National Comprehensive Cancer Network®

NCCN

Bladder Cancer, Version 5.2017

Clinical Practice Guidelines in Oncology

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Overview

An estimated 79,030 new cases of urinary bladder cancer (60,490 men and 18,540 women) will be diagnosed in the United States in 2017 and approximately 16,870 deaths (12,240 men and 4630 women) will occur.[1] Bladder cancer, the sixth most common cancer in the United States,[1] is rarely diagnosed in individuals aged <40 years. Given that the median

Abstract

This selection from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Bladder Cancer focuses on systemic therapy for muscle-invasive urothelial bladder cancer, as substantial revisions were made in the 2017 updates, such as new recommendations for nivolumab, pembrolizumab, atezolizumab, durvalumab, and avelumab. The complete version of the NCCN Guidelines for Bladder Cancer addresses additional aspects of the management of bladder cancer, including non–muscle-invasive urothelial bladder cancer and nonurothelial histologies, as well as staging, evaluation, and follow-up.

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NCCN Categories of Evidence and Consensus

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.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

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

Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representation or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their applications or use in any way. **The full NCCN Guidelines for Bladder Cancer are not printed in this issue of *JNCCN* but can be accessed online at NCCN.org.**

Disclosures for the NCCN Bladder Cancer Panel

At the beginning of each NCCN Guidelines panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Bladder Cancer Panel members can be found on page 1267 (The most recent version of these guidelines and accompanying disclosures are available on the NCCN Web site at NCCN.org.)

These guidelines are also available on the Internet. For the latest update, visit NCCN.org.

age at diagnosis is 73 years,[2] medical comorbidities are a frequent consideration in patient management.

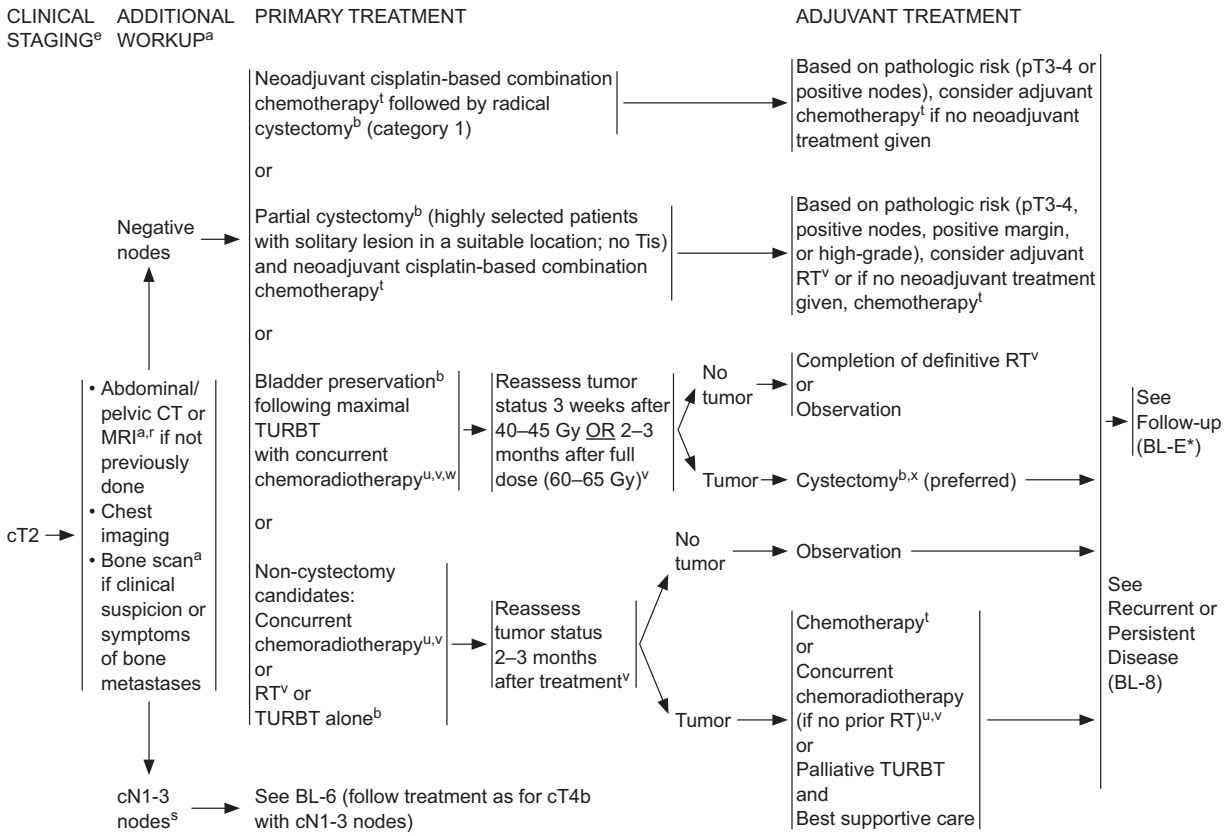
The clinical spectrum of bladder cancer can be divided into 3 categories that differ in prognosis, management, and therapeutic aims. The first category consists of non–muscle-invasive bladder cancer, for which treatment is directed at reducing recurrences and preventing progression to a more advanced stage. The second group encompasses muscle-invasive bladder cancer (MIBC). 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 whether 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 how to use these agents to achieve the best possible outcome.

Histology

More than 90% of urothelial tumors originate in the urinary bladder, 8% originate in the renal pelvis, and the remaining 2% originate in the ureter and urethra. Urothelial carcinomas are classified as low- or high-grade as defined by the extent of nuclear anaplasia and architectural abnormalities.

Urothelial (transitional cell) carcinomas are the most common histologic subtype in the United States and Europe and may develop anywhere

Text cont. on page 1254.



*Available online, in these guidelines, at NCCN.org.

[a]See Principles of Imaging for Bladder/Urothelial Cancer (BL-A*).
[b]See Principles of Surgical Management (BL-B*).
[e]The modifier "c" refers to clinical staging based on bimanual examination under anesthesia and endoscopic surgery (biopsy or transurethral resection) and imaging studies. The modifier "p" refers to pathologic staging based on cystectomy and lymph node dissection.
[r]Consider PET/CT scan (category 2B).
[s]Clinically suspicious nodes.
[t]See Principles of Systemic Therapy (BL-G 1 of 4).
[u]See Principles of Systemic Therapy (BL-G 3 of 4).
[v]See Principles of Radiation Management of Invasive Disease (BL-H).
[w]There are data to support equivalent survival rates. Not all institutions have experience with these multidisciplinary treatment approaches, which require a dedicated team.
[x]Other options may include TURBT, best supportive care, or observation depending on patient and tumor characteristics.

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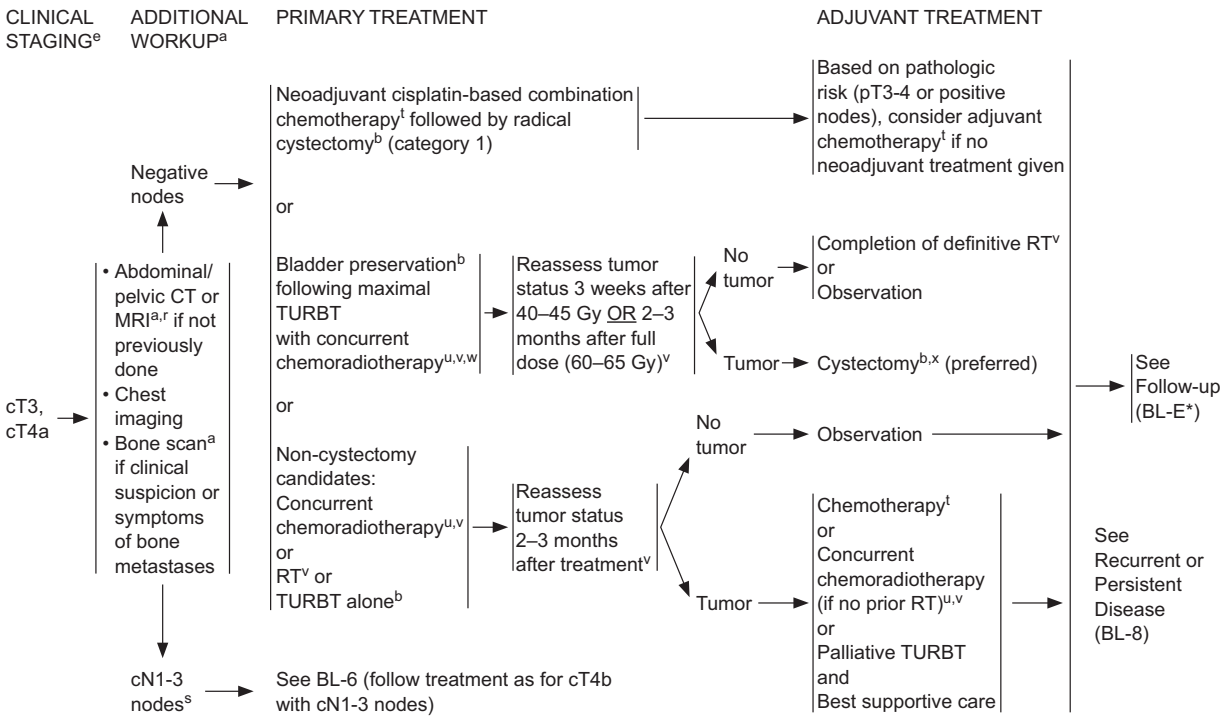

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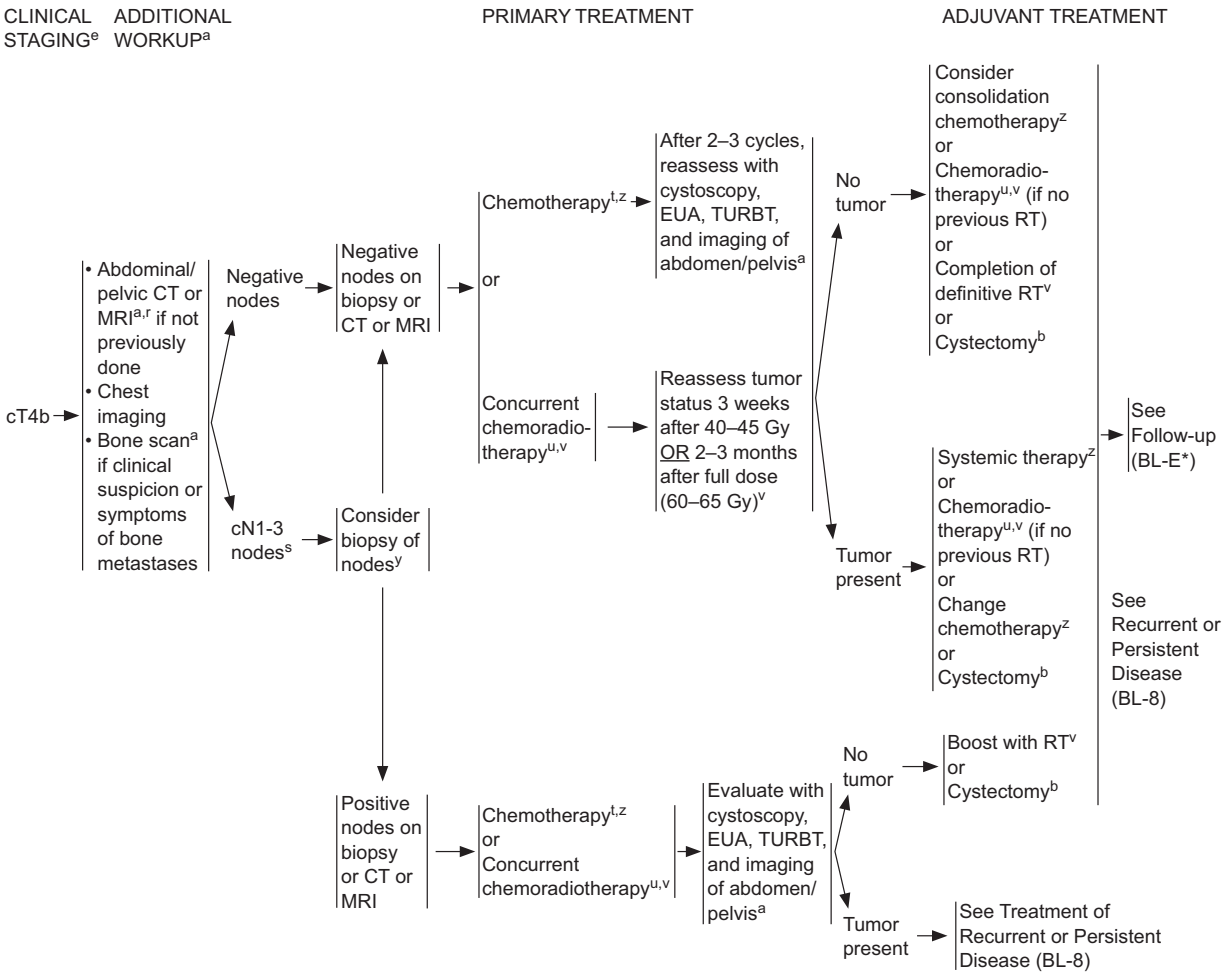

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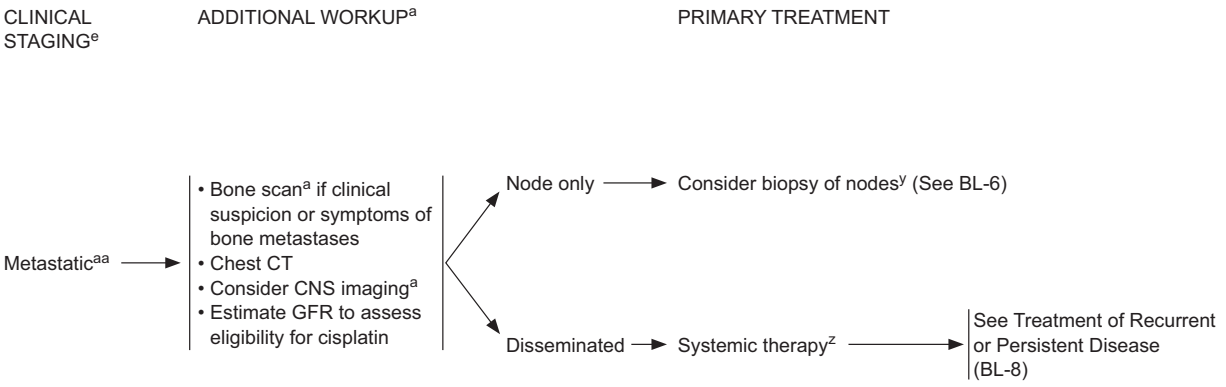
[v]See Principles of Radiation Management of Invasive Disease (BL-H).
[y]If technically possible.
[z]See Principles of Systemic Therapy (BL-G 2 of 4).



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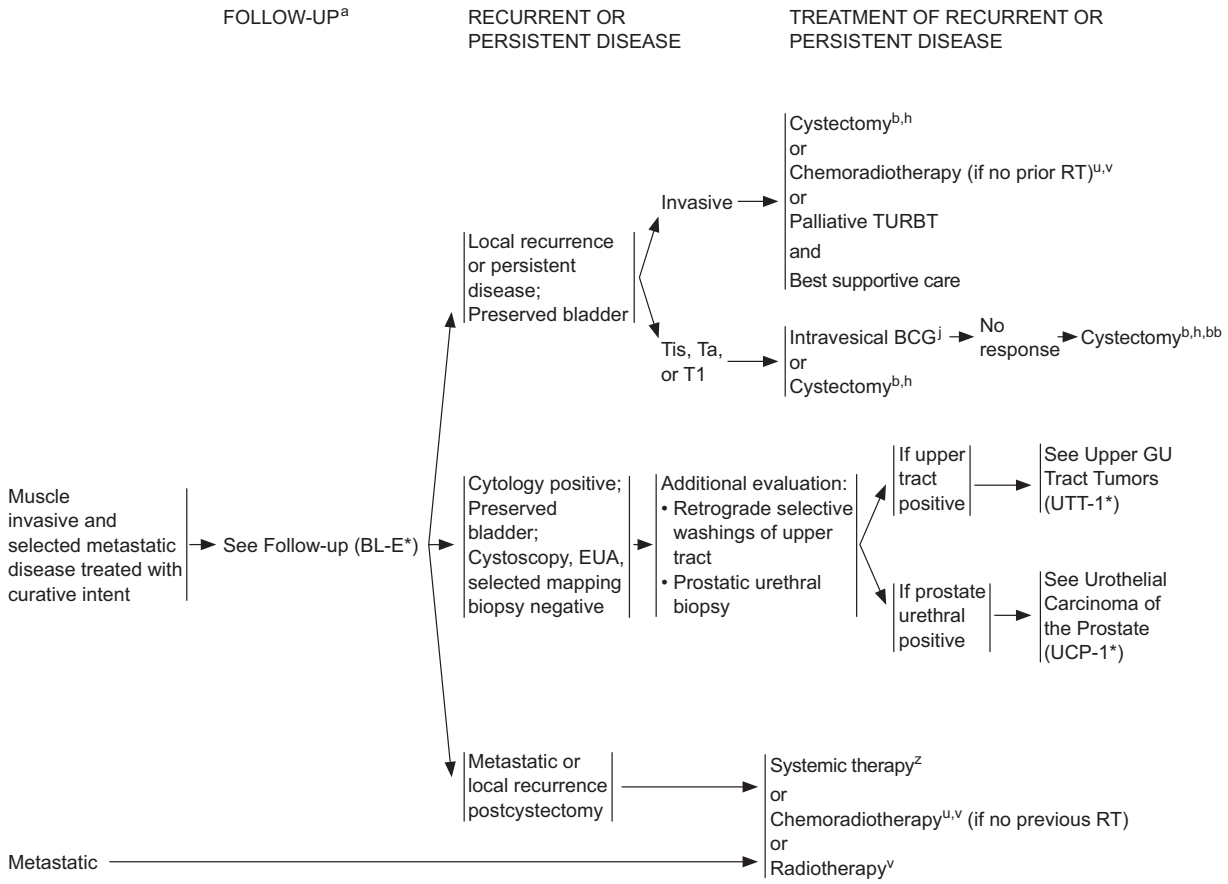
[y]If technically possible.

[z]See Principles of Systemic Therapy (BL-G 2 of 4).

[aa]Consider molecular testing in a CLIA-approved laboratory. See Discussion.



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[a]See Principles of Imaging for Bladder/Urothelial Cancer (BL-A*).
[b]See Principles of Surgical Management (BL-B*).
[h]See Follow-Up (BL-E*).
[j]See Principles of Intravesical Treatment (BL-F*).
[u]See Principles of Systemic Therapy (BL-G 3 of 4).
[v]See Principles of Radiation Management of Invasive Disease (BL-H).
[z]See Principles of Systemic Therapy (BL-G 2 of 4).
[bb]If not a cystectomy candidate, consider concurrent chemoradiotherapy (See BL-G 3 of 4) (if no prior RT), change in intravesical agent, or a clinical trial.

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 six weeks) if
      - Incomplete initial resection
      - No muscle in original specimen for high-grade disease
      - Large or multi-focal lesions
      - Any T1 lesion
      - Select high-grade Ta lesions, especially if no muscle in specimen
  - Transurethral Resection for Sessile or Invasive Appearing Tumor (likely muscle invasive) Repeat
    - Repeat TURBT if
      - No muscle in specimen for 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
- Blue light cystoscopy may be helpful in identifying lesions not visible using white light cystoscopy
- Immediate postoperative intravesical chemotherapy within 24 h if NMIBC and if no concern for bladder perforation
  - The most commonly used option for intravesical chemotherapy is mitomycin.

TURBT/Maximal TURBT for Treatment

- Primary treatment option for cT2, cT3, and cT4a disease.
- Bladder preservation with maximal TURBT and concurrent chemoradiotherapy is generally reserved for patients with smaller solitary tumors, negative nodes, no carcinoma in situ, no tumor-related hydronephrosis, and good pre-treatment bladder function.
- TURBT alone can be considered for non-cystectomy candidates.
- A visually and microscopically complete TURBT is associated with improved patient outcomes.

Transurethral Resection of the Prostate (TURP)

- Primary treatment option for urothelial carcinoma of the prostate with ductal/acini or prostatic urethra pathology.
- Postsurgical intraprostatic BCG is recommended (see Principles of Intravesical Therapy).

Transurethral Resection (TUR) of the Urethral Tumor

- Primary treatment of Tis, Ta, T1 primary carcinoma of the urethra.
- Patients with a prior radical cystectomy or a cutaneous diversion should consider a total urethrectomy.
- Postsurgical intraurethral therapy is recommended (see Principles of Intravesical Therapy).

Partial Cystectomy

- Reserved for cT2 muscle invasive disease with solitary lesion in location amenable to segmental resection with adequate margins
- No carcinoma in situ as determined by random biopsies
- Should be given with neoadjuvant cisplatin-based combination chemotherapy.
- Bilateral pelvic lymphadenectomy should be performed and include at a minimum common, internal iliac, external iliac, and obturator nodes

Radical Cystectomy/Cystoprostatectomy

- In non-muscle invasive disease, radical cystectomy is generally reserved for residual high-grade cT1 or muscle-invasive disease at re-resection
- Cystectomy should be done within 3 months of diagnosis if no therapy given.
- Primary treatment option for cT2, cT3, and cT4a disease. Highly select patients with cT4b disease that responds to primary treatment may be eligible for cystectomy
- Should be given with neoadjuvant cisplatin-based combination chemotherapy. For patients who cannot receive neoadjuvant chemotherapy, radical cystectomy alone is an option
- Bilateral pelvic lymphadenectomy should be performed and include at a minimum common, internal iliac, external iliac, and obturator nodes

Radical Nephroureterectomy with Cuff of Bladder

- Primary treatment option for non-metastatic high grade upper GU tract tumors
- Upper GU tract urothelial carcinoma, strongly consider single-dose immediate postoperative intravesical chemotherapy as randomized trials have shown a decrease in intravesical recurrence. The most commonly used option for intravesical chemotherapy is mitomycin.
- Neoadjuvant chemotherapy should be considered in select patients with high-grade disease

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PRINCIPLES OF SURGICAL MANAGEMENT

Urethrectomy

- Male patients with T2 primary carcinoma of the urethra in the bulbar urethra may be treated with a urethrectomy with or without a cystoprostatectomy.
- Male patients with T2 primary carcinoma of the urethra in the pendulous urethra may receive a distal urethrectomy. Alternatively, a partial penectomy can be considered. A total penectomy may be necessary in cases of recurrence.
- Female patients with T2 primary carcinoma of the urethra may be treated with urethrectomy with cystectomy.
- Neoadjuvant chemotherapy (category 2B) or chemoradiation should be considered.
- Distal urethrectomy may include inguinal lymph node dissection in selected cases.
- Total urethrectomy may include inguinal lymphadenectomy in selected cases.

Regional Lymphadenectomy

- Recommended for patients with high-grade upper GU tract tumors tumors
- Left-sided renal pelvic, upper ureteral, and midureteral tumors
  - Regional lymphadenectomy should include at a minimum the paraaortic lymph nodes from the renal hilum to the aortic bifurcation.
  - Most midureteral tumors will also include the common iliac, external iliac, obturator, and hypogastric lymph nodes.
- Right-sided renal pelvic, upper ureteral, and midureteral tumors
  - Regional lymphadenectomy should include at a minimum the paracaval lymph nodes from the renal hilum to the aortic bifurcation.
  - Most midureteral tumors will also include the common iliac, external iliac, obturator, and hypogastric lymph nodes.
- Distal ureteral tumors
  - Regional lymphadenectomy should be performed and include at a minimum the common iliac, external iliac, obturator, and hypogastric lymph nodes

Pelvic Exenteration (category 2B)

- Therapy for recurrence in female patients with ≥T2 primary carcinoma of the urethra.
- Ilioinguinal lymphadenectomy and/or chemoradiotherapy can be considered in patients with ≥T3 disease.

PRINCIPLES OF SYSTEMIC THERAPY

Perioperative chemotherapy (neoadjuvant or adjuvant)

Standard regimens
• DDMVAC (dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin) with growth factor support for 3 or 4 cycles[1,2] • Gemcitabine and cisplatin for 4 cycles[3,4] • CMV (cisplatin, methotrexate, and vinblastine) for 3 cycles[5]

- For patients who are not candidates for cisplatin, there are no data to support a recommendation for perioperative chemotherapy.
- Randomized trials and meta-analyses show a survival benefit for cisplatin-based neoadjuvant chemotherapy (3 or 4 cycles) in patients with muscle-invasive bladder cancer.[1,6,7]
- Meta-analysis suggests a survival benefit to adjuvant therapy for pathologic T3, T4 or N+ disease at cystectomy.[7]
- Neoadjuvant chemotherapy is preferred over adjuvant-based chemotherapy on a higher level of evidence data.
- DDMVAC is preferred over standard MVAC based on category 1 evidence showing DDMVAC to be better tolerated and more effective than conventional MVAC in advanced disease.[2,8] Based on these data, the traditional dose and schedule for MVAC is no longer recommended.
- Perioperative gemcitabine and cisplatin is a reasonable alternative to DDMVAC based on category 1 evidence showing equivalence to conventional MVAC in the setting of advanced disease.[4,9]
- For gemcitabine/cisplatin, both 21- and 28-day regimens are acceptable. Better dose compliance may be achieved with fewer delays in dosing using the 21-day schedule.[10]
- Neoadjuvant chemotherapy may be considered for select patients with upper tract urothelial carcinoma, particularly for higher stage and/or grade tumors, as renal function will decline after nephroureterectomy and may preclude adjuvant therapy.
- Carboplatin should not be substituted for cisplatin in the perioperative setting.
  - For patients with borderline renal function or minimal dysfunction, a split-dose administration of cisplatin may be considered (such as 35 mg/m^2 on days 1 and 2 or days 1 and 8) (category 2B). While safer, the relative efficacy of the cisplatin-containing combination administered with such modifications remains undefined.
- For patients with borderline renal function, estimate GFR to assess eligibility for cisplatin.

First-line chemotherapy for locally advanced or metastatic disease

	Standard regimens	Alternate regimens for select patients
Cisplatin eligible	• Gemcitabine and cisplatin[4] (category 1) • DDMVAC with growth factor support (category 1)[2,8]	
Cisplatin ineligible	• Gemcitabine and carboplatin[11] • Atezolizumab[12] • Pembrolizumab[13]	• Gemcitabine[14] • Gemcitabine and paclitaxel[15] • Ifosfamide, doxorubicin, and gemcitabine[16] (for patients with good kidney function and good PS)

- The presence of both visceral metastases and ECOG performance score ≥2 strongly predict poor outcome with chemotherapy. Patients without these adverse prognostic factors have the greatest benefit from chemotherapy.
- 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.

Subsequent systemic therapy for locally advanced or metastatic disease

- Participation in clinical trials of new agents is recommended.

Standard regimens	Alternate regimens for select patients
• Pembrolizumab (category 1)[18] • Atezolizumab[19] • Nivolumab[20] • Durvalumab[21] • Avelumab[22,23] • Paclitaxel or docetaxel[24] • Gemcitabine[14] • Pemetrexed[25]	• Nab-paclitaxel[26] • Ifosfamide[27] • Methotrexate • Ifosfamide, doxorubicin, and gemcitabine[16] • Gemcitabine and paclitaxel[15] • Gemcitabine and cisplatin[4] • DDMVAC[2]

Continued on BL-G 3 of 4

PRINCIPLES OF SYSTEMIC THERAPY

Radiosensitizing chemotherapy regimens for bladder-preserving chemoradiation following a maximal TURBT

- First-line chemotherapy

Standard regimens (doublet chemotherapy is preferred)	Alternate regimens
• Cisplatin[a] and 5-FU[28] • Cisplatin[a] and paclitaxel[28,29] • 5-FU and mitomycin[30]	• Cisplatin[a] alone[31] • Low-dose gemcitabine[32,33] (category 2B)

Radiosensitizing chemotherapy given concurrently with conventionally fractionated radiation for palliation of metastases or for pelvic recurrence after cystectomy

- Cisplatin[a]
- Taxane (docetaxel or paclitaxel) (category 2B)
- 5-FU (category 2B)
- 5-FU and mitomycin (category 2B)
- Capecitabine (category 3)
- Low-dose gemcitabine (category 2B)

References on BL-G 4 of 4

[a]Carboplatin is not an effective radiation sensitizer and should not be substituted for cisplatin with radiation. (Rödel C, Grabenbauer GG, Kühn R, et al. Combined-modality treatment and selective organ preservation in invasive bladder cancer: long-term results. J Clin Oncol 2002; 20:3061.)

PRINCIPLES OF SYSTEMIC THERAPY
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PRINCIPLES OF RADIATION MANAGEMENT OF INVASIVE DISEASE

Carcinoma of the Bladder:

- Precede radiation therapy alone or concurrent chemoradiotherapy by maximal TUR of the tumor when safely possible.
- Simulating and treating patients when they have an empty bladder is preferred for daily reproducibility (bladder full for tumor boosts is acceptable with image guidance).
- Use multiple fields from high-energy linear accelerator beams.
- For invasive tumors, consider low-dose preoperative radiation therapy prior to segmental cystectomy (category 2B).
- Concurrent chemoradiotherapy or radiation therapy alone is most successful for patients without hydronephrosis and without extensive carcinoma in situ associated with their muscle-invading tumor.
- For patients with stage Ta, T1, or Tis, external beam radiation therapy (EBRT) alone is rarely appropriate. For patients with recurrent Ta-T1 disease usually following BCG therapy but without extensive Tis who are not candidates for cystectomy, concurrent chemoradiotherapy may be considered as a potentially curative alternative to radical cystectomy, which is the standard treatment by NCCN Guidelines.
- Treat the whole bladder with or without pelvic nodal radiotherapy 39.6–50.4 Gy using conventional or accelerated hyperfractionation. Elective treatment to the lymph nodes is optional and should take into account patient comorbidities and the risks of toxicity to adjacent critical structures. Then boost either the whole or partial bladder between 60–66 Gy. For node-positive disease, consider boosting grossly involved nodes to the highest achievable dose that does not violate DVH parameters based on the clinical scenario. Reasonable alternatives to conventional fractionation include taking the whole bladder to 55 Gy in 20 fractions, or using simultaneous integrated boosts to sites of gross disease.
- When irradiating the bladder only or bladder tumor boost, consider daily image guidance.
- Concurrent chemoradiotherapy is encouraged for added tumor cytotoxicity, and can be given without significant increased toxicity over radiation therapy alone. Concurrent 5-FU and mitomycin C can be used instead of cisplatin in patients with low or moderate renal function. Such therapy is optimally given by dedicated multidisciplinary teams.
- Concurrent chemoradiotherapy or radiation therapy alone should be considered as potentially curative therapy for medically inoperable patients or for local palliation in patients with metastatic disease.
- When giving palliative radiation for metastatic bladder cancer or for recurrent pelvic tumor, combining radiation with radiosensitizing chemotherapy should be considered. See BL-G 3 of 4 for agents. Chemotherapy should not be used concurrently with high-dose (>3 Gy per fraction) palliative radiation.
- Treatment field should include whole bladder and all sites of gross disease plus or minus uninvolved regional lymph nodes. Regional lymph nodes include the hypogastric, obturator, internal and external iliac, perivesical, sacral, and presacral nodes. For involved nodal disease, the common iliac nodes are site of secondary involvement.
- For patients with pT3/pT4 pN0-2 urothelial (pure urothelial or primary urothelial mixed with other subtypes) bladder cancer following radical cystectomy with ileal conduit, consider postoperative adjuvant pelvic radiation therapy. Treatment field should encompass areas at risk for harboring residual microscopic disease based on pathologic findings at resection and may include cystectomy bed and pelvic lymph nodes with doses in the range of 45 to 50.4 Gy. Involved resection margins and areas of extranodal extension could be boosted to 54–60 Gy if feasible based on normal tissue constraints.
- Tumor status assessment after completion of full-dose primary chemoradiotherapy: After 2–3 months, imaging with CT of chest/abdomen/pelvis with contrast ± bone scan. Cystoscopic surveillance and biopsy are also recommended as follow-up after completion of full-dose chemoradiotherapy.
- In highly selected T4b tumor cases, may consider intraoperative RT.

Carcinoma of the Urethra:

- Data support the use of radiation therapy for urothelial carcinoma and squamous cell carcinoma of the urethra (case series and experience treating these carcinomas arising from other disease sites); radiation can also be considered for adenocarcinomas of the urethra.
- Definitive Radiation Therapy (organ preservation)
  - cT2 cN0
    - 66 to 70 Gy EBRT delivered to gross disease with a margin to encompass areas of potential microscopic spread. Concurrent chemotherapy with regimens used for bladder cancer is encouraged for added tumor cytotoxicity.
    - Strongly consider prophylactic radiation treatment of regional-nodal basins (inguinal and low pelvic nodes for female and distal male tumors; pelvic lymph nodes for proximal male tumors).
  - cT3-T4, or lymph node positive
    - 45 to 50.4 Gy EBRT delivered to gross disease with a margin to encompass areas of microscopic spread and to regional-nodal basins (inguinal and low pelvic nodes for female and distal male tumors; pelvic lymph nodes for proximal male tumors). Boost gross primary disease to 66 to 70 Gy and gross nodal disease to 54 to 66 Gy, if feasible. Dose delivered to gross nodal disease may be limited secondary to normal tissue dose constraints. Concurrent chemotherapy should be administered for added tumor cytotoxicity.
  - Postoperative Adjuvant Radiation Therapy
    - Treatment field should encompass areas at risk for harboring residual microscopic disease based on pathologic findings at resection and may include resection bed, inguinal lymph nodes, and pelvic lymph nodes. Areas at risk for harboring residual microscopic disease should receive 45 to 50.4 Gy EBRT. Involved resection margins and areas of extranodal extension should be boosted to 54 to 60 Gy if feasible based on normal tissue constraints. Areas of gross residual disease should be boosted to 66 to 70 Gy, if feasible based on normal tissue constraints. Concurrent chemotherapy with regimens used for bladder cancer should be considered for added tumor cytotoxicity.

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transitional epithelium is present, from the renal pelvis to the ureter, bladder, and proximal two-thirds of the urethra. Variant histology is common with higher grades. The fourth edition of the WHO Classification of Tumors has reclassified these histologic subtypes into the following: infiltrating urothelial carcinoma with divergent differentiation; nested, including large nested; microcystic; micropapillary; lymphoepithelioma-like; plasmacytoid/signet ring cell/diffuse; sarcomatoid; giant cell; poorly differentiated; lipid-rich; and clear cell.[3] Two review articles highlight the changes between the third and fourth additions of this classification.[4,5] The presence of histologic variants in urothelial carcinoma should be documented, because data suggest that the subtype may reflect the risk of disease progression and different genetic origin, and subsequently determine whether a more aggressive treatment approach should be considered (see "Bladder Cancer: Non-Urothelial and Urothelial With Variant Histology" in the complete version of these guidelines, at NCCN.org). In some cases with a mixed histology, systemic treatment may only target cells of urothelial origin and the nonurothelial component can remain.

Squamous cell neoplasms of the urothelial tract are a second histologic subtype, which constitute 3% of the urinary tumors diagnosed in the United States. In regions where Schistosoma is endemic, this subtype is more prevalent and may account for up to 75% of bladder cancer cases. The distal third of the urethra is dominated by squamous epithelium. The diagnosis of squamous cell tumors requires the presence of keratinization in the pathologic specimen.[6] Squamous cell carcinoma of the bladder is morphologically indistinguishable from squamous cell carcinoma of other sites and generally presents at an advanced stage. The 3 variants within this subtype are pure squamous cell carcinoma, verrucous carcinoma, and squamous cell papilloma.

Other histologic subtypes derived from cells of urothelial origin include glandular neoplasms, epithelial tumors of the upper urinary tract, and tumors arising in a bladder diverticulum. Glandular neoplasms include adenocarcinoma and villous adenoma. Urachal tumors are nonurothelial tumors, most commonly adenocarcinomas, which arise from the urachal ligament and involve the midline/dome of the bladder secondarily.[7] Tumors arising within the genitourinary tract but not of urothelial origin (eg, tumors of müllerian type, melanocytic tumors, mesenchymal tumors) are beyond the scope of these guidelines.

Muscle-Invasive Urothelial Bladder Cancer

Additional Workup

Several workup procedures are recommended to accurately determine clinical staging of MIBC. Laboratory studies, such as a complete blood cell count and chemistry profile, including alkaline phosphatase, must be performed, and the patient should be assessed for the presence of regional or distant metastases. This evaluation should include chest imaging and a bone scan in patients with symptoms or clinical suspicion of bone metastasis (eg, elevated alkaline phosphatase, focal bone pain). Imaging studies help assess the extent of tumor spread to lymph nodes or distant organs.[8] An abdominal/pelvic CT or MRI is used to assess the local and regional extent of disease. Unfortunately, CT scans, ultrasound, and MRI cannot accurately predict the true depth of invasion.

The overwhelming majority of muscle-invasive tumors are high-grade urothelial carcinomas. Further treatment following initial transurethral resection of bladder tumor (TURBT) is often required for muscle-invasive tumors, although select patients may be treated with TURBT alone.[9,10] Different treatment modalities are discussed herein, including radical cystectomy, partial cystectomy, neoadjuvant or adjuvant therapy, bladder-preserving approaches, and chemotherapy for advanced disease.

Radical Cystectomy

Radical surgical treatment of bladder cancer involves a cystoprostatectomy in men and a cystectomy and commonly a hysterectomy in women, followed by the formation of a urinary diversion. This surgery can be performed in an open or robotic manner. Prostatectomy includes removal of the prostate, seminal vesicles, proximal vas deferens, and proximal urethra. Hysterectomy should include removal of the uterus, ovaries, fallopian tubes, urethra, and part of the vagina. Forms of urinary diversion include an ileal conduit or directing urine to an internal urinary reservoir (such as a continent pouch), with drainage to the abdominal wall or the urethra (orthotopic

neobladder). Relative contraindications to urethral drainage include Tis in the prostatic ducts or positive urethral margin. Orthotopic diversion or a neobladder provides the closest bladder function to that of a native bladder albeit with an increased risk for nighttime incontinence as well as urinary retention requiring intermittent self-catheterization.

Unfortunately, the accuracy of the staging cystoscopy, examination under anesthesia (EUA), and TURBT is modest, even when combined with cross-sectional imaging, and understaging is frequently encountered. A retrospective study of 778 patients with bladder cancer found that 42% were upstaged following cystectomy.[11] A pelvic lymph node dissection (PLND) is considered an integral part of the surgical management of bladder cancer. A more extensive PLND, which may include the common iliac or even lower para-aortic or para-caval nodes, yields more nodes to be examined, increases yield of positive nodes, and may be associated with better survival and a lower pelvic recurrence rate.[12–16] Patient factors that may preclude a PLND include severe scarring secondary to previous treatments or surgery, advanced age, or severe comorbidities.

Partial Cystectomy

In <5% of cases, an initial invasive tumor develops in an area of the bladder where an adequate margin of soft tissue and amount of noninvolved urothelium can be removed along with the tumor without compromising continence or significantly reducing bladder capacity. Partial cystectomy is most frequently recommended for lesions that develop on the dome of the bladder and have no associated Tis in other areas of the urothelium. Relative contraindications to this procedure are lesions that occur in the trigone or bladder neck. The requirement for a ureteral reimplantation, however, is not an absolute contraindication. Outcome data on partial cystectomy are varied and, in general, partial cystectomy is not considered the gold-standard surgical treatment of MIBC. Ideal candidates are patients with cancer in a diverticulum or with significant medical comorbidities.

Similar to radical cystectomy, partial cystectomy begins with a laparotomy (intraperitoneal) and resection of the pelvic lymph nodes. Alternatively, partial cystectomy may be safely performed laparoscopically. If the intraoperative findings preclude a partial cystectomy, a radical cystectomy is performed. The decision to recommend adjuvant radiation or chemotherapy is based on the pathologic stage (ie, positive nodes or perivesical tissue involvement) or presence of a positive margin, similar to that for patients who undergo a radical cystectomy.

Neoadjuvant Chemotherapy

One of the most noteworthy issues in treatment is the optimal use of perioperative chemotherapy for MIBC. Data support the role of neoadjuvant chemotherapy before cystectomy for T2, T3, and T4a lesions without nodal involvement.[17–22] In a SWOG randomized trial of 307 patients with MIBC, radical cystectomy alone versus 3 (28-day) cycles of neoadjuvant methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) followed by radical cystectomy were compared. Neoadjuvant chemotherapy increased median survival (77 vs 46 months; P=.06) and lowered the rate of residual disease (15% vs 38%; P<.001) with no apparent increase in treatment-related morbidity or mortality.[17] In a meta-analysis of 11 trials involving 3,005 patients, cisplatin-based multiagent neoadjuvant chemotherapy was associated with improved 5-year overall survival (OS) and disease-free survival (DFS; 5% and 9% absolute improvement, respectively).[21]

Since the neoadjuvant trial with MVAC, the use of dose-dense MVAC (ddMVAC) with growth factor support in the metastatic setting has been shown to have good comparable tolerance with an increased complete response (CR) rate compared with standard (28-day) dosing of MVAC (11% vs 25%; 2-sided P=.006).[23] Based on these findings, ddMVAC has also been investigated in the neoadjuvant setting. In a multicenter prospective phase II trial, patients with cT2 to cT4a tumor staging and N0 or N1 MIBC (n=44) were given 3 cycles of ddMVAC with pegfilgrastim followed by radical cystectomy and lymph node dissection.[24] ddMVAC was anticipated to have a safer profile, a shorter time to surgery, and a similar pathologic CR rate compared with historical control data for neoadjuvant MVAC chemotherapy given in previous studies. Patients receiving ddMVAC had no grade 3 or 4 renal toxicities and no toxicity-related deaths. Grade 1 or 2 treatment-related toxicities were seen in 82% of patients. The median time to cystectomy was 9.7 weeks from start of chemotherapy.[24] A separate single-arm phase II study also reported pathologic downstaging

in 49% of patients receiving neoadjuvant ddMVAC with a similar safety profile.[25] An additional neoadjuvant clinical trial of ddMVAC with bevacizumab reported 5-year survival outcomes of 63% and 64% (OS and disease-specific survival, respectively; median follow-up, 49 months), with pT0N0 and ≤pT1N0 downstaging rates of 38% and 53%, respectively.[26] Bevacizumab had no definitive impact on overall outcomes. An international, multicenter, randomized trial (BA06 30894) investigating the effectiveness of neoadjuvant cisplatin, methotrexate, and vinblastine (CMV) in 976 patients showed a 16% reduction in mortality risk (hazard ratio [HR], 0.84; 95% CI, 0.72–0.99; *P*=.037) at a median follow-up of 8 years.[22]

The NCCN Panel strengthened the recommendations for neoadjuvant chemotherapy for patients with cT2, cT3, and cT4a bladder cancer without nodal disease and for adjuvant chemotherapy for patients with pT3 or pT4 disease or positive nodes (see cT2, Primary and Adjuvant Treatment [page 1242] and cT3, cT4a, Primary and Adjuvant Treatment [page 1243]). Neoadjuvant chemotherapy followed by radical cystectomy is a category 1 recommendation. Patients with hearing loss or neuropathy, poor performance status, or renal insufficiency may not be eligible for cisplatin-based chemotherapy. If neoadjuvant cisplatin-based chemotherapy cannot be given, neoadjuvant chemotherapy is not recommended. For patients with borderline renal function or minimal dysfunction, a split-dose administration of cisplatin may be considered (category 2B). Although split-dose is a safer alternative, the relative efficacy remains undefined.

Adjuvant Chemotherapy

Data are less clear regarding the role of adjuvant systemic chemotherapy in invasive bladder cancer. Studies have shown that adjuvant chemotherapy may delay recurrences and improve OS,[27–29] but no randomized comparisons of adequate sample size have definitively shown a survival benefit, in large part due to poor accrual.[30] Clinical trials of adjuvant chemotherapy with cyclophosphamide, doxorubicin, and cisplatin (CAP); MVAC; and methotrexate, vinblastine, epirubicin, and cisplatin (MVEC) regimens have each suggested a survival advantage.[31–33] However, methodologic issues call into question the applicability of these studies to all patients with urothelial tumors. In the MVEC trial, patients who experienced relapse in the control arm did not receive chemotherapy, which is not typical of more contemporary treatment approaches. Many of these trials were not randomized, raising the question of selection bias in the analysis of outcomes.

A meta-analysis of 6 trials found a 25% mortality reduction with adjuvant chemotherapy, but the authors pointed out several limitations of the data and concluded that evidence is insufficient for treatment decisions.[34] Interestingly, the follow-up analysis included 3 more studies for a total of 9 trials (N=945 patients).[29] A 23% risk reduction for death was observed in the updated analysis (HR, 0.77; 95% CI, 0.59–0.99; *P*=.049) and improved DFS was achieved (HR, 0.66; 95% CI, 0.45–0.91; *P*=.014). Patients with node-positive disease had an even greater DFS benefit.[29] An observational study evaluated 5,653 patients, of which 23% received adjuvant chemotherapy after cystectomy.[28] Patients who received adjuvant chemotherapy had an improved OS (HR, 0.70; 95% CI, 0.06–0.76).[28] Although evidence for adjuvant therapy is not as strong as for neoadjuvant therapy, the growing body of data support the administration of adjuvant chemotherapy for patients with a high risk for relapse who did not receive neoadjuvant therapy.

The NCCN Guidelines suggest that adjuvant chemotherapy may be given to patients with high-risk pathology who did not receive neoadjuvant chemotherapy, and it is considered a category 2A recommendation. For highly select patients who receive a partial cystectomy, neoadjuvant chemotherapy is a category 2A recommendation, with the option of adjuvant chemotherapy for patients who did not receive neoadjuvant chemotherapy.

A minimum of 3 cycles of a cisplatin-based combination, such as ddMVAC; gemcitabine plus cisplatin (GC); or CMV, may be used in patients undergoing perioperative chemotherapy. Regimen and dosing recommendations are mainly based on studies in advanced disease.[17,22,35–37] Carboplatin has not demonstrated a survival benefit and should not be substituted for cisplatin in the perioperative setting. It should be noted that patients with tumors that are ≤pT2 and have no nodal involvement or lymphovascular invasion after cystectomy are considered to have lower risk and are not recommended to receive adjuvant chemotherapy.

Adjuvant Radiation

Patients with locally advanced disease (pT3–4) have high rates of pelvic failure and poor OS after radical cystectomy, pelvic lymph node dissection, and perioperative chemotherapy (pelvic failure, 20%–45% and survival, 10%–50% at 5 years, depending on risk factors factors).[38–40] There is an interest in using adjuvant radiation to improve these outcomes, but data are limited and further prospective studies are needed to confirm its benefits. One older randomized study of 236 patients with pT3a to pT4a bladder cancer demonstrated improvement in 5-year DFS and local control compared with surgery alone.[41] A more recent randomized phase II trial comparing adjuvant sequential chemotherapy and radiation versus adjuvant chemotherapy alone in 120 patients with locally advanced disease (pT3–4 or node-positive) showed a significant improvement in local control for chemoradiation (3-year local control of 96% vs 69%); however, the improvement in DFS and OS was not significant. Late grade ≥3 gastrointestinal toxicity on the chemoradiation arm was low.[42]

Although no conclusive data demonstrate improvements in overall survival, it is reasonable to consider adjuvant radiation in patients with pT3/pT4 pN0–2 urothelial bladder cancer after radical cystectomy. Patients meeting these characteristics with positive surgical margins and/or lymph nodes identified in the pelvic dissection have especially high pelvic failure rates (40%–45% by 5 years), and adjuvant radiation is reasonably well tolerated and improves pelvic failure rates. Radiation with a dose range of 45 to 50.4 Gy without concurrent chemotherapy may be used. In patients who have not had prior neoadjuvant chemotherapy, it may be reasonable to sandwich adjuvant radiation between cycles of adjuvant chemotherapy.[42] The safety and efficacy of concurrent sensitizing chemotherapy and radiation in the adjuvant setting needs to be further studied.

Bladder Preservation

All bladder-sparing approaches are based on the principle that not all cases require an immediate cystectomy, and the decision to remove the bladder can be deferred until the response to organ-sparing therapy is assessed. Bladder-preserving approaches are reasonable alternatives to cystectomy for patients who are medically unfit for surgery and those seeking an alternative to radical cystectomy. Combined modality chemoradiation therapy as an alternative to immediate cystectomy for MIBC is endorsed by multiple international organizations that have developed evidence-based consensus guidelines and recommendations including the International Consultation on Urologic Diseases-European Association of Urology (ICUD-EAU), UK National Institute for Health and Care Excellence (NICE), and the AUA/ASCO/ASTRO/SUO.[43–45] There is an apparent underutilization of aggressive bladder-preserving therapies for noncystectomy candidates, especially the elderly and racial minorities.[46,47] Between 23% and 50% of patients with MIBC who are ≥65 years of age receive no treatment or nonaggressive therapy.

With any of the alternatives to cystectomy, there is a concern that bladders that appear to be endoscopically free of tumor based on a clinical assessment (cT0) that includes a repeat TURBT may not be pathologically free of tumor (pT0). Reports have suggested that up to 45% of bladders may be clinically understaged after TURBT.[47–49] Conversely, one series reported that all patients who achieved a CR after radiotherapy (RT) with concurrent cisplatin and 5-FU were pT0 on immediate cystectomy.[50] Although studies report differing frequencies of residual disease after cytotoxic agents (either radiation or chemotherapy), there is consensus that the rate is lower for patients who present with T2 disease versus T3 disease, which should be considered when proposing a bladder-sparing approach.

The decision to use a bladder-preserving approach is partially based on the location of the lesion, depth of invasion, size of the tumor, status of the "uninvolved" urothelium, and status of the patient (eg, bladder capacity, bladder function, comorbidities). Bladder preservation as an alternative to cystectomy is generally reserved for patients with smaller solitary tumors, negative nodes, no carcinoma in situ, no tumor-related hydronephrosis, and good pretreatment bladder function. Patients who are medically fit for radical cystectomy but who have hydronephrosis are poor candidates for bladder-sparing procedures.[51,52] Maximal TURBT with concurrent chemoRT should be given as primary treatment for these patients, with RT alone or TURBT alone reserved for select patients.

For patients who have tumor after reassessment, cystectomy is preferred if feasible. Close cystoscop-

ic observation with TURBT alone, chemotherapy alone, and concurrent chemoRT (if no previous RT) are potential treatment options. When possible, bladder-sparing options should be chosen in the context of clinical trials.

RT With Concurrent Chemotherapy Following TURBT as Primary Treatment for MIBC: Several groups have investigated the combination of concurrent or sequential chemotherapy and RT after TURBT. First, an endoscopic resection that is as complete as possible is performed. Incomplete resection is an unfavorable prognostic factor for the ability to preserve the bladder.[53–55]

Radiation Therapy Oncology Group protocol 89-03 compared concurrent cisplatin and RT with or without 2 cycles of induction CMV.[52] No difference in complete clinical response or 5-year OS was observed between the treatment arms. Other studies also reported no significant survival benefit for neoadjuvant chemotherapy before bladder-preserving chemotherapy with radiation therapy.[54,56]

Conversely, results from several prospective trials have demonstrated the effectiveness of this approach. In the RTOG 89-03 trial in which 123 patients with clinical stage T2–T4a were treated with RT plus concurrent cisplatin, with or without induction CMV, 5-year OS was approximately 49% in both arms.[52] The subsequent RTOG 95-06 trial treated 34 patients with twice-daily irradiation and concurrent cisplatin and 5-FU and reported a 3-year OS rate of 83%.[57] In the RTOG 97-06 trial, 47 patients received twice-daily irradiation and concurrent cisplatin, and also received adjuvant chemotherapy with CMV[58]; the 3-year OS rate was 61%. In the RTOG 99-06 study, 80 patients received twice-daily irradiation plus cisplatin and paclitaxel, followed by adjuvant cisplatin and gemcitabine; the 5-year OS rate was 56%.[59] In RTOG 0233, 97 patients received twice-daily radiation with concurrent paclitaxel plus cisplatin or 5-FU plus cisplatin; the 5-year OS was 73%.[60] Taken together, the CR rates ranged from 59% to 81%.

Up to approximately 80% of long-term survivors maintain an intact bladder, whereas others ultimately require radical cystectomy.[51–59] A combined analysis of survivors from these 4 trials, with a median follow-up of 5.4 years, showed that combined-modality therapy was associated with low rates of late grade 3 toxicity (5.7% genitourinary and 1.9% gastrointestinal).[61] No late grade 4 toxicities or treatment-related deaths were recorded.

Chemotherapy Following TURBT as Primary Treatment for MIBC

Chemotherapy alone is considered to be inadequate without additional treatment to the bladder and remains investigational. Studies showed that the proportions of pathologic CR rates in the bladder using neoadjuvant chemotherapy alone were only up to 38%.[17] A higher proportion of bladders can be rendered tumor-free and therefore preserved when chemotherapy is combined with concurrent RT.

RT Following TURBT as Primary Treatment for MIBC: RT alone is inferior to RT combined with chemotherapy for patients with an invasive bladder tumor, and is not considered standard for patients who can tolerate combined therapy.[62,63] In a randomized trial of 360 patients, RT with concurrent mitomycin C and 5-FU improved the 2-year locoregional DFS rate from 54% (RT alone) to 67% (P=.01), and 5-year OS rate from 35% to 48% (P=.16), without increasing grade 3/4 acute or late toxicity.[63] Hence, RT alone is only indicated for those who cannot tolerate a cystectomy or chemotherapy because of medical comorbidities.

TURBT Alone as Primary Treatment for MIBC: TURBT alone may be an option for patients with cT2, cT3, or cT4a disease who are not candidates for cystectomy. TURBT alone may be curative in selected cases that include solitary lesions <2 cm that have minimally invaded the muscle. These cases should also have no associated in situ component, palpable mass, or associated hydronephrosis.[64]

If considered for TURBT alone, patients should undergo an aggressive re-resection of the site within 4 weeks of the primary procedure to ensure that no residual disease is present. If the repeat TURBT is negative for residual tumor, patients can be managed conservatively with repeat endoscopic evaluations and cytologies every 3 months until a relapse is documented. The stage of the lesion documented at relapse would determine further management decisions.

Treatment of T2, T3, and T4a Tumors

The critical issues in the management and prognosis of these patients are whether a palpable mass is appreciated at EUA and if the tumor has extended through the bladder wall. Tumors that are organ-

confined (T2) have a better prognosis than those that have extended through the bladder wall into the perivesical fat (T3) and beyond. T4a tumors involve the prostatic stroma, uterus, or vagina and are typically surgically managed similar to T3 tumors.

Primary surgical treatment for cT2, cT3, and cT4a lesions with no nodal disease seen on abdominal/pelvic CT or MRI scan is a radical cystectomy and pelvic lymphadenectomy. Neoadjuvant chemotherapy is recommended (category 1). If no neoadjuvant cisplatin-based chemotherapy is given, postoperative adjuvant chemotherapy may be considered based on pathologic risk, such as positive nodes or pT3–T4 lesions.

Partial cystectomy along with neoadjuvant cisplatin-based chemotherapy can be considered for cT2 disease with a single tumor in a suitable location and no presence of Tis. Partial cystectomy is not an option for cT3 or cT4a patients. If no neoadjuvant therapy is given, adjuvant RT or chemotherapy based on pathologic risk (ie, positive nodes, positive margin, high-grade lesions, pT3–T4 lesions) may be considered.

Bladder preservation with maximal TURBT followed by concurrent chemoRT may be considered. Candidates for this bladder-sparing approach include patients with tumors that present without hydronephrosis or with tumors that allow a visibly complete or a maximally debulking TURBT. RT with concurrent cisplatin-based chemotherapy or 5-FU plus mitomycin as a radiosensitizer is the most common and well-studied chemoRT method used to treat MIBC.[50–54,62,63,65] The following radiosensitizing regimens are recommended: cisplatin plus 5-FU; cisplatin plus paclitaxel; and 5-FU plus mitomycin C. Doublet chemotherapy is generally preferred. Cisplatin alone or low-dose gemcitabine (category 2B) may be considered as alternative regimens.

After a complete TURBT, 60 to 66 Gy of external-beam RT is administered. Two doses of concurrent radiosensitizing chemotherapy may be given on weeks 1 and 4 (although weekly schedules are possible as well). Alternatively, an induction RT dose of 40 to 45 Gy may be given following complete TURBT. The overall tumor status should be reassessed 3 weeks after radiation if 40 to 45 Gy was initially administered, or 2 to 3 months after if the full dose of 60 to 66 Gy was delivered. If no residual tumor is detected, appropriate options include observation or completion of RT up to 66 Gy. If residual disease is present, cystectomy is preferred.

In patients with extensive comorbid disease or poor performance status who are noncystectomy candidates, treatment options include concurrent chemoRT, RT alone, or TURBT alone. Based on high-level evidence showing superiority to RT alone, the NCCN Panel recommends chemoRT with cisplatin alone or 5-FU and mitomycin C.[62,63] The overall tumor status should be reassessed 2 to 3 months after treatment. If no tumor is evident, the patient should be observed. If tumor is observed, chemotherapy, concurrent chemoRT (if no prior RT), palliative TURBT, or best supportive care may be given.

Treatment of T4b Disease or Positive Nodes

For patients with cT4b disease and negative nodes on abdominal/pelvic CT or MRI scans or biopsy, the primary treatment recommendation includes 2 to 3 courses of chemotherapy with or without RT followed by evaluation with cystoscopy, EUA, TURBT, and imaging of the abdomen and pelvis. If no evidence of tumor is present after primary treatment, consolidation chemotherapy or completion of definitive RT may be considered. If a partial radiation dose of 40 to 45 Gy was given as primary treatment, completion of definitive RT is recommended. Alternatively, adjuvant treatment with chemoRT may be initiated if the patient did not receive prior RT. In general, cT4b disease is considered unresectable. However, in patients with disease that responds to treatment, cystectomy may be an option if the tumor becomes technically resectable.

If residual disease is noted upon evaluation after primary therapy, systemic therapy or cystectomy is recommended. Systemic therapy may include a checkpoint inhibitor, chemoRT (if no prior RT), or a change in chemotherapy. Cystectomy, if feasible, is an option.

For patients with abnormal nodes documented by imaging, a biopsy should be considered, if technically possible, to confirm nodal spread. Patients with positive nodes should receive chemotherapy with or without radiation and should be evaluated with cystoscopy, EUA, TURBT, and abdominal/pelvic imaging. If no residual tumor is detected, patients may receive a radiation boost or a cystectomy. If tumor is still present following primary therapy, these pa-

tients should follow treatment of recurrent or persistent disease.

Follow-up

Results from a meta-analysis of 13,185 patients who have undergone cystectomy reported a 0.75% to 6.4% prevalence of upper tract recurrence.[66] Surveillance by urine cytology or upper tract imaging detected recurrences in 7% and 30% of cases, respectively.

Follow-up after cystectomy should include urine cytology, liver function tests, creatinine, and electrolytes. Imaging of the chest, upper tracts, abdomen, and pelvis should be conducted at intervals based on the recurrence risk. Patients should be monitored annually for vitamin B_{12} deficiency if a continent urinary diversion was created. Consider urethral wash cytology for patients with an ileal conduit or continent catheterizable diversion, particularly if Tis was found within the bladder or prostatic urethra. For details of follow-up recommendations, see "Follow-up" in the complete version of these guidelines, at NCCN.org (page BL-E).

Follow-up after a partial cystectomy is similar to that for a radical cystectomy, with the addition of monitoring for relapse in the bladder by serial cytologic examinations and cystoscopies (may include selected mapping biopsy).

For patients who have a preserved bladder, there is a risk for recurrence in the bladder or elsewhere in the urothelial tract and distantly. Imaging studies and laboratory testing should be performed as outlined under post-cystectomy follow-up. Additionally, continued monitoring of the urothelium with cystoscopy and urinary cytologies with or without mapping biopsy is a routine part of the management of all cases in which the bladder is preserved.

Recurrence or Persistent Disease

Metastatic disease or local recurrence may be managed with cystectomy, systemic therapy, or palliative TURBT and best supportive care.

A positive cytology with no evidence of disease in the bladder should prompt retrograde selective washings of the upper tract and a biopsy of the prostatic urethra. If the results are positive, patients are managed as described in the following sections for treatment of upper genitourinary tract tumors or urothelial carcinoma of the prostate.

For patients with a preserved bladder, local recurrence or persistent disease should be evaluated as a new cancer. Recurrences are treated based on the extent of disease at relapse, with consideration of prior treatment. As previously discussed, Tis, Ta, or T1 tumors are generally managed with intravesical bacillus Calmette-Guérin (BCG) therapy or cystectomy. If no response is noted after BCG treatment, a cystectomy is advised. Invasive disease is generally managed with radical cystectomy, and a second attempt at bladder preservation is not advisable. Cystectomy may not be possible in a patient who has undergone a full course of external-beam RT and has bulky residual disease. For these patients, palliative TURBT and best supportive care is advised.

Subsequent-line therapy for metastatic disease or local recurrence includes checkpoint inhibitors, chemotherapy, chemoRT (if no previous RT) or RT (see "Follow-up" in the complete version of these guidelines, at NCCN.org [BL-E], "Recurrent or Persistent Disease" on page 1246, and "Metastatic Urothelial Bladder Cancer," below).

Metastatic Urothelial Bladder Cancer

Approximately 4% 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 approximately 10% to 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. If the evidence of spread is limited to nodes, nodal biopsy should be considered and patients should be managed as previously outlined for positive nodal disease (see "Treatment of cT4b Disease or Positive Nodes," page 1259, and cT4b, Primary and Adjuvant Treatment, page 1244). Patients who present with disseminated metastatic disease are generally treated with systemic

chemotherapy. Management of persistent disseminated disease may involve chemotherapy, radiation, or a combination.

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[67,68] and ddMVAC[23,35] 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.[37] 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% and PFS, 9.8% vs 11.3%, respectively).[68] Another large, randomized, phase III trial compared ddMVAC with standard (28-day) MVAC.[23,35] 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 1 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 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, atezolizumab or pembrolizumab are now appropriate first-line options (see "Targeted Therapies," page 1262). Alternatively, carboplatin may be substituted for cisplatin in the metastatic setting for cisplatin-ineligible patients, such as those with a GFR <60 mL/min. A phase II/III study assessed 2 carboplatin-containing regimens in medically unfit patients (performance status 2).[69] The overall response rate 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 both front-line and palliative therapies. Based on these results, several groups are exploring 2- and 3-drug combinations using these agents, with and without cisplatin, as initial therapy. A randomized phase III trial was conducted to compare GC and GC plus paclitaxel in 626 patients with locally advanced or metastatic urothelial cancer.[70] 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,[71] gemcitabine/paclitaxel,[72] cisplatin/gemcitabine/paclitaxel,[73] carboplatin/gemcitabine/paclitaxel,[74] and cisplatin/gemcitabine/docetaxel,[75] 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," page 1262).

Although current data are insufficient to recommend the above 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 comor-

bidities (see "Principles of Systemic Therapy," page 1249–1251). Additionally, 2 checkpoint inhibitors, atezolizumab and pembrolizumab, have been FDA-approved for use as a first-line therapy in these patients. Consideration of checkpoint inhibitors must be integrated into the therapeutic planning for all patients with locally advanced and metastatic disease (see "Targeted Therapies," next column). The NCCN 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.

Studies have shown that surgery or RT 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 Panel for all patients when appropriate, but is strongly recommended for subsequent-line therapy, 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, and the following chemotherapies: docetaxel, paclitaxel, gemcitabine, or pemetrexed monotherapy.[76–79] Other options include nab-paclitaxel; ifosfamide; methotrexate; ifosfamide, doxorubicin, and gemcitabine; gemcitabine and paclitaxel; GC; and ddMVAC.

Chemoradiotherapy for Metastatic Disease

Chemotherapy is sometimes combined with palliative radiation to treat metastases or pelvic recurrence after cystectomy. However, concurrent chemotherapy is inappropriate if high-dose radiation (>3 Gy fractions) is used. The radiosensitizing chemotherapy regimens remain controversial in this setting. Possible options include cisplatin (category 2A); docetaxel or paclitaxel (category 2B); 5-FU with or without mitomycin C (category 2B); capecitabine (category 3); and low-dose gemcitabine (category 2B). RT alone can also be considered as a subsequent-line therapy for patients with metastatic disease.

Targeted Therapies

Platinum-based chemotherapy has been the standard of care in patients with metastatic disease, with an OS of 9 to 15 months.[68,80] However, in patients with disease that relapses after this type of chemotherapy, the median survival is reduced to 5 to 7 months.[81] Several new agents, notably checkpoint inhibitors for the treatment of metastatic urothelial carcinoma, have data supporting improved outcomes compared with standard therapies. Cancers with higher rates of somatic mutations have been shown to respond better to checkpoint inhibitors.[82–87] Data from The Cancer Genome Atlas rank bladder cancer as the third highest mutated cancer,[88,89] 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. All of these approvals as a subsequent treatment option have been based on category 2 level evidence, with the exception of pembrolizumab, which has category 1 level evidence supporting the approval.

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.[90] An open-label, randomized, phase III trial compared pembrolizumab versus 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 adverse events (AEs) occurred in the pembrolizumab-treated patients compared with those treated with chemotherapy (15.0% vs 49.4%).[91] Results from this phase III trial have lead the NCCN Panel to assign pembrolizumab a category 1 recommendation as a second-line therapy. A 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 29%, with 7% of patients achieving a CR. Grade 3 or 4 treatment-related AEs occurred in 18% of patients treated with pembrolizumab.[92]

Data from a 2-cohort, multicenter, phase II trial evaluated atezolizumab in patients with metastatic disease. Cohort 2 of the trial enrolled 310 patients with metastatic urothelial carcinoma post-platinum treatment and showed a significantly improved overall response rate compared with historical controls (15% vs 10%; *P*=.0058).[93] 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, there were no treatment-related deaths in this trial, suggesting good tolerability. In cohort 1 of the same phase II 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 objective response rate (ORR) of 23%, with 9% of patients showing a CR. Median OS was 15.9 months, and grade 3 or 4 treatment-related AEs occurred in 16% of patients.[94] A May 2017 press release reported that the phase III IMvigor211 study evaluating atezolizumab compared with chemotherapy in patients with metastatic urothelial carcinoma post-platinum treatment did not meet its primary end point of OS.[95] Further examination of the data is ongoing to better understand the results and define the role of atezolizumab as a post-platinum treatment option for metastatic urothelial carcinoma.

A phase II trial in patients with locally advanced or metastatic urothelial carcinoma that progressed after at least 1 platinum-containing regimen reported an overall objective response in 52 of 265 patients (19.6%; 95% CI, 15.0–24.9) after treatment with nivolumab, which was unaffected by PD-1 tumor status.[96] Of the 270 patients enrolled in the study, grade 3 or 4 treatment-related AEs were reported in 18%, and 3 resulted from treatment.[96] 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 early phase I/II data reporting an ORR of 24% (95% CI, 15.3%–35.4%) that was unaffected by PD-1 tumor status.[97] 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.[97]

Early results from a phase I/II multicenter study of durvalumab for 61 patients with PD-L1–positive inoperable or metastatic urothelial bladder cancer whose tumor had 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.[98] A 2017 update on this study (N=103) showed a 29.5% ORR for PD-L1–high disease and a 7.7% ORR for PD-L1–low/negative disease. The OS rate at 6 months was 68.4% for the PD-L1–high group and 44.7% for the PD-L1–low/negative group. Median duration of response was not yet reached at the time of data cutoff. Grade 3 or 4 treatment-related AEs occurred in 5.2% of treated patients and 3 patients had a grade 3 or 4 immune-mediated AE.[99]

Avelumab is another PD-L1 inhibitor currently in clinical trials to evaluate its activity in the treatment of bladder cancer. Results from the phase 1b

trial for 44 patients with platinum-refractory disease demonstrated an ORR of 18.2% that consisted of 5 CRs and 3 partial responses following treatment with avelumab. The median PFS was 11.6 weeks and 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.[100] A recent abstract reported results of the same trial for 241 patients with platinum-refractory metastatic urothelial carcinoma or who were ineligible for cisplatin-based chemotherapy. This study reported an ORR of 17.6%, with 9 CRs and 18 partial responses. Median PFS was 6.4 weeks and median OS was 7.0 months. Grade 3 or 4 treatment-related AEs occurred in 7.5% of patients treated with avelumab, and 2.5% of patients had a grade 3 or 4 immune-related AE.[101]

The value of checkpoint inhibitors is reflected in the unanimous decision by the NCCN Panel to include pembrolizumab, atezolizumab, nivolumab, durvalumab, and avelumab as second-line systemic therapy options after platinum-based therapy (and, in the case of atezolizumab and pembrolizumab, as first-line therapy options for patients who are not eligible for cisplatin-containing chemotherapy) for locally advanced or metastatic disease (see "Systemic Therapy" on page 1249–1251). With the exception of pembrolizumab as a subsequent treatment option (category 1), the use of checkpoint inhibitors 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. Continued monitoring for recurrence is an essential part of management, because most recurrences are superficial 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 Bladder Cancer Panel

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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 conflict:
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A. Karim Kader, MD, PhD, FRCSC: SNP Bio Inc
[b]The following individuals have disclosed that they have a spouse/domestic partner/dependent potential conflict:
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