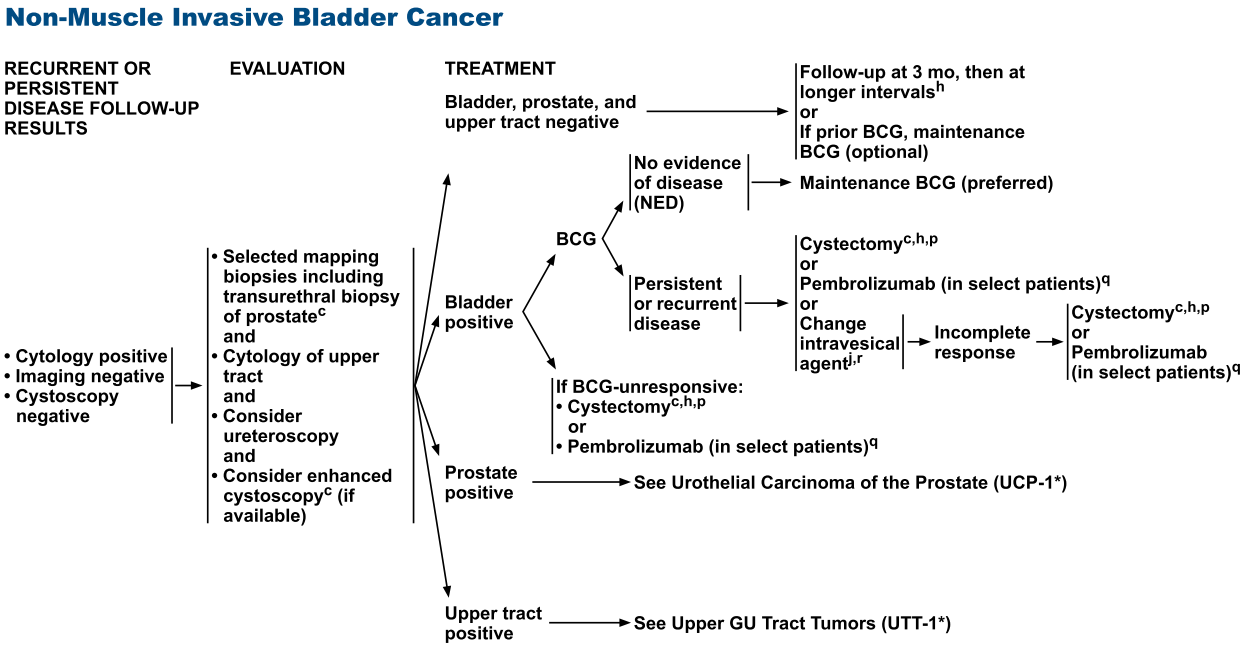
Clinical investigation of the specimen obtained by TURBT or biopsies is an important step in the diagnosis and subsequent management of bladder cancer. The modifier "c" before the stage refers to clinical staging based on bimanual examination under anesthesia, endoscopic surgery (biopsy or TURBT), and imaging studies. A modifier "p" would refer to pathologic staging based on cystectomy and lymph node dissection.

Pathology and Staging

The most commonly used staging system is the tumor, node, metastasis (TNM) staging system by the AJCC[13] (see "Staging" in the complete version of these guidelines, at NCCN.org). The NCCN Guidelines for Bladder Cancer divide treatment recommendations for urothelial carcinoma of the bladder according to non–muscle-invasive disease (Ta, T1, and Tis) and muscle-invasive disease (≥T2 disease). Management of bladder cancer is based on the findings of the biopsy and TURBT specimens, with attention to histology, grade, and depth of invasion. These factors are used to estimate the probability of recurrence and progression to a more advanced stage. Patient bladder function, comorbidities, and life expectancy are also important considerations.

Approximately 75% of newly detected cases are non–muscle-invasive disease—exophytic papillary tumors confined largely to the mucosa (Ta; 70%–75%) or, less often, to the lamina propria (T1; 20%–25%) or flat high-grade lesions (CIS; 5%–10%).[14,15] These tumors tend to be friable and have a high propensity for bleeding. Their natural history is characterized by a tendency to recur in the bladder, and these recurrences can be either at the same stage as the initial tumor or at a more advanced stage.

Papillary tumors confined to the mucosa or submucosa are generally managed endoscopically with



[c] See Principles of Surgical Management (BL-B).
[h] See Follow-Up (BL-E).
[j] See Principles of Intravesical Treatment (BL-F).
[p] If not a cystectomy candidate, and recurrence is cTa or cT1, consider concurrent chemoradiotherapy (category 2B for cTa, category 2A for cT1) or a clinical trial. See Principles of Systemic Therapy (BL-G 5 of 7*).
[q] Pembrolizumab is indicated for the treatment of patients with BCG-unresponsive, high-risk, non-muscle invasive bladder cancer with Tis with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy.
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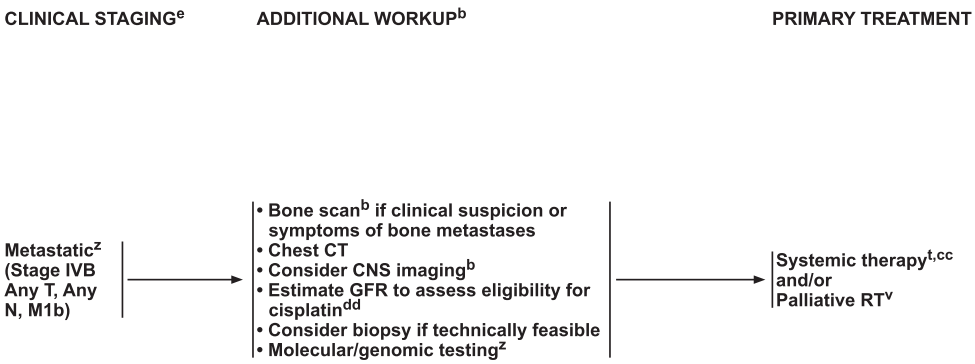
complete resection. Progression to a more advanced stage may result in local symptoms or, less commonly, symptoms related to metastatic disease. An estimated 31%–78% of patients with a tumor confined to the mucosa or submucosa will experience a recurrence or new occurrence of urothelial carcinoma within 5 years.[16] These probabilities of recurrence vary as a function of the initial stage and grade, size, and multiplicity. Refining these estimates for individual patients is an area of active research.

Muscle-invasive disease (T2) is defined by malignant extension into the detrusor muscle, and perivesical tissue involvement defines T3 disease. Extravesical invasion into the surrounding organs (ie, the prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall) delineates T4 disease. The depth of invasion is the most important determinant of prognosis and treatment of localized bladder cancer.

The 8th edition of the AJCC Staging Manual included changes to the staging of urinary bladder carcinoma, including the subdivision of stages III and IV disease (stage III into stage IIIA and stage IIIB; stage IV into stage IVA and stage IVB).[13] Notably, the new staging system groups T1–T4a, N1 within stage IIIA and T1–T4a, N2–3 within stage IIIB; N1–3 was previously grouped within stage IV, regardless of T stage.[13,17] The NCCN Guidelines for Bladder Cancer were updated to reflect appropriate treatment options based on this new staging system (see "Treatment of Stage II and IIIA Tumors," "Treatment of Stage IIIB Tumors," and "Treatment of Stage IVA Tumors" in the complete version of these guidelines, at NCCN.org).

Enhanced Cystoscopy

White light cystoscopy (WLC) is the current standard in the evaluation and staging of bladder cancer. Although WLC has a high sensitivity for detecting papillary lesions, the technique is limited in its ability to discern non-papillary and flat lesions from inflammatory lesions, thus reducing the accuracy of tumor staging. Additionally, small or multifocal lesions are more difficult to detect with WLC. Several techniques proposed to enhance imaging are available and include blue light cystoscopy (BLC) and narrow band imaging (NBI). Both methods report improved staging when used in conjunction with WLC and with expertise; however, data are still limited for both methods and WLC remains the mainstay of bladder cancer staging.



[b] See Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
[e] The modifier "c" refers to clinical staging based on bimanual examination under anesthesia, endoscopic surgery (biopsy or transurethral resection), and imaging studies. The modifier "p" refers to pathologic staging based on cystectomy and lymph node dissection.
[t] See Principles of Systemic Therapy (BL-G 2 of 7).
[v] See Principles of Radiation Management of Invasive Disease (BL-H*).
[z] Molecular/genomic testing in a CLIA-approved laboratory, including FGFR RGQ RT-PCR for *FGFR3* or *FGFR2* genetic alterations. See Discussion.
[cc] See Principles of Systemic Therapy (BL-G 3 of 7 and 4 of 7).
[dd] For patients with borderline GFR, consider timed urine collection which may more accurately determine eligibility for cisplatin.

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Blue Light Cystoscopy

BLC is a technique that identifies malignant cells through the absorption of the photosensitizing drug into the urothelial cytoplasm where it enters heme-biosynthesis metabolism. In normal cells, the photosensitizer is excreted; however, enzymatic abnormalities in malignant cells result in the formation of photoactive porphyrins that remain in the cell and fluorescence with a red emission in the presence of blue light. Earlier studies used the photosensitizer 5-aminolevulinic acid, although more recent studies use the only FDA-approved photosensitizer hexyl-aminolevulinate.

Several prospective clinical studies have evaluated BLC in conjunction with WLC and found higher detection rates of non–muscle-invasive lesions with BLC.[18–23] Particularly CIS, which is often missed by WLC, was detected at a higher rate. A meta-analysis of BLC TURBT in non–muscle-invasive bladder cancer included 12 randomized controlled trials with a total of 2,258 patients.[24] A lower recurrence rate was observed (OR, 0.5; $P<.00001$) with a delayed time to first recurrence by 7.39 weeks ($P<.0001$). Recurrence-free survival was improved at 1 year (hazard ratio [HR], 0.69; $P<.00001$) and at 2 years (HR, 0.65; $P=.0004$). However, no significant reduction in the rate of progression to muscle-invasive bladder cancer was seen (OR, 0.85; $P=.39$).

In a meta-analysis from Burger et al,[25] 1,345 patients with Ta, T1, or CIS disease showed improved detection of bladder tumors and a reduction in recurrence.[25] Compared with WLC, BLC detected more Ta tumors (14.7%; $P<.001$; OR, 4.898; 95% CI, 1.937–12.390) and CIS lesions (40.8%; $P<.001$; OR, 12.372; 95% CI, 6.343–0.924). Importantly, 24.9% of patients had at least one additional Ta/T1 tumor detected ($P<.001$) and improved detection was seen in both primary (20.7%; $P<.001$) and recurrent disease (27.7%; $P<.001$). Another review of the literature included 26 studies with 5-aminolevulinic acid, 15 studies with hexyl-aminolevulinate, and 2 studies that used both methodologies. The results from this review also support greater detection and reduced recurrence but no reduction in disease progression.[26]

Although most studies have not found a significant reduction in disease progression, a recent analysis reported a trend toward a lower rate with the use of BLC compared with WLC (12.2% vs 17.6%, respectively; $P=.085$) with a longer time to progression ($P=.05$).[27] Although BLC has shown improved detection and reduced recurrence, the value of this technique in reducing disease progression remains less established. Therefore,

PRINCIPLES OF IMAGING FOR BLADDER/UROTHELIAL CANCER

No single follow-up plan is appropriate for all patients. Follow-up frequency and duration should be individualized based on patient requirements, and may be extended beyond 5 years after shared decision-making between the patient and physician.

Non-Muscle-Invasive Bladder Cancer (NMIBC)

Chest Imaging

- **Staging:**
  - **Chest imaging may not be necessary in initial staging of noninvasive disease.**
- **Follow-up of NMIBC:**
  - **Routine chest imaging is not recommended.[1]**

Abdominal and Pelvic Imaging

- **Staging:**
  - **CT urography (CTU) (CT of the abdomen and pelvis without and with IV contrast with excretory imaging).**
  - **MR urography (MRU) may be appropriate in patients with poor renal function or iodinated contrast allergy but with GFR >30 and no acute renal failure. May be performed without gadolinium-based contrast utilizing T2 imaging and native image contrast to evaluate upper tracts. Will have decreased sensitivity to plaque-like or non-obstructive lesions and metastasis.**
  - **Renal ultrasound (US) or CT without contrast may be utilized in conjunction with retrograde ureteropyelography in patients who cannot receive either iodinated or gadolinium-based contrast material.**
  - **Consider: In sessile or high-grade tumors, MRI of the pelvis without and with IV contrast for local staging.**
    - **May be performed in addition to CTU.**
    - **Can be performed without contrast if renal function does not allow for contrast administration, as early data suggest T2 and diffusion-weighted images may help with local staging.[2,3]**
- **Follow-up of NMIBC: (See BL-E)**
  - **Upper tract (CTU, MRU, or retrograde ureteropyelography with CT or US) and abdominal/pelvic imaging at baseline. For high-risk patients, UT imaging also should be performed at 12 mo and every 1–2 years thereafter up to 10 years.**

Evaluation for Suspected Bone Metastasis

- **Bone imaging not generally recommended as bone metastasis is unlikely.**

Neurologic/Brain Imaging[4,5]

- **Staging**
  - **Brain MRI not generally recommended.**

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BL-A
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BLC may have the greatest advantage in detecting difficult-to-visualize tumors (eg, CIS tumors) that may be missed by WLC but has more limited applicability in disease monitoring. Other impediments to BLC include the need for appropriate expertise and equipment to use this new technology. High false positives are also attributed to this method and may be increased in patients who have had a recent TURBT or bacillus Calmette-Guérin (BCG) instillation, or who have inflammation.[26] The limitations of BLC require judicious application of this additional diagnostic tool.

Narrow Band Imaging

NBI uses 2 narrow bands of light at 415 nm and 540 nm that are absorbed by hemoglobin. The shorter wavelength provides analysis of the mucosa and the longer wavelength allows for evaluation of the deeper submucosal blood vessels. Studies suggest that there is an increase in bladder tumor detection compared with WLC, although the rate of false-positive results is higher.[28–32]

A systematic review and meta-analysis including 7 prospective studies and 1,040 patients with non–muscle-invasive disease evaluated the accuracy of NBI compared with WLC. In total, 1,476 tumors were detected using biopsy in 611 patients. The additional detection rate for NBI was higher on the patient level (17%; 95% CI, 10%–25%) and tumor level (24%; 95% CI, 17%–31%). In total, 107 patients were further identified as having non–muscle-invasive disease by NBI compared with the 16 patients by WLC. Similarly, 276 additional tumors were reported in 5 studies using NBI versus 13 additional tumors using WLC. Although individual studies showed an increase in the rate of false-positive results, the meta-analysis reported no statistical significance. However, it was acknowledged that data are limited due to the relatively new application of this technique, and interpretation is impeded by the degree of heterogeneity among the studies. Finally, the meta-analysis was unable to determine if there was a long-term advantage with NBI, as measured by a reduction in recurrence or progression.

A randomized prospective trial followed up with patients for 1 year after NBI- or WLC-guided transurethral resection (TUR) to evaluate recurrence. NBI had a reduced 1-year recurrence rate (32.9%; 25 of 76 patients) compared with WLC (32.9% vs 51.4%, respectively; OR, 0.62).[33] However, the small number of patients in this study is limiting. A larger international, multicenter, randomized controlled trial compared 1-year recurrence rates in 965 patients who received either NBI- or WLC-guided TUR for treatment of non–muscle-invasive

PRINCIPLES OF SURGICAL MANAGEMENT

Transurethral Resection of the Bladder Tumor (TURBT) for Staging

- Adequate resection with muscle in specimen
  - Muscle may be omitted in cases of documented low-grade Ta disease
  - In cases of suspected or known carcinoma in situ:
    - ◊ Biopsy adjacent to papillary tumor
    - ◊ Consider prostate urethral biopsy
  - Papillary appearing tumor (likely non-muscle invasive)
    - ◊ Early repeat TURBT (within 6 weeks) if:
      - – Incomplete initial resection
      - – No muscle in original specimen for high-grade disease
      - – Large (≥3 cm) or multi-focal lesions
      - – Any T1 lesion
  - Transurethral resection for sessile or invasive appearing tumor (likely muscle invasive)
    - ◊ Repeat TURBT if:
      - – Prior resection did not include muscle in the setting of high-grade disease
      - – Any T1 lesion
      - – First resection does not allow adequate staging/attribution of risk for treatment selection
      - – Incomplete resection and considering tri-modality bladder preservation therapy
- Enhanced (blue light and narrow-band imaging) cystoscopy may be helpful in identifying lesions not visible using white light cystoscopy.
- Immediate postoperative intravesical chemotherapy within 24 hours is recommended if NMIBC and if no concern for bladder perforation and visibly complete resection.
  - Gemcitabine (preferred) (category 1) and mitomycin (category 1) are the most commonly used options for intravesical chemotherapy.

TURBT/Maximal TURBT for Treatment

- Bladder preservation with maximally complete and safe TURBT and concurrent chemoradiotherapy is most suitable for patients with solitary tumors, negative nodes, no extensive or multifocal carcinoma in situ, no tumor-related hydronephrosis, and good pre-treatment bladder function.
- TURBT alone can be considered for non-cystectomy candidates.
- A visually complete TURBT is associated with improved patient outcomes in non-metastatic settings.

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bladder cancer. This study found that although recurrence rates were similar between the 2 groups in the study population overall, NBI-guided TUR significantly reduced the likelihood of disease recurrence at 1 year in low-risk patients (5.6% for NBI vs 27.3% for WLC; $P=.002$).[34] These results are supported by the systemic reviews and meta-analyses that have also shown reduced recurrence rates after NBI-guided TUR compared with WLC-guided TUR.[35,36]

A benefit of NBI is that it does not require a contrast agent and can therefore be used as part of office cystoscopy. Higher detection rates of flat lesions and a reduction in tumor recurrence have been reported.[34–37]

Non–Muscle-Invasive Urothelial Bladder Cancer

Non–muscle-invasive tumors were previously referred to as "superficial," which is an imprecise term that should be avoided. The NCCN Guidelines for Bladder Cancer generally manage non–muscle-invasive disease with intravesical therapy or, for those at particularly high risk, cystectomy.

Intravesical Therapy

Intravesical therapy is implemented to reduce recurrence or delay progression of bladder cancer to a higher grade or stage.

Immediate Intravesical Therapy Post TURBT

An immediate intravesical instillation of chemotherapy may be given within 24 hours of TURBT to prevent tumor cell implantation and early recurrence. Immediate intravesical chemotherapy has been shown to decrease recurrence in select subgroups of patients. A systematic review and meta-analysis of 13 randomized trials demonstrated a decreased risk of recurrence by 35% (HR, 0.65; 95% CI, 0.58–0.74; $P<.001$) and a decreased 5-year recurrence rate from 58.8% to 44.8% when comparing immediate intravesical chemotherapy after TURBT to TURBT alone, although the instillation did not prolong the time to progression or time to death from bladder cancer.[11] This study also found that the instillation did not reduce recurrences in patients who had a prior recurrence rate of >1 recurrence per year or with an EORTC recurrence score ≥5.

Phase III trials have reported a reduced risk of recurrence for patients with suspected non–muscle-invasive disease who are treated with immediate postoperative gemcitabine or mitomycin. A randomized, double-blind, phase III trial of 406 patients with suspected low-grade non–muscle-invasive bladder cancer based on cystoscopic appearance showed that immediate post-TURBT instillation of gemcitabine reduced the rate of recurrence compared with saline instillation

FOLLOW-UP

No single follow-up plan is appropriate for all patients. The follow-up tables are to provide guidance, and should be modified for the individual patient based on sites of disease, biology of disease, and length of time on treatment. Reassessment of disease activity should be performed in patients with new or worsening signs or symptoms of disease, regardless of the time interval from previous studies. Further study is required to define optimal follow-up duration.

Table 1: AUA Risk Stratification for Non-Muscle Invasive Bladder Cancer*

Low Risk	Intermediate Risk	High Risk
• Low grade (LG) solitary Ta ≤3 cm • Papillary urothelial neoplasm of low malignant potential	• Recurrence within 1 year, LG Ta • Solitary LG Ta >3 cm • LG Ta, multifocal • High grade (HG) Ta, ≤3 cm • LG T1	• HG T1 • Any recurrent, HG Ta • HG Ta, >3 cm (or multifocal) • Any carcinoma in situ (CIS) • Any BCG failure in HG patient • Any variant histology • Any lymphovascular invasion • Any HG prostatic urethral involvement

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Table 2: Low-Risk,[1] Non-Muscle-Invasive Bladder Cancer

Test	Year						
	1	2	3	4	5	5–10	>10
Cystoscopy	3, 12	Annually				As clinically indicated	
Upper tract[2] and abdominal/ pelvic[3] imaging[4]	Baseline imaging	As clinically indicated					
Blood tests	N/A						
Urine tests	N/A						

[1] See Table 1: AUA Risk Stratification for Non-Muscle Invasive Bladder Cancer definitions on BL-E (1 of 5) above.
[2] Upper tract imaging includes CTU, MRU, intravenous pyelogram (IVP), retrograde pyelography, or ureteroscopy.
[3] Abdominal/pelvic imaging includes CT or MRI.
[4] See Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
[5] Urine cytology should be done at time of cystoscopy if bladder in situ.

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(placebo).[9] In the intention to treat analysis, 35% of patients treated with gemcitabine and 47% of those who received placebo had disease recurrence within 4 years (HR, 0.66; 95% CI, 0.48–0.90; $P<.001$).[9] Intravesical therapy for a previous non–muscle-invasive bladder cancer was allowed in the study if received at least 6 months before enrollment. Another phase III, prospective, multicenter, randomized study of 2,844 patients with non–muscle-invasive bladder cancer showed that an immediate instillation of mitomycin C after TURBT reduces recurrence regardless of the number of adjuvant instillations. Recurrence risk was 27% for immediate instillation versus 36% for delayed instillation ($P<.001$) for all patients in the study, with the benefit of immediate instillation present across risk groups.[10] Previous intravesical chemotherapy was permitted in study participants as long as it was received at least 3 years before participation.

For both studies, the rate of adverse events (AEs) did not significantly differ between the treatment and control groups, indicating that immediate intravesical instillation of gemcitabine or mitomycin was well tolerated.[9,10] Gemcitabine is preferred over mitomycin based on toxicity profiles and lower cost.[38] For tumors with an intermediate or high risk of progression, subsequent treatment with intravesical induction (adjuvant) therapy may be given. Perioperative intravesical treatment should not be given if there is extensive TURBT or suspected bladder perforation.

Induction (Adjuvant) Intravesical Chemotherapy or BCG

Although only intravesical chemotherapy is recommended in the immediate postoperative setting, both intravesical chemotherapy and BCG have been given as induction therapy in patients with non–muscle-invasive bladder cancer.[39] The most commonly used chemotherapy agents are mitomycin C and gemcitabine, although gemcitabine is preferred over mitomycin due to better tolerability and cost.

Induction BCG has been shown to decrease the risk of bladder cancer recurrences after TURBT. BCG therapy is commonly given once a week for 6 weeks, followed by a rest period of 4 to 6 weeks, with a full re-evaluation at week 12 (ie, 3 months) after the start of therapy.[40] Four meta-analyses demonstrated that BCG after TURBT is superior to TURBT alone or TURBT and chemotherapy in preventing recurrences of high-grade Ta and T1 tumors.[41–44] A meta-analysis including 9 trials of 2,820 patients with non–muscle-invasive bladder cancer reported that mitomycin C was superior to BCG without maintenance in preventing recurrence but inferior to

FOLLOW-UP

No single follow-up plan is appropriate for all patients. The follow-up tables are to provide guidance, and should be modified for the individual patient based on sites of disease, biology of disease, and length of time on treatment. Reassessment of disease activity should be performed in patients with new or worsening signs or symptoms of disease, regardless of the time interval from previous studies. Further study is required to define optimal follow-up duration.

Table 3: Intermediate Risk,[1] Non-Muscle-Invasive Bladder Cancer

Test	Year						
	1	2	3	4	5	5–10	>10
Cystoscopy	3, 6, 12	Every 6 mo	Annually			As clinically indicated	
Upper tract[2] and abdominal/ pelvic[3] imaging[4]	Baseline imaging	As clinically indicated					
Blood tests	N/A						
Urine tests	Urine cytology[5] 3, 6, 12	Urine cytology every 6 mo	Annually			As clinically indicated	

Table 4: High-Risk,[1] Non-Muscle-Invasive Bladder Cancer

Test	Year						
	1	2	3	4	5	5–10	>10
Cystoscopy	Every 3 mo		Every 6 mo			Annually	As clinically indicated
Upper tract[2] imaging[4]	Baseline imaging, and at 12 mo	Every 1–2 y					As clinically indicated
Abdominal/ pelvic[3] imaging[4]	Baseline imaging	As clinically indicated					
Blood tests	N/A						
Urine tests	• Urine cytology[5] every 3 mo • Consider urinary urothelial tumor markers (category 2B)		Urine cytology every 6 mo			Annually	As clinically indicated

[1] See Table 1: AUA Risk Stratification for Non-Muscle Invasive Bladder Cancer definitions on BL-E (1 of 5).
[2] Upper tract imaging includes CTU, MRU, intravenous pyelogram (IVP), retrograde pyelography, or ureteroscopy.
[3] Abdominal/pelvic imaging includes CT, MRI, or FDG PET/CT (category 2B) (PET/CT not recommended for NMIBC).
[4] See Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
[5] Urine cytology should be done at time of cystoscopy if bladder in situ.

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BCG in trials using BCG maintenance.[45] Using the SEER database, a reduction in mortality of 23% was reported in patients receiving BCG therapy.[46] Another study reported long-term data that BCG was better at reducing recurrence in intermediate- and high-risk non–muscle-invasive bladder cancer when compared with mitomycin C.[47]

BCG has also been compared with gemcitabine and epirubicin. A prospective, randomized phase II trial compared the quality of life in patients receiving either BCG (n=59) or intravesical gemcitabine (n=61) and found no significant difference.[48] More frequent local and systemic side effects occurred in the BCG arm; however, they were mild to moderate and the treatment was well-tolerated in both groups. The benefit of BCG with or without isoniazid compared with epirubicin alone in a long-term study of 957 patients with intermediate- or high-risk Ta or T1 disease was measured by a reduced recurrence, greater time to distant metastases, and greater overall survival (OS) and disease-specific survival (DSS); progression was similar.[49] Long-term data comparing BCG to epirubicin in combination with interferon[49,50] in patients with T1 disease showed a better reduction in recurrence with BCG; however, no differences in progression or AEs were seen.[50] Patients in both studies received 2 to 3 years of maintenance therapy.

Maintenance Therapy

Maintenance intravesical therapy may be considered after induction with chemotherapy or BCG. The role of maintenance chemotherapy is controversial. When given, maintenance chemotherapy is generally monthly. The role of maintenance BCG in those patients with intermediate to high-risk non–muscle-invasive bladder cancer is more established, although the exact regimens have varied across studies. Some of the previous controversy over the effectiveness of BCG maintenance reflects the wide array of schedules and conflicting reports of efficacy. Quarterly and monthly installations and 3-week and 6-week schedules have been evaluated. To date, the strongest data support the 3-week BCG regimen used in the SWOG trial that demonstrated reduced disease progression and metastasis.[51] The 3-week timing of BCG has shown improved outcomes compared with epirubicin[50] or isoniazid.[49] Most patients receive maintenance BCG for 1 to 3 years. In an evaluation of randomized controlled trials and meta-analyses, limited evidence was found for 1 year of BCG maintenance.[52] A study of 1,355 patients with a median follow-up of 7.1 years found no benefit in 3 years of maintenance BCG compared with 1 year for intermediate-risk patients.[53] Conversely, 3-year maintenance BCG reduced recurrence

PRINCIPLES OF INTRAVESICAL TREATMENT

Indications: Based on probability of recurrence and progression to muscle-invasive disease, such as size, number, and grade.

Intravesical Therapy for Bladder Cancer

Immediate Postoperative Intravesical Chemotherapy
- **See Clinical Presentation and Initial Evaluation (BL-1)**
- **A single instillation of chemotherapy is administered within 24 hours of surgery (ideally within 6 hours).**
- **Gemcitabine (preferred) (category 1)[1] and mitomycin (category 1)[2] are the most commonly used agents in the United States for intravesical chemotherapy. Thiotepa does not appear to be effective.[3]**
- **Immediate postoperative intravesical chemotherapy reduces the 5-year recurrence rate by approximately 35% and has a number needed to treat to prevent a recurrence of 7. However, it does not reduce the risk of progression or the risk of cancer mortality.[3]**
- **It is not effective in patients with an elevated EORTC recurrence risk score (≥5). This includes patients with ≥8 tumors and those with ≥1 recurrence per year.**
- **Contraindications include: bladder perforation, known drug allergy**

Induction (Adjuvant) Intravesical Chemotherapy or BCG
- **Treatment option for NMIBC (See BL-2, BL-3, and BL-10).**
- **The most commonly used agents are BCG, mitomycin, and gemcitabine.**
- **In the event of a BCG shortage, BCG should be prioritized for induction of high-risk patients (eg, high-grade T1 and CIS). Preferable alternatives to BCG include mitomycin or gemcitabine.**
  - **Other options include: epirubicin, valrubicin, docetaxel, or sequential gemcitabine/docetaxel or gemcitabine/mitomycin.**
  - **If feasible, the dose of BCG may be split (1/3 or 1/2 dose) so that multiple patients may be treated with a single vial in the event of a shortage.**
- **Initiated 3–4 weeks after TURBT with or without maintenance.**
- **Weekly instillations during induction are given for approximately 6 weeks.**
- **Maximum of 2 consecutive cycle inductions without complete response.**
- **Withhold if traumatic catheterization, bacteriuria, persistent gross hematuria, persistent severe local symptoms, or systemic symptoms.**

Maintenance Intravesical BCG
- **Although there is no standard regimen for maintenance BCG, many NCCN Member Institutions follow the SWOG regimen consisting of a 6-week induction course of BCG followed by maintenance with 3 weekly instillations at months 3, 6, 12, 18, 24, 30, and 36.[4]**
- **In the event of a BCG shortage, BCG should be prioritized for high-risk patients (eg, high-grade T1 and CIS), especially in the early maintenance period (ie, 3 and 6 months post-induction).**
  - **If feasible, the dose of BCG may be split (1/3 or 1/2 dose) so that multiple patients may be treated with a single vial in the event of a shortage.**
- **Ideally maintenance should be given for 1 year for intermediate-risk and 3 years for high-risk NMIBC.**
- **BCG would be withheld if traumatic catheterization, bacteriuria, persistent gross hematuria, persistent severe local symptoms, or systemic symptoms.**
- **Dose reduction is encouraged if there are substantial local symptoms during maintenance therapy.**
- **Data suggest the benefit of maintenance BCG therapy through a decreased rate of recurrence for NMIBC.[4]**

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compared with 1-year maintenance but did not impact progression or survival in high-risk patients. These data suggest that 1 year may be suitable for patients at intermediate risk whereas 3 years of maintenance is preferred for high-risk disease. It should also be noted that duration of treatment may be limited by toxicity and patient refusal to continue.

For patients showing no residual disease at follow-up cystoscopy, whether 1 or 2 courses of induction therapy were administered, maintenance therapy with BCG is preferred. This recommendation is based on findings that an induction course of intravesical therapy followed by a maintenance regimen produced better outcomes than intravesical chemotherapy.[39,41,42,51,54,55]

BCG Toxicity

There are concerns regarding potentially severe local and systemic side effects and the inconsistent availability of BCG. BCG induces a systemic nonspecific immunostimulatory response leading to secretion of proinflammatory cytokines. This causes patients to experience flu-like symptoms that may last 48 to 72 hours.[56] Installation of BCG into the bladder also mimics a urinary tract infection and may produce intense local discomfort. The side effects of treatment have translated to patient refusal of BCG therapy. Dysuria has been reported in 60% of patients in clinical trials.[56] However, the side effects are treatable in almost all cases,[57] and no increase in toxicity has been reported with cumulative doses. Symptom management with single-dose, short-term quinolones and/or anticholinergics have been reported to reduce AEs.[58,59]

A reduced (one-third) dose of BCG was evaluated for the possible reduction of side effects. In a phase III study, 1,316 patients with intermediate- or high-risk Ta, T1 papillary carcinoma of the bladder were randomized to receive reduced- or full-dose BCG with either 1 or 3 years of maintenance.[60] Among all 4 groups, the percentage of patients with ≥1 side effect was similar (P=.41). Although the one-third dose of BCG was effective, side effects were not reduced. Conversely, other publications suggest that the one-third dose may reduce side effects.[61–63] Full-dose BCG is recommended by the panel until more data are available to evaluate the low-dose BCG regimen. However, dose reduction may be used if there are substantial local symptoms during maintenance.

BCG Shortage

An ongoing shortage of BCG has existed in the United States, necessitating development of strategies to prioritize use of intravesical BCG and identify alternative treatment

PRINCIPLES OF SYSTEMIC THERAPY

First-line systemic therapy for locally advanced or metastatic disease (Stage IV)	
Cisplatin eligible	**Preferred regimens** • Gemcitabine and cisplatin[4] (category 1) • DDMVAC with growth factor support (category 1)[2,8]
Cisplatin ineligible	**Preferred regimens** • Gemcitabine and carboplatin[11] • Atezolizumab[12] (only for patients whose tumors express PD-L1[a] or who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression) • Pembrolizumab[13] (only for patients whose tumors express PD-L1[b] or who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression) **Other recommended regimens** • Gemcitabine[14] • Gemcitabine and paclitaxel[15] **Useful under certain circumstances** • Ifosfamide, doxorubicin, and gemcitabine[16] (for patients with good kidney function and good PS)

- The presence of both non-nodal metastases and ECOG performance score ≥2 strongly predict poor outcome with chemotherapy. Patients without these adverse prognostic factors have the greatest benefit from chemotherapy. The impact of these factors in relation to immune checkpoint inhibition is not fully defined, but they remain poor prognostic indicators in general.
- For most patients, the risks of adding paclitaxel to gemcitabine and cisplatin outweigh the limited benefit seen in the randomized trial.[17]
- A substantial proportion of patients cannot receive cisplatin-based chemotherapy due to renal impairment or other comorbidities.
  - Participation in clinical trials of new or more tolerable therapy is recommended.

[a] Atezolizumab: SP142 assay, PD-L1–stained tumor-infiltrating immune cells covering ≥5% of the tumor area.
[b] Pembrolizumab: 22C3 antibody assay, Combined Positive Score (CPS) ≥10.

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approaches for some patients with non–muscle-invasive bladder cancer.[64] Several organizations, including the American Urological Association (AUA), American Association of Clinical Urologists (AACU), Bladder Cancer Advocacy Network (BCAN), Society of Urologic Oncology (SUO), the Large Urology Group Practice Association (LUGPA), and the Urology Care Foundation (UCF), issued a notice outlining strategies to maximize care for patients with non–muscle-invasive bladder cancer in the context of this shortage.[65] NCCN Bladder Cancer Panel Members recommend several strategies to help alleviate problems associated with this shortage.

In the event of a BCG shortage, priority for treatment should be to provide patients with high-risk non–muscle-invasive bladder cancer (cT1 high grade or CIS) with induction BCG. For patients who do not receive BCG, intravesical chemotherapy may be used as an alternative. The intravesical chemotherapies most commonly used for this purpose are gemcitabine[38,66] and mitomycin.[67] Two separate meta-analyses of randomized trials reported that there were no differences in risk of recurrence between BCG and mitomycin,[39,68] although BCG may show more favorable outcomes from maintenance regimens.[39] Other options include epirubicin,[49,69] valrubicin,[70] docetaxel,[71] sequential gemcitabine/docetaxel,[72] or gemcitabine/mitomycin.[73] Another alternative to intravesical BCG for patients with non–muscle-invasive bladder cancer at high risk of recurrence and, particularly, at high risk of progression, is initial radical cystectomy.[74]

Another option during a shortage is splitting the dose of BCG so that multiple patients may be treated using a single vial. Although several randomized trials have reported that one-third dose BCG showed similar outcomes when compared with full-dose BCG,[62,75,76] a phase 3 trial of 1,355 patients with intermediate- or high-risk non–muscle-invasive bladder cancer reported that patients receiving the full dose of BCG show a longer disease-free interval, compared with those receiving the one-third dose.[53] In this study, the 5-year disease-free rate was 58.5% for the one-third dose compared with 61.7% for the full dose; therefore, the null hypothesis of inferiority for duration of the disease-free interval of one-third dose BCG could not be rejected (HR, 1.15; 95% CI, 0.98–1.35; P=.045), although no differences in progression or survival rates were seen.[53] Based on these data, the panel recommends that one-half or one-third dose may be considered for BCG induction during times of shortage and should be used for BCG maintenance, if supply allows. Maintenance BCG should be prioritized for patients with high-risk non–muscle-invasive bladder

PRINCIPLES OF SYSTEMIC THERAPY

Second-line systemic therapy for locally advanced or metastatic disease (Stage IV) (post-platinum)[c] Participation in clinical trials of new agents is recommended.	
Preferred regimen • Pembrolizumab (category 1)[18]	**Other recommended regimens** • Paclitaxel[26] or docetaxel[27] • Gemcitabine[14]
Alternative preferred regimens • Immune checkpoint inhibitor ▸ Atezolizumab[19,20] ▸ Nivolumab[21] ▸ Durvalumab[22] ▸ Avelumab[23,24] • Erdafitinib[d,25]	**Useful in certain circumstances based on prior medical therapy** • Ifosfamide, doxorubicin, and gemcitabine[16] • Gemcitabine and paclitaxel[15] • Gemcitabine and cisplatin[4] • DDMVAC with growth factor support[2]

Second-line systemic therapy for locally advanced or metastatic disease (Stage IV) (post-checkpoint inhibitor) Participation in clinical trials of new agents is recommended.	
Preferred regimen for cisplatin ineligible, chemotherapy naïve • Gemcitabine/carboplatin	**Other recommended regimens** • Erdafitinib[d,25] • Paclitaxel or docetaxel[27] • Gemcitabine[14]
Preferred regimens for cisplatin eligible, chemotherapy naïve • Gemcitabine and cisplatin[4] • DDMVAC with growth factor support[2]	**Useful in certain circumstances based on prior medical therapy** • Ifosfamide, doxorubicin, and gemcitabine[16] • Gemcitabine and paclitaxel[15]

[c] If PFS >12 months after platinum (eg, cisplatin or carboplatin), consider re-treatment with platinum if the patient is still platinum eligible.
[d] Only for patients with susceptible *FGFR3* or *FGFR2* genetic alterations.

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cancer (cT1 high grade or CIS) in the early maintenance period (eg, 3- and 6-months postinduction), although in cases of shortage, BCG induction therapy should be prioritized over maintenance BCG.

Pembrolizumab for Non–Muscle-Invasive Bladder Cancer

Pembrolizumab is a PD-1 inhibitor that has been evaluated as treatment of BCG-unresponsive, non–muscle-invasive bladder cancer with CIS in the single-arm, phase II KEYNOTE-057 study, reported to date in abstract form (pembrolizumab is also indicated for treatment of metastatic urothelial carcinoma, for the metastatic setting see "Targeted Therapies," page 346). In the KEYNOTE-057 study, 103 patients with high-risk CIS, with or without papillary tumor, who received previous BCG therapy and were either unable or unwilling to undergo cystectomy were treated with pembrolizumab. The 3-month complete response rate was 38.8% (95% CI, 29.4%–48.9%), with 72.5% of complete responses maintained at last follow-up (median 14.0 months). Therefore, of the total study population, 28% had a complete response at the time of last follow-up. The median duration of complete response had not yet been reached at the time of analysis. Grade ≥3 treatment-related AEs were reported in 12.6% of patients, and immune-mediated AEs in 18.4%. One patient died as a result of treatment-related colitis.[77] Clinical data included in the package insert for 96 patients on this trial report a complete response rate of 41% (95% CI, 31%–51%) and a median duration of response (DOR) of 16.2 months with 46% of complete responses maintained for at least a year.[78]

Treatment of cTa, Low-Grade Tumors

TURBT is the standard treatment of cTa, low-grade tumors. Although a complete TURBT alone can eradicate these tumors, there is a relatively high risk for recurrence. Therefore, after TURBT, the panel recommends administering a single dose of immediate intravesical chemotherapy (gemcitabine or mitomycin; both are category 1, although gemcitabine is preferred due to better tolerability and cost) within 24 hours of resection. The immediate intravesical chemotherapy may be followed by observation or a 6-week induction course of intravesical therapy. Although intravesical chemotherapy is preferred in these patients due to the low risk of disease progression, BCG may be considered when not in a shortage.

The need for adjuvant therapy depends on patient prognosis. If the patient has a low risk for recurrence, a single immediate intravesical treatment may be sufficient.

PRINCIPLES OF SYSTEMIC THERAPY

Subsequent-line systemic therapy for locally advanced or metastatic disease (Stage IV)[e] Participation in clinical trials of new agents is recommended.	
Preferred regimen • Enfortumab vedotin[28] • Erdafitinib[d]	Other recommended regimens • Gemcitabine[14] • Paclitaxel[26] or docetaxel[27] • Ifosfamide, doxorubicin, and gemcitabine[16] • Gemcitabine and paclitaxel[15] • Gemcitabine and cisplatin[4] • DDMVAC with growth factor support[2]

[d] Only for patients with susceptible *FGFR3* or *FGFR2* genetic alterations.
[e] Patient should have already received platinum and a checkpoint inhibitor, if eligible.

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Factors to consider include the size, number, T category, and grade of the tumor(s), as well as concomitant CIS and prior recurrence.[16] Meta-analyses have confirmed the efficacy of adjuvant intravesical chemotherapy in reducing the risk of recurrence.[79,80] Close follow-up of all patients is needed, although the risk for progression to a more advanced stage is low (see "Surveillance," page 343).

Treatment of cTa, High-Grade Tumors

Tumors staged as cTa, high-grade lesions are papillary tumors with a relatively high risk for recurrence and progression toward more invasiveness. Restaging TURBT detected residual disease in 27% of Ta patients when muscle was present in the original TURBT.[81] In the absence of muscularis propria in the initial TURBT specimen, 49% of patients with non–muscle-invasive disease will be understaged versus 14% if muscle is present.[82] Repeat resection is recommended if there is incomplete resection, or should be strongly considered if there is no muscle in the specimen. Repeat resection may also be considered for high-risk (large or multifocal) lesions, as recommended in the AUA/SUO Guideline.[14]

After TURBT, patients with cTa, high-grade tumors may be treated with intravesical BCG (preferred), intravesical chemotherapy, or observation. In the literature, 4 meta-analyses confirmed that BCG after TURBT is superior to TURBT alone or TURBT and chemotherapy in preventing recurrences of high-grade Ta and T1 tumors.[41–44] The NCCN Bladder Cancer Panel Members recommend BCG as the preferred option over intravesical chemotherapy for adjuvant treatment of high-grade lesions, followed by maintenance therapy according to risk and availability of intravesical agents.

Treatment of cT1 Tumors

Based on the histologic differentiation, most cT1 lesions are high grade and considered to be potentially dangerous, with a higher risk for recurrence and progression. These tumors may occur as solitary lesions or as multifocal tumors with or without an associated Tis component.

These tumors are treated with a complete endoscopic resection, and repeat TURBT is strongly advised.[83] This is supported by a trial that prospectively randomized 142 patients with pT1 tumors to a second TURBT within 2 to 6 weeks of the initial TURBT or no repeat TURBT.[84] All patients received adjuvant intravesical therapy. Although OS was similar, the 3-year recurrence-free survival was significantly higher in the repeat TURBT arm versus the control arm (69% vs 37%, respectively), especially among patients with high-grade tumors.

If residual cT1 disease is found at repeat TURBT, treatment should consist of BCG (category 1) or cystectomy. Within T1 disease, a particularly high-risk stratum can be identified: multifocal lesions, tumors associated with CIS or lymphovascular invasion, variant histology (eg, micropapillary, plasmacytoid, nested variants), or lesions that recur after BCG treatment. Some data suggest that early cystectomy may be preferred in these patients because of the high risk for progression to a more advanced stage.[85,86]

If no residual disease is found after the second resection, intravesical therapy with BCG (preferred; category 1) or intravesical chemotherapy is recommended. Observation may be reasonable in highly select cases where low-grade, small-volume tumors had limited lamina propria invasion and no CIS.[87,88]

Treatment of Tis

Primary Tis is a high-grade lesion of the urothelium. Standard therapy for this lesion is resection followed by intravesical therapy with BCG. BCG is preferred over intravesical chemotherapy based on a meta-analysis of randomized trials showing that patients with CIS treated with BCG had higher complete response rates (68.1% vs 51.5%) and a longer DOR compared with intravesical chemotherapy.[39] If the patient is unable to tolerate BCG, intravesical chemotherapy may be considered, but data supporting this approach are limited.

Surveillance

For cTa high grade, cT1, and Tis, follow-up is recommended with a urinary cytology and cystoscopy at 3- to 6-month intervals for the first 2 years, and at longer intervals as appropriate thereafter. Imaging of the upper tract should be considered every 1 to 2 years for high-risk tumors (see "Follow-up," pages 337 [BL-E 1 of 5] and 338 [BL-E 2 of 5]). Urine molecular tests for urothelial tumor markers are now available.[89] Many of these tests have a better sensitivity for detecting bladder cancer than urinary cytology, but specificity is lower. Considering this, evaluation of urinary urothelial tumor markers may be considered during surveillance of high-risk non–muscle-invasive bladder cancer. However, it remains unclear whether these tests offer additional information that is useful for detection and management of non–muscle-invasive bladder tumors. Therefore, the panel considers this to be a category 2B recommendation.

For patients with low-risk non–muscle-invasive bladder cancer, if the initial follow-up surveillance cystoscopy is negative within 4 months of TURBT, the next cystoscopy is recommended 6 to 9 months later and then yearly for up to 5 years. Follow-up cystoscopy after 5 years should only be performed based on clinical indication. Beyond baseline imaging, upper tract imaging is not indicated without symptoms for patients with low-risk non–muscle-invasive bladder cancer.

Posttreatment of Recurrent or Persistent Disease

Treatment of Patients With Positive Cystoscopy

Patients under observation after initial TURBT who show a documented recurrence using positive cystoscopy should undergo another TURBT and then adjuvant intravesical therapy or cystectomy based on the stage and grade of the recurrent lesion. Patients should be followed up as indicated based on the risk of their disease (see "Follow-up," pages 337 [BL-E 1 of 5] and 338 [BL-E 2 of 5]).

Recurrence After Intravesical Treatment

In a phase II multicenter study of non–muscle-invasive bladder cancer that recurred after 2 courses of BCG, intravesical gemcitabine demonstrated activity that was relegated to high-risk non–muscle-invasive bladder cancer.[90] In the 47 patients with evaluable response, 47% had disease-free survival at 3 months. The 1-year relapse-free survival (RFS) was 28% with all cases except for 2 attributed to the high-risk group. The 2-year RFS was 21%. Intravesical gemcitabine had some activity in the high-risk group and may be an option if a candidate is not eligible for a cystectomy; however, the study results indicate that cystectomy is preferred when possible. Similarly, for patients with recurrence of high-grade cT1 disease after TURBT and induction BCG, cystectomy is the recommended option with the best data for cure,[91] although pembrolizumab may be appropriate for patients with BCG-unresponsive, high-risk, non–muscle-invasive bladder cancer with CIS, with or without papillary tumors, who are ineligible for or have elected not to undergo cystectomy (see "Pembrolizumab for Non–Muscle-Invasive Bladder Cancer," page 341). The data are currently not mature enough to determine if pembrolizumab can be considered curative in this setting.

After the initial intravesical treatment and 12-week evaluation, patients with persistent cTa, cT1, or Tis disease tumors can be given a second induction course of induction therapy (see: Recurrent or Persistent Disease," page 332 [BL-3]). No more than 2 consecutive induction courses should be given. If a second course is given, TURBT is performed to determine the presence of residual disease at the second 12-week follow-up. If no residual disease is found, maintenance BCG is recommended for patients who received prior BCG.

If residual disease is seen after TURBT, patients with persistent cT1 tumors are recommended to proceed to cystectomy. Nonsurgical candidates can consider concurrent chemoradiation, change of the intravesical agent, or a clinical trial. Patients with persistent Tis or cTa disease after TURBT may be treated with a different intravesical agent, cystectomy, or pembrolizumab if Tis is present and the patient is not a candidate for cystectomy.

Concurrent chemoradiotherapy can be considered for noncystectomy candidates with persistent Ta or Tis disease after TURBT, although it is a category 2B recommendation for this setting. Valrubicin is approved for CIS that is refractory to BCG, although panelists disagree on its value.[70] For patients with disease that does not respond or shows an incomplete response to treatment, subsequent management is cystectomy. Recurrences that are found to be muscle-invasive or metastatic disease should be treated as described in the appropriate section below.

Treatment of Patients With Positive Cytology

In patients without a documented recurrence but with positive cytology and negative cystoscopy and imaging, selected mapping biopsies, including TUR of the prostate, are indicated. In addition, the upper tract must be evaluated and ureteroscopy may be considered for detecting tumors of the upper tract. If available, enhanced cystoscopy should be considered (see "Enhanced Cystoscopy," page 333).

If the selected mapping biopsy of the bladder is positive (eg, Tis), then the recommendation is to administer intravesical BCG followed by maintenance BCG (preferred) if a complete response is seen. For tumors that are unresponsive to BCG, the subsequent management options include cystectomy, changing the intravesical agent, or participation in a clinical trial. Pembrolizumab is also an option for patients with BCG-unresponsive, high-risk, non–muscle-invasive bladder cancer with Tis, with or without papillary tumors, who are ineligible for or have elected not to undergo cystectomy (see "Pembrolizumab for Non–Muscle-Invasive Bladder Cancer," page 341). Further investigation and validation of results are warranted for establishing the efficacy of alternative agents in second-line treatments.

If transurethral biopsy of the prostate is positive, treatment of the prostate should be initiated as described subsequently (see "Urothelial Carcinomas of the Prostate" in the complete version of these guidelines, at NCCN.org). If upper tract urothelial carcinoma is identified, then the described treatment should be followed (see "Upper Tract Urothelial Carcinoma (UTUC)" in the complete version of these guidelines, at NCCN.org).

If the transurethral biopsies of the bladder, prostate, and upper tract are negative, follow-up at 3 months and then at longer intervals is recommended. If prior BCG was given, maintenance therapy with BCG should be considered.

Metastatic (Stage IVB) Urothelial Bladder Cancer

Approximately 5% of patients have metastatic disease at the time of diagnosis.[2] Additionally, about half of all patients relapse after cystectomy depending on the pathologic stage of the tumor and nodal status. Local recurrences account for about 10%–30% of relapses, whereas distant metastases are more common.

Evaluation of Metastatic Disease

If metastasis is suspected, additional workup to evaluate the extent of the disease is necessary. This includes a chest CT and a bone scan if enzyme levels are abnormal or the patient shows signs or symptoms of skeletal involvement. Central nervous system imaging should be considered. An estimated glomerular filtration rate (GFR) should be obtained to assess patient eligibility for cisplatin. For patients with borderline GFR results, a timed or measured urine collection may be considered to more accurately determine cisplatin eligibility.[92] If the evidence of spread is limited to nodes and biopsy is technically feasible, nodal biopsy should be considered and patients should be managed as previously outlined for positive nodal disease (stage IIIA, stage IIIB, or stage IVA). Molecular testing should also be performed for patients with metastatic disease (see "Molecular/Genomic Testing," page 345).

Patients who present with disseminated metastatic disease are generally treated with systemic therapy. Metastasectomy and/or palliative radiotherapy of metastases may also be useful for select patients.

Metastasectomy for Oligometastatic Disease

Highly select patients with oligometastatic disease who are without evidence of rapid progression may benefit from metastasectomy after response to systemic therapy. While there are limited prospective data supporting the role of metastasectomy for treatment of urothelial bladder cancer, several retrospective studies have demonstrated that metastasectomy can be a valid treatment option for certain patients with metastatic bladder cancer, particularly those with favorable response to systemic therapy, solitary metastatic lesions, and lung or lymph node sites of disease.

A phase II trial of 11 patients with bladder primary urothelial carcinoma metastatic to the retroperitoneal lymph nodes who underwent complete bilateral retroperitoneal lymph node dissection reported 4-year DSS and RFS rates of 36% and 27%. Patients with viable tumor in no more than 2 lymph nodes and/or excellent response to presurgical systemic chemotherapy showed the best survival rates, indicating that a low burden of disease or good response to presurgical chemotherapy may be important in achieving benefit from metastastectomy.[93] Another phase II trial of 70 patients who underwent complete surgical resection of bladder cancer metastases investigated survival, performance status, and quality of life after surgery. This study reported no survival advantage from surgery, although the quality of

life and performance status were improved for symptomatic patients.[94]

Beyond these prospective data, several retrospective studies have shown a survival advantage after metastasectomy.[95–98] A retrospective series of 55 patients with bladder primary urothelial carcinoma metastatic to the pelvic or retroperitoneal lymph nodes, who underwent postchemotherapy lymph node dissection, reported 5-year DSS and RFS rates of 40% and 39%. The best outcomes were associated with radiologic nodal complete response to preoperative chemotherapy and pN0 versus pN+, but similar for cN1-3 versus cM1.[99] A systematic review and meta-analysis of available studies, including a total of 412 patients with metastatic urothelial carcinoma, reported an improved OS for patients who underwent metastasectomy compared with nonsurgical treatment of metastatic lesions. Five-year survival in these studies ranged from 28% to 72%.[100] Another population-based analysis of 497 patients aged ≥65 years who had at least one metastasectomy for treatment of urothelial carcinoma found that with careful patient selection, metastasectomy is safe and can be associated with long-term survival in this patient population.[101]

Due to the limited evidence supporting metastasectomy for bladder cancer, and the often extensive and difficult nature of the surgery, it is important to carefully select appropriate patients for metastasectomy, including consideration of patient performance status, comorbidities, and overall clinical picture.

Molecular/Genomic Testing

The panel recommends that molecular/genomic testing be performed for stages IVA and IVB bladder cancer and may be considered for stage IIIB. This testing should be performed only in laboratories that are certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA-88) as qualified to perform highly complex molecular pathology testing.[102] The NCCN Bladder Cancer Panel recommends that molecular/genomic testing be performed early, ideally at diagnosis of advanced bladder cancer, to facilitate treatment decision-making and to prevent delays in administering later lines of therapy. In addition to determining eligibility for FDA-approved therapies, molecular/genomic testing may be used to screen for clinical trial eligibility.

Based on the FDA approval of erdafitinib (see "Targeted Therapies," page 346), molecular testing should include analysis for *FGFR3* or *FGFR2* genetic alterations. The therascreen FGFR RGQ RT-PCR Kit has been approved as a companion diagnostic for erdafitinib.[103,104] For certain patients who are ineligible to receive cisplatin, the checkpoint inhibitors atezolizumab or pembrolizumab may be considered for first-line therapy based on PD-L1 testing results (see "Targeted Therapies," page 346). Companion diagnostics have been approved for each of these therapies when used in this setting.[104,105]

Genetic alterations are known to be common in bladder cancer, with data from the Cancer Genome Atlas ranking bladder cancer as the third highest mutated cancer.[106,107] Supporting this, a study that looked at comprehensive genomic profiling of 295 cases of advanced urothelial carcinoma found that 93% of cases had at least 1 clinically relevant genetic alteration, with a mean of 2.6 clinically relevant genetic alterations per case. The most commonly identified clinically relevant genetic alterations were cyclin-dependent kinase inhibitor 2A (*CDKN2A*, 34%), *FGFR3* (21%), phosphatidylinositol 3-kinasecatalytic subunit alpha (*PIK3CA*, 20%), and *ERBB2* (17%).[108]

Chemotherapy for Metastatic Disease

The specific chemotherapy regimen recommended partially depends on the presence or absence of medical comorbidities, such as cardiac disease and renal dysfunction, along with the risk classification of the patient based on disease extent. In general, long-term survival with combination chemotherapy alone has been reported only in good-risk patients, defined as those with good performance status, no visceral (ie, liver, lung) or bone disease, and normal alkaline phosphatase or lactic dehydrogenase levels. Poor-risk patients, defined as those with poor performance status or visceral disease, have consistently shown very poor tolerance to multiagent combination programs and few complete remissions, which are prerequisites for cure.

GC[109,110] and ddMVAC[111,112] are commonly used in combinations that have shown clinical benefit. A large, international, phase III study randomized 405 patients with locally advanced or metastatic disease to GC or standard (28-day) MVAC.[113] At a median follow-up of 19 months, OS and time to progression were similar in the 2 arms. Fewer toxic deaths were recorded among patients receiving GC compared with MVAC (1% vs 3%), although this did not reach statistical significance. A 5-year update analysis confirmed that GC was not superior to MVAC in terms of survival (OS, 13.0% vs 15.3%; progression-free survival [PFS], 9.8% vs 11.3%, respectively).[110] Another large, randomized, phase III trial compared ddMVAC to standard (28-day) MVAC.[111,112] At a median follow-up of 7.3 years, 24.6% of patients were alive in the ddMVAC cohort compared with 13.2% in the standard MVAC cohort. There was one toxic death in each arm, but less overall toxicity was seen in the dose-dense group. From these data, ddMVAC had improved toxicity and efficacy as compared with standard MVAC; therefore, standard (28-day) MVAC is no longer used.

Both GC and ddMVAC with growth factor support are category 1 recommendations for metastatic disease. Alternative first-line regimens also include carboplatin or taxane-based regimens (category 2B) or single-agent chemotherapy (category 2B).

The performance status of the patient is a major determinant in the selection of a regimen. Regimens with lower toxicity profiles are recommended in patients with compromised liver or renal status or serious comorbid conditions. In patients who are not cisplatin-eligible and whose tumors express PD-L1 or in patients who are not eligible for any platinum-containing chemotherapy, atezolizumab or pembrolizumab are appropriate first-line options (See "Targeted Therapies," on this page). Alternatively, carboplatin may be substituted for cisplatin in the metastatic setting for cisplatin-ineligible patients such as those with a GFR less than 60 mL/min. A phase II/III study assessed 2 carboplatin-containing regimens in medically unfit patients (performance status 2).[114] The overall response rate (ORR) was 42% for gemcitabine plus carboplatin and 30% for methotrexate, carboplatin, and vinblastine. However, the response rates dropped to 26% and 20%, respectively, with increased toxicity among patients who were both unfit and had renal impairment (GFR <60 mL/min).

Taxanes have been shown to be active as treatment options for urothelial bladder cancer.[115–118] Based on these results, several groups are exploring 2- and 3-drug combinations using these agents, with and without cisplatin. A randomized phase III trial was conducted to compare GC and GC plus paclitaxel in 626 patients with locally advanced or metastatic urothelial cancer.[119] The addition of paclitaxel to GC resulted in higher response rates and a borderline OS advantage, which was not statistically significant in the intent-to-treat analysis. Analysis of eligible patients only (92%) resulted in a small (3.2 months) but statistically significant survival advantage in favor of the 3-drug regimen (P=.03). There was no difference in PFS. The incidence of neutropenic fever was substantially higher with the 3-drug combination (13.2% vs 4.3%; P<.001). Panelists feel that the risk of adding paclitaxel outweighs the limited benefit reported from the trial. The alternative regimens, including cisplatin/paclitaxel,[120] gemcitabine/paclitaxel,[121] cisplatin/gemcitabine/paclitaxel,[122] carboplatin/gemcitabine/paclitaxel,[123] and cisplatin/gemcitabine/docetaxel,[124] have shown modest activity in patients with bladder cancer in phase I–II trials. Category 1 level evidence now supports the use of checkpoint inhibitors in patients with advanced disease previously treated with a platinum-containing regimen (see "Targeted Therapies," opposite column).

Although current data are insufficient to recommend the previously noted alternative regimens as routine first-line options, non–cisplatin-containing regimens may be considered in patients who cannot tolerate cisplatin because of renal impairment or other comorbidities (see "Principles of Systemic Therapy', pages 340–342 [BL-G 2 of 7–BL-G 4 of 7]). Additionally, 2 checkpoint inhibitors, atezolizumab and pembrolizumab, have been FDA approved for use as a first-line therapy in certain patients. Consideration of checkpoint inhibitors must be integrated into the therapeutic planning for all patients with locally advanced and metastatic disease (see "Targeted Therapies," below). The panel recommends enrollment in clinical trials of potentially less toxic therapies.

Independent of the specific regimen used, patients with metastatic disease are re-evaluated after 2 to 3 cycles of chemotherapy, and treatment is continued for 2 more cycles in patients whose disease responds or remains stable. Chemotherapy may be continued for a maximum of 6 cycles, depending on response. If no response is noted after 2 cycles or if significant morbidities are encountered, a change in therapy is advised, taking into account the patient's current performance status, extent of disease, and specific prior therapy. A change in therapy is also advised for patients who experience systemic relapse after adjuvant chemotherapy.

Surgery or radiotherapy may be feasible in highly select cases for patients who show a major partial response in a previously unresectable primary tumor or who have a solitary site of residual disease that is resectable after chemotherapy. In selected series, this approach has been shown to afford a survival benefit. If disease is completely resected, 2 additional cycles of chemotherapy can be considered, depending on patient tolerance.

Clinical trial enrollment is recommended by the NCCN Bladder Cancer Panel for all patients when appropriate, but is strongly recommended for second-line and subsequent therapies because data for locally advanced or metastatic disease treated with subsequent-line therapy are highly variable. The available options depend on what was given as first line. Regimens used in this setting include checkpoint inhibitors, erdafitinib, enfortumab vedotin, and the following chemotherapies: docetaxel; paclitaxel; gemcitabine; ifosfamide, doxorubicin, and gemcitabine; gemcitabine and paclitaxel; GC; and ddMVAC.

Targeted Therapies

Platinum-based chemotherapy has been the standard of care in patients with metastatic disease with an OS of 9 to 15 months.[110,125] However, in patients with disease that relapses after this type of chemotherapy, the median survival is reduced to 5–7 months.[126] Several new agents, notably checkpoint inhibitors, have data supporting improved outcomes compared with standard therapies

for metastatic urothelial carcinoma. Additionally, the FGFR inhibitor, erdafitinib, and the antibody-drug conjugate, enfortumab vedotin, have demonstrated effectiveness for the treatment of previously treated urothelial carcinoma. Cancers with higher rates of somatic mutations have been shown to respond better to checkpoint inhibitors.[127–132] Data from the Cancer Genome Atlas rank bladder cancer as the third highest mutated cancer,[106,107] suggesting that checkpoint inhibitors may have a substantial impact as a treatment option for this cancer.

The FDA has approved the PD-L1 inhibitors atezolizumab, durvalumab, and avelumab as well as the PD-1 inhibitors nivolumab and pembrolizumab for patients with urothelial carcinoma. Pembrolizumab, atezolizumab, nivolumab, durvalumab, and avelumab are approved for the treatment of locally advanced or metastatic urothelial cell carcinoma that has progressed during or after platinum-based chemotherapy or that has progressed within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy, regardless of PD-L1 expression levels. Additionally, atezolizumab and pembrolizumab are approved as a first-line treatment option for patients with locally advanced or metastatic urothelial cell carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression. Companion diagnostic tests have been approved by the FDA for measurement of PD-L1 expression.[104,105] All of these approvals have been based on category 2 level evidence with the exception of pembrolizumab as a subsequent treatment option, which has category 1 level evidence supporting the approval.[133]

Pembrolizumab

Pembrolizumab is a PD-1 inhibitor that has been evaluated as second-line therapy for patients with bladder cancer who previously received platinum-based therapy and subsequently progressed or metastasized.[134] An open-label, randomized, phase III trial compared pembrolizumab to chemotherapy (paclitaxel, docetaxel, or vinflunine) in 542 patients with advanced urothelial carcinoma that recurred or progressed after platinum-based chemotherapy. Data from this trial showed a longer median OS for patients treated with pembrolizumab compared with chemotherapy (10.3 vs 7.4 months; P=.002). In addition, fewer grade 3, 4, or 5 treatment-related AEs occurred in the pembrolizumab-treated patients compared with those treated with chemotherapy (15.0% vs 49.4%).[135] Long-term results (>2 years' follow-up) from this same phase III trial were consistent with earlier reports, with longer 1- and 2- year OS and PFS results for pembrolizumab compared with chemotherapy.[136] The median DOR was not reached for pembrolizumab compared with 4.4 months for chemotherapy. Pembrolizumab also showed lower rates of any grade (62% vs 90.6%) and grade ≥3 AEs (16.5% vs 50.2%) compared with chemotherapy. Results from this phase 3 trial have led the panel to assign pembrolizumab a category 1 recommendation as a second-line therapy.

A single-arm, phase II trial evaluated pembrolizumab as a first-line therapy in 370 patients with advanced urothelial carcinoma who were ineligible for cisplatin-based therapy. Data from this study showed an overall response rate of 24%, with 5% of patients experiencing complete response. Grade 3 or higher treatment-related AEs occurred in 16% of patients treated with pembrolizumab at data cutoff.[137] In May 2018, the FDA issued a safety alert for the use of first-line pembrolizumab and atezolizumab, which warned that early reviews of data from 2 ongoing clinical trials (KEYNOTE-361 and IMvigor-130) showed decreased survival for patients receiving pembrolizumab or atezolizumab as first-line monotherapy compared with those receiving cisplatin- or carboplatin-based therapy.[105] Based on these data, the pembrolizumab prescribing information was subsequently amended to restrict first-line use to patients who either (1) are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 as measured by a combined positive score of at least 10; or (2) are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.[78]

Atezolizumab

Data from the 2-cohort, multicenter, phase II IMvigor-210 trial evaluated atezolizumab in patients with metastatic disease. Cohort 2 of the trial enrolled 310 patients with metastatic urothelial carcinoma after platinum treatment and showed a significantly improved overall response rate compared with historical controls (15% vs 10%; P=.0058).[138] Follow-up to date suggests these responses may be durable, with ongoing responses recorded in 38 (84%) of 45 responders with a median follow-up of 11.7 months. Although a similar response rate was seen regardless of PD-L1 status of tumor cells, a greater response was associated with increased PD-L1 expression status on infiltrating immune cells in the tumor microenvironment. Grade 3 or 4 treatment-related or immune-mediated AEs occurred in 16% and 5% of patients, respectively. Furthermore, no treatment-related deaths were seen in this trial, which suggests good tolerability. At the investigator's discretion, patients on this trial could continue atezolizumab beyond RECIST progression.[139] An analysis of postprogression outcomes showed that those who continued atezolizumab had

longer postprogression OS (8.6 months) compared with those who received a different treatment (6.8 months) and those who received no further treatment (1.2 months).

The multicenter, randomized, controlled, phase III IMvigor-211 study compared atezolizumab to chemotherapy (vinflunine, paclitaxel, or docetaxel) in 931 patients with locally advanced or metastatic urothelial carcinoma after progression with platinum-based chemotherapy.[140] The primary endpoint of this study, median OS in patients with IC2/3 PD-L1 expression levels (n=234), showed no significant difference between atezolizumab and chemotherapy (11.1 vs 10.6 months; P=.41). Likewise, confirmed ORR was similar between atezolizumab and chemotherapy treatments in this group of patients (23% vs 22%). Although atezolizumab was not associated with significantly longer OS compared with chemotherapy, the safety profile of atezolizumab was favorable, with 20% of patients experiencing grade 3 or 4 adverse effects compared with 43% with chemotherapy. Atezolizumab was also associated with a longer DOR than chemotherapy, including durable responses, consistent with the observations in the previous phase II study.

The phase IIIb SAUL study evaluated atezolizumab in 1,004 patients with pretreated, locally advanced or metastatic urothelial or nonurothelial carcinoma of the urinary tract.[141] This study sought to evaluate the safety and efficacy of atezolizumab in patients more similar to the real world population, including those ineligible for IMvigor-211. Median OS was 8.7 months (95% CI, 7.8–9.9), median PFS was 2.2 months (95% CI, 2.1–2.4), and the ORR was 13% (95% CI, 11%–16%). Grade ≥3 AEs occurred in 45% of patients, leading 8% to discontinue treatment based on toxicity. These results confirmed the tolerability of atezolizumab in a real-world, pretreated population, with similar efficacy results to the pivotal clinical trial.[141] Another smaller expanded access study of atezolizumab in patients with pretreated metastatic urothelial carcinoma reached a similar conclusion.[142]

In cohort 1 of the previously mentioned IMvigor-210 trial, atezolizumab was evaluated as a first-line therapy in 119 patients with locally advanced or metastatic urothelial carcinoma who were ineligible for cisplatin. Data from this study showed an ORR of 23%, with 9% of patients showing a complete response. Median OS was 15.9 months. Grade 3 or 4 treatment-related AEs occurred in 16% of patients.[143] In May 2018, the FDA issued a safety alert for the use of first-line pembrolizumab and atezolizumab, which warned that early reviews of data from 2 ongoing clinical trials (KEYNOTE-361 and IMvigor-130) showed decreased survival for patients receiving pembrolizumab or atezolizumab as first-line monotherapy compared with those receiving cisplatin- or carboplatin-based therapy.[105] Based on these data, the atezolizumab prescribing information was subsequently amended to restrict first-line use to patients who either (1) are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 as measured by PD-L1–stained tumor-infiltrating immune cells covering at least 5% of the tumor area; or (2) are not eligible for any platinum-containing chemotherapy regardless of the level of tumor PD-L1 expression.[144]

Nivolumab

Data from a phase II trial in patients with locally advanced or metastatic urothelial carcinoma who progressed after at least one platinum-containing regimen reported an ORR in 52 of 265 patients (19.6%; 95% CI, 15.0–24.9) after treatment with nivolumab that was unaffected by PD-1 tumor status.[145] Of the 270 patients enrolled in the study, grade 3 or 4 treatment-related AEs were reported in 18% of patients. Three patient deaths were the result of treatment.[145] The median OS was 8.74 months (95% CI, 6.05–not yet reached). Based on PD-L1 expression of <1% and ≥1%, OS was 5.95 to 11.3 months, respectively. These data are comparable to the phase I/II data that reported an ORR of 24.4% (95% CI, 15.3%–35.4%) that was unaffected by PD-1 tumor status. Of the 78 patients enrolled in this study, 2 experienced grade 5 treatment-related AEs, and grade 3 or 4 treatment-related AEs were reported in 22% of patients.[146] An extended follow-up of this same phase I/II study (minimum follow-up of 37.7 months) reported a similar ORR of 25.6% (95% CI, 16.4%–36.8%) for nivolumab monotherapy, with a median DOR of 30.5 months.[147]

Durvalumab

Early results from a phase I/II multicenter study of durvalumab for 61 patients with PD-L1–positive inoperable or metastatic urothelial bladder cancer who have tumor that has progressed during or after one standard platinum-based regimen showed that 46.4% of patients who were PD-L1 positive had disease that responded to treatment; no response was seen in patients who were PD-L1 negative.[148] A 2017 update on this study (n=191) showed an ORR of 17.8% (27.6% ORR for PD-L1–high disease and a 5.1% ORR for PD-L1–low or –negative disease). Median OS was 18.2 months, with 55% of patients surviving at 1 year. Median DOR was not yet reached at data cutoff. Grade 3 or 4 treatment-related AEs occurred in 6.8% of treated patients and 4 patients had a grade 3 or 4 immune-mediated AE.[149]

Avelumab

Avelumab is another PD-L1 inhibitor currently in clinical trials to evaluate its activity in the treatment of bladder

cancer. Results from the phase Ib trial for 44 patients with platinum-refractory disease demonstrated an ORR of 18.2% that consisted of 5 complete responses and 3 partial responses following treatment with avelumab. The median PFS was 11.6 weeks, and the median OS was 13.7 months with a 54.3% OS rate at 12 months. Grade 3 or 4 treatment-related AEs occurred in 6.8% of patients treated with avelumab.[150] A pooled analysis of 2 expansion cohorts of the same trial reported results for 249 patients with platinum-refractory metastatic urothelial carcinoma or who were ineligible for cisplatin-based chemotherapy. Of the 161 postplatinum patients with at least 6 months of follow-up, the ORR as determined by independent review was 17%, with 6% reporting complete responses and 11% reporting partial responses. Grade 3 or 4 treatment-related AEs occurred in 8% of patients and, likewise, 8% of patients had a serious AE related to treatment with avelumab.[151]

Erdafitinib

Erdafitinib is a pan-FGFR inhibitor that has been evaluated in a global, open-label phase II trial of 99 patients with a prespecified *FGFR* alteration who had either previously received chemotherapy or who were cisplatin ineligible, chemotherapy naïve. Of these patients, 12% were chemotherapy naïve and 43% had received 2 or more prior lines of therapy. The confirmed ORR was 40% (95% CI, 31%–50%), consisting of 3% complete responses and 37% partial responses. Among patients who had previously received immunotherapy, the confirmed ORR was 59%. Median PFS was 5.5 months and the median OS was 13.8 months. Grade ≥3 treatment-related AEs were reported in 46% of patients and 13% of patients discontinued treatment due to AEs.[152] Based on these data, the FDA has approved erdafitinib for patients with locally advanced or metastatic urothelial carcinoma that has progressed during or after platinum-based chemotherapy and whose tumors have susceptible *FGFR3* or *FGFR2* genetic alterations.[153]

Enfortumab Vedotin

Enfortumab vedotin is a Nectin-4-directed antibody–drug conjugate that has been evaluated in a global, phase II, single-arm study of 125 patients with metastatic urothelial carcinoma who had previously received both a platinum-containing chemotherapy regimen and a PD-1/PD-L1 checkpoint inhibitor. The confirmed ORR was 44% (95% CI, 35.1%–53.2%), including 12% complete responses. Similar response rates were seen in subgroups of patients with liver metastases and in those with no response to prior checkpoint inhibitor therapy. The median duration of response was 7.6 months. Grade ≥3 treatment-related AEs were reported in 54% of patients and treatment-related AEs lead to dose reductions or discontinuation of therapy in 32% and 12% of patients, respectively.[154]

NCCN Recommendations for Targeted Therapies

Based on these data, the NCCN Bladder Cancer Panel recommends pembrolizumab, atezolizumab, nivolumab, durvalumab, avelumab, or erdafitinib as preferred second-line systemic therapy options after platinum-based therapy. Atezolizumab and pembrolizumab are also recommended as preferred first-line therapy options for patients who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression for locally advanced or metastatic disease. In addition to chemotherapy options, erdafitinib is also recommended for second-line systemic therapy after a first-line checkpoint inhibitor and as a third- or subsequent-line therapy option for patients who have already received both a platinum-containing therapy and a checkpoint inhibitor, if eligible on the basis of *FGFR3* or *FGFR2* genetic alterations. Enfortumab vedotin is also recommended as a preferred subsequent-line systemic therapy option. See the "Principles of Systemic Therapy" (BL-G 2 of 7–BL-G 4 of 7, pages 340–342) for more information on these recommendations. With the exception of pembrolizumab as a second-line, postplatinum treatment option (category 1), the use of targeted therapies are all category 2A recommendations.

Summary

Urothelial tumors represent a spectrum of diseases with a range of prognoses. After a tumor is diagnosed anywhere within the urothelial tract, the patient remains at risk for developing a new lesion at the same or a different location and with a similar or more advanced stage. For patients with non–muscle-invasive disease, continued monitoring for recurrence is an essential part of management, because most recurrences are non–muscle-invasive and can be treated endoscopically. Within each category of disease, more refined methods to determine prognosis and guide management, based on molecular staging, are under development with the goal of optimizing each patient's likelihood of cure and chance for organ preservation.

For patients with more extensive disease, newer treatments typically involve combined modality approaches using recently developed surgical procedures or 3-dimensional treatment planning for more precise delivery of RT. Although these are not appropriate in all cases, they offer the promise of an improved quality of life and prolonged survival.

Finally, within the category of metastatic disease, several new agents have been identified that seem

superior to those currently considered standard therapies. Checkpoint inhibitors, in particular, have emerged as a new therapy for the treatment of persistent disease. Experts surmise that the treatment of urothelial tumors will evolve rapidly over the next few years, with improved outcomes across all disease stages.

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Individual Disclosures for the NCCN Bladder Cancer Panel

Panel Member	Clinical Research Support/Data Safety Monitoring Board	Scientific Advisory Boards, Consultant, or Expert Witness	Promotional Advisory Boards, Consultant, or Speakers Bureau	Specialties
Neeraj Agarwal, MD	None	Astellas Pharma US, Inc.; Bristol-Myers Squibb Company; CRISPR; Eisai Inc.; Eli Lilly and Company; EMD Serono, Inc.; Exelixis Inc.; Foundation Medicine; Janssen Pharmaceutica Products, LP; Nektar Therapeutics; and Pharmacyclics, Inc.	None	Hematology/Hematology Oncology, and Medical Oncology
Rick Bangs, MBA	None	Bristol-Myers Squibb Company, and Incyte Corporation	None	Patient Advocate
Stephen A. Boorjian, MD	FKD Therapeutics	Ferring Pharmaceuticals	sanofi-aventis U.S.	Urology
Mark K. Buyyounouski, MD, MS	Varian Medical Systems, Inc.	None	None	Radiotherapy/Radiation Oncology
Sam Chang, MD, MBA	None	Bristol-Myers Squibb Company; Ferring Pharmaceuticals; Janssen Pharmaceutica Products, LP; Merck & Co., Inc.; and Pfizer Inc.	None	Surgery/Surgical Oncology
Tracy M. Downs, MD	None	None	Photocure	Urology
Jason A. Efstathiou, MD, DPhil	None	BlueEarth Diagnostics; Boston Scientific Corporation; Janssen Pharmaceutica Products, LP; and Taris Biomedical	None	Radiotherapy/Radiation Oncology
Thomas W. Flaig, MD[a]	Agensys, Inc.; Aragon Pharmaceuticals, Inc.; Astellas Pharma US, Inc.; AstraZeneca Pharmaceuticals LP; Aurora Oncology; Bavarian Nordic; Bristol-Myers Squibb Company; Dendreon Corporation; Eli Lilly and Company; Exelixis Inc.; Genentech, Inc.; Hoffman La Roche; Janssen Pharmaceutica Products, LP; Merck & Co., Inc.; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Roche Laboratories, Inc.; sanofi-aventis U.S. LLC; Seattle Genetics, Inc.; SOTIO, LLC; and Tokai Pharmaceuticals, Inc.	None	None	Medical Oncology
Terence Friedlander, MD	None	AstraZeneca Pharmaceuticals LP; EMD Serono, Inc.; Genentech, Inc.; and Pfizer Inc.	None	Medical Oncology
Richard E. Greenberg, MD	None	None	None	Urology
Khurshid Guru, MD	None	None	None	Urology
Thomas Guzzo, MD, MPH	None	None	None	Urology
Harry W. Herr, MD	None	None	None	Urology
Jean Hoffman-Censits, MD	NA	NA	NA	Medical Oncology
Christopher Hoimes, MD	Alkermes; Astellas Pharma US, Inc.; Bristol-Myers Squibb Company; CytoMx Therapeutics, Inc.; Merck & Co., Inc.; Nektar Therapeutics; and Seattle Genetics, Inc.	Genentech, Inc.; Merck & Co., Inc.; and Seattle Genetics	Bristol-Myers Squibb Company, and Genentech, Inc.	Medical Oncology
Brant A. Inman, MD, MSc	Anchiano Therapeutics; Combat Medical; Dendreon Corporation; FKD Therapies; Genentech, Inc.; Nucleix, Ltd.; and Taris Biomedical	Boston Biomedical, and Ferring Pharmaceuticals	None	Surgery/Surgical Oncology, and Urology
Masahito Jimbo, MD, PhD, MPH	None	Fowler White Bennett	None	Internal Medicine
A. Karim Kader, MD, PhD[a]	None	Pacific Edge Diagnostics, and Pellficure	None	Surgery/Surgical Oncology, and Urology
Subodh M. Lele, MD	None	None	None	Pathology
Jeff Michalski, MD, MBA	Boston Scientific Corporation	Blue Earth Diagnostics, and Merck & Co., Inc.	Mevion, Inc.	Radiotherapy/Radiation Oncology
Jeffrey S. Montgomery, MD, MHSA	None	Ferring Pharmaceuticals	None	Urology
Lakshminarayanan Nandagopal, MD	None	None	None	Medical Oncology
Lance C. Pagliaro, MD	Astellas Pharma US, Inc.; Exelixis Inc.; Merck & Co., Inc.; Pfizer Inc.; and Roche Laboratories, Inc.	Merck & Co., Inc.	None	Medical Oncology
Sumanta K. Pal, MD	Acceleron Pharma, Inc.	Astellas Pharma US, Inc.; Bristol-Myers Squibb Company; Exelixis Inc.; Genentech, Inc.; Ipsen; Novartis Pharmaceuticals Corporation; and Pfizer Inc.	Astellas Pharma US, Inc., and Genentech, Inc.	Medical Oncology
Anthony Patterson, MD	None	None	None	Urology
Elizabeth R. Plimack, MD, MS	Astellas Pharma US, Inc.; AstraZeneca Pharmaceuticals LP; Bristol-Myers Squibb Company; Genentech, Inc.; Infinity Pharmaceuticals, Inc.; Merck & Co., Inc.; Peloton Therapeutics, Inc.; and Pfizer Inc.	Bristol-Myers Squibb Company; Flatiron Health, Inc.; Genentech, Inc.; Merck & Co., Inc.; and Seattle Genetics, Inc.	None	Medical Oncology, and Internal Medicine
Kamal S. Pohar, MD	None	None	None	Surgery/Surgical Oncology, and Urology
Mark A. Preston, MD, MPH	None	None	None	Urology
Wade J. Sexton, MD	None	Expert Witness	None	Urology
Arlene O. Siefker-Radtke, MD	Bristol-Myers Squibb Company; Janssen Pharmaceutica Products, LP; Merck & Co., Inc.; and Nektar Therapeutics	AstraZeneca Pharmaceuticals LP; Genentech, Inc.; Janssen Pharmaceutica Products, LP; Merck & Co., Inc.; Nektar Therapeutics; and Seattle Genetics, Inc.	None	Medical Oncology
Philippe E. Spiess, MD, MS	None	Expert Witness	None	Surgery/Surgical Oncology, and Urology
Jonathan Tward, MD, PhD	Bayer HealthCare, and Myriad Genetic Laboratories, Inc.	Blue Earth Diagnostics; Janssen Pharmaceutica Products, LP; and Merck & Co., Inc.	None	Radiotherapy/Radiation Oncology
Jonathan L. Wright, MD[a]	Altor Biosciences; Merck & Co., Inc.; Movember Foundation; and Nucleix Ltd.	sanofi-aventis U.S. LLC	OncLive	Urology

The NCCN Guidelines Staff have no conflicts to disclose.

[a]The following individuals have disclosed that they have an employment/governing board, patent, equity, or royalty:
Thomas W. Flaig, MD: Aurora Oncology
A. Karim Kader, MD, PhD: Stratify Genomics
Jonathan L. Wright, MD: UpToDate