National Comprehensive Cancer Network®

## NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

# Bladder Cancer

Version 1.2025 — March 25, 2025

**NCCN.org**

**NCCN recognizes the importance of clinical trials and encourages participation when applicable and available. Trials should be designed to maximize inclusiveness and broad representative enrollment.**

**NCCN Guidelines for Patients® available at www.nccn.org/patients**

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¶ Surgery/Surgical oncology
ϖ Urology
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NCCN Guidelines Panel Disclosures

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Find an NCCN Member Institution: https://www.nccn.org/home/member-institutions.

**NCCN Categories of Evidence and Consensus:** All recommendations are category 2A unless otherwise indicated.

See NCCN Categories of Evidence and Consensus.

**NCCN Categories of Preference:** All recommendations are considered appropriate.

See NCCN Categories of Preference.

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**Updates in Version 1.2025 of the NCCN Guidelines for Bladder Cancer from Version 7.2024 include:**

Global
• Language changed: ~~Tis~~ *CIS*

BL-2
• AUA Risk Stratification for Non-Muscle Invasive Bladder Cancer, High Risk, bullet 2, sub-bullet 1: ~~Variant histologies~~ *Certain histopathologic subtypes*
• Reference revised: ~~Reproduced~~ *Adapted* with permission from Chang SS, Boorjian SA, Chou R, et al. Diagnosis and treatment of non-muscle invasive bladder cancer: AUA/SUO guideline. J Urol 2016;196:1021-1029.
• Footnote m revised: ~~Montironi R, et al. Int J Surg Pathol 2005;13:143-153.~~ *See aggressive subtype histologies listed on Bladder Cancer: Non-Urothelial and Urothelial with Subytpe Histology (BL-D).*

BL-3
• Footnote removed: Valrubicin is approved for BCG-refractory CIS.

BL-4
• Evaluation: ~~If initial positive cytology, consider repeating cytology test within 3 months or If repeated positive cytology,~~
• Evaluation, sub-bullet 1 added: Repeat cytology within 3 months
• Footnote v added: If enhanced cystoscopy is not readily available, proceed to cystoscopy with bladder biopsies with or without uroscopy.

BL-5
• Primary treatment, statement removed: or TURBT (also for BL-7)

BL-6
• Adjuvant treatment
  ▸ Sub-sub bullet 2 modified: Consider adjuvant nivolumab *or pembrolizumab*
  ▸ Sub-bullet 2 modified: If cisplatin neoadjuvant chemotherapy given and ypT2–ypT4a or ypN+, consider nivolumab *or pembrolizumab*

BL-8
• Primary treatment: Concurrent chemoradiotherapy pathway removed
• Subsequent treatment modified: ~~Treat as metastatic disease~~ *Treat recurrence according to disease stage* ~~(BL-10)~~
• Footnote removed: Principles of Instillation Therapy (BL-F).
• Footnote gg modified: ~~Molecular/genomic testing in a Clinical Laboratory Improvement Amendments (CLIA)- approved laboratory, including FGFR RGQ RT-PCR for FGFR3 genetic alterations and IHC for HER2 overexpression. See Discussion.~~ *See Principles of Alternative Risk Classifiers and Biomarkers (BL-I).* (Also for BL-9 and BL-10)
• Footnote ii added: in the setting of previous complete response, if recurrence, treat according to stage of recurrent disease.

BL-A 3 of 5
• Follow-up, sub-bullet 1 modified: Upper tract and abdomen/pelvis imaging *with contrast* as defined previously at 3- to 6-month intervals for 2 years, then abdomen/pelvis imaging *with contrast* annually for up to 5 years and as indicated thereafter.

BL-B 2 of 4
• Radical Cystectomy/Cystoprostatectomy, bullet 1 modified: In non–muscle-invasive disease, radical cystectomy is generally reserved for residual high-grade cT1, ~~subtype histology~~ *aggressive histopathologic subtypes,* lymphovascular invasion, concomitant CIS, and BCG-unresponsive disease *(see Bladder Cancer: Non-Urothelial and Urothelial with Subtype Histology [BL-D])*.

BL-B 4 of 4
• Percutaneous or ureteroscopic surgical procedures, sub-bullet 3 modified: Laser therapies ~~(Nd:YAG – penetration 4–6 mm; Ho:YAG – shallow penetration <0.5 mm)~~

Continued
UPDATES

 

**Updates in Version 1.2025 of the NCCN Guidelines for Bladder Cancer from Version 7.2024 include:**

• Bullet 7 modified: Topical immunotherapy and chemotherapy management *(see Principles of Instillation Therapy [BL-F 3 of 4] for more information).*
• Bullets removed (added to BL-F 3 of 4):
  ▸ BCG, mitomycin
  ▸ Route of administration might include percutaneous antegrade (preferred) or retrograde ureteral catheters
  ▸ Induction and maintenance therapy regimens, similar to intravesical therapy, can be used

BL-D 1 of 2
• Page has been extensively modified

BL-E 1 of 6
• Table 1, High Risk, very high risk features, bullet modified: ~~Variant histologies~~ *Certain histopathologic subtypes*
• Footnotes removed:
  ▸ Abdominal/pelvic imaging include CT or MRI.
  ▸ Principles of Imaging for Bladder/Urothelial Cancer
• Footnotes modified:
  ▸ ~~Upper tract imaging includes CTU, MRU, intravenous pyelogram (IVP), retrograde pyelography, or ureteroscopy.~~ *Principles of Imaging for Bladder/ Urothelial Cancer (BL-A).*
  ▸ ~~Montironi R, et al. Int J Surg Pathol 2005;13:143-153.~~ *See Principles of Pathology (BL-D 1 of 2)*

BL-E 3 of 6
• Blood tests, year 2-5, bullet 3 modified: $B_{12}$ annually *based on clinical judgment* (also for BL-E 4 of 6)
• Blood tests, year 5-10 and >10: $B_{12}$ annually *based on clinical judgment* (also for BL-E 4 of 6)
• Urine tests, year 1, bullet 1 modified: *Consider* urine cytology every 6–12 mo (also for BL-E 4 of 6)

BL-E 6 of 6
• Blood tests, bullet 2 modified: B12 annually for patients who had undergone a cystectomy *based on clinical judgment*

BL-F 3 of 4
• Topical or Percutaneous Administration of Chemotherapy or BCG
  ▸ Bullet added: Topical immunotherapy and chemotherapy management
  ▸ Sub-bullet added: BCG, mitomycin
  ▸ Sub-bullet added: Route of administration might include percutaneous antegrade (preferred) or retrograde ureteral catheters
  ▸ Sub-bullet added: Induction and maintenance therapy regimens, similar to intravesical therapy, can be used

BL-G
• Section extensively modified

BL-I
• Section new to Guidelines

UTT-1
• Primary treatment, low grade: Endoscopic resection ± postsurgical intrapelvic chemotherapy ~~or BCG~~

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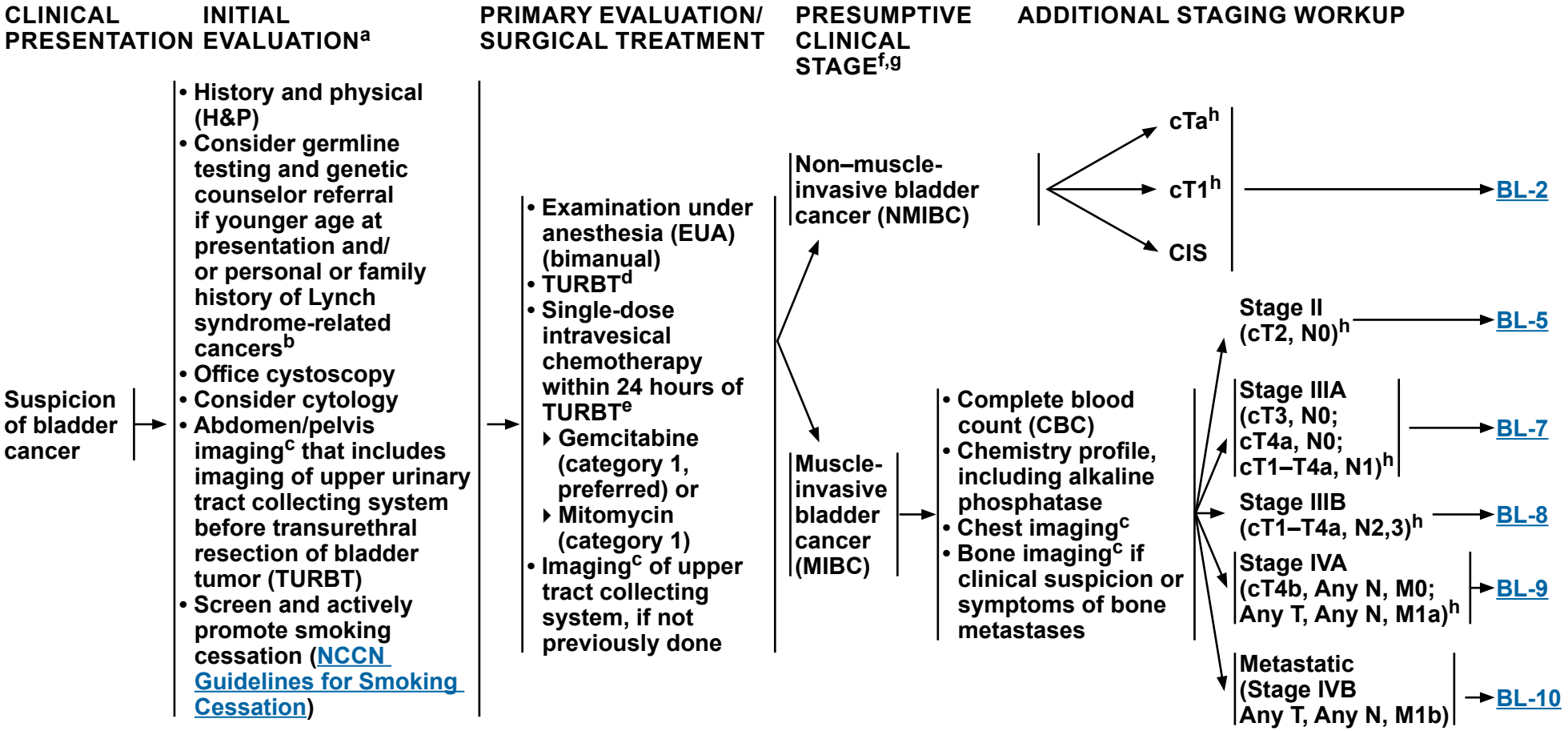
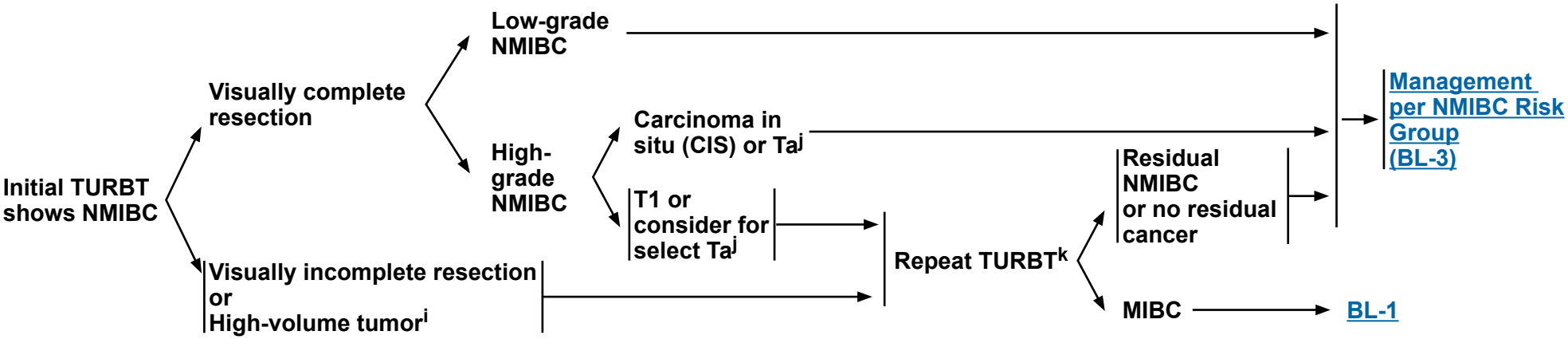



[a] For tools to aid optimal assessment and comprehensive care of older adults with cancer, see NCCN Guidelines for Older Adult Oncology.
[b] NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric – Criteria for the Evaluation of Lynch Syndrome Based on Personal or Family History of Cancer.
[c] Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
[d] Principles of Surgical Management (BL-B).
[e] Immediate intravesical chemotherapy reduces the recurrence rate by 35% for selected patients. Most efficacious in patients with low-grade, low-volume Ta urothelial cancer. Post-TURBT intravesical chemotherapy should not be utilized if concern for bladder perforation. See Principles of Instillation Therapy (BL-F).
[f] Principles of Pathology Management (BL-C).
[g] Bladder Cancer: Non-Urothelial and Urothelial with Subtype Histology (BL-D).
[h] The modifier "c" refers to clinical staging based on bimanual EUA, endoscopic surgery (biopsy or transurethral resection [TUR]), and imaging studies. The modifier "p" refers to pathologic staging based on cystectomy and lymph node dissection.

**Note: All recommendations are category 2A unless otherwise indicated.**

## RISK STRATIFICATION OF NMIBC




### AUA Risk Stratification for Non–Muscle-Invasive Bladder Cancer*

| Low Risk | Intermediate Risk | High Risk |
|---|---|---|
| • Papillary urothelial neoplasm of low malignant potential<br>• Low grade urothelial carcinoma<br>▸ Ta and<br>▸ ≤3 cm and<br>▸ Solitary | • Low grade urothelial carcinoma<br>▸ T1 or<br>▸ >3 cm or<br>▸ Multifocal or<br>▸ Recurrence within 1 year<br><br>• High grade urothelial carcinoma<br>▸ Ta and<br>▸ ≤3 cm and<br>▸ Solitary | • High grade urothelial carcinoma<br>▸ CIS or<br>▸ T1 or<br>▸ >3 cm or<br>▸ Multifocal<br><br>• Very high risk features (any):<br>▸ BCG unresponsive[l]<br>▸ Certain histopathologic subtypes[m]<br>▸ Lymphovascular invasion<br>▸ Prostatic urethral invasion |

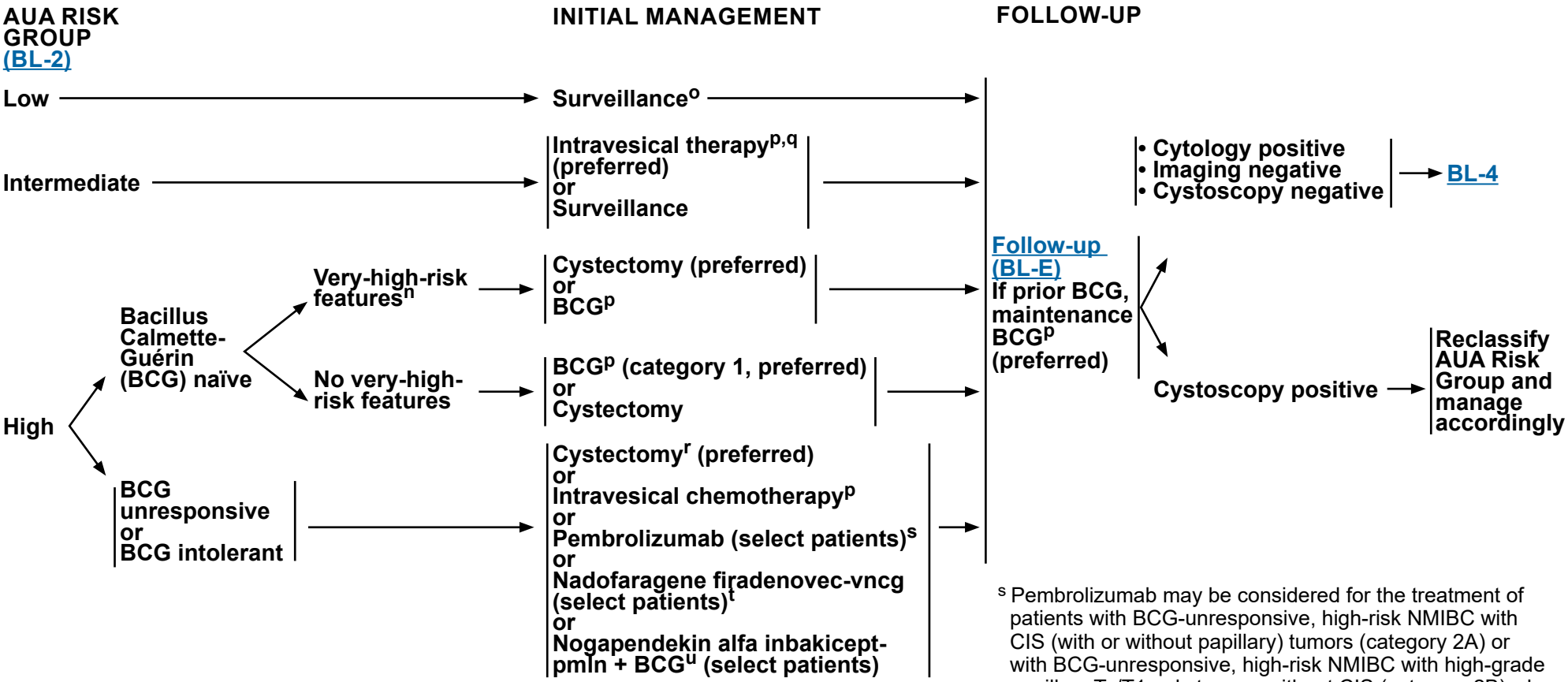
Adapted with permission from Chang SS, Boorjian SA, Chou R, et al. Diagnosis and treatment of non-muscle invasive bladder cancer: AUA/SUO guideline. J Urol 2016;196:1021-1029.
*Within each of these risk strata an individual patient may have more or fewer concerning features that can influence care.

[i] High-volume tumors (large or highly multifocal) are at high risk of residual tumor.
[j] Consider repeat TURBT for high-grade Ta particularly if large, and/or no muscle in specimen.
[k] Muscle should be present in repeat TURBT pathology specimen if possible.

[l] Kamat AM, et al. J Clin Oncol 2016;34:1935-1944.
[m] See aggressive subtype histologies listed on Bladder Cancer: Non-Urothelial and Urothelial with Subtype Histology (BL-D).

**Note: All recommendations are category 2A unless otherwise indicated.**

## MANAGEMENT PER NMIBC RISK GROUP




[n] Lymphovascular invasion, prostatic urethral involvement of tumor, subtype histology (eg, micropapillary, plasmacytoid, sarcomatoid).
[o] Should consider single perioperative instillation of intravesical chemotherapy at time of TURBT.
[p] Principles of Instillation Therapy (BL-F).
[q] Options for intravesical therapy for intermediate-risk disease include BCG and chemotherapy; should consider BCG availability in decision-making.
[r] If not a cystectomy candidate, and recurrence is high-grade 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).
[s] Pembrolizumab may be considered for the treatment of patients with BCG-unresponsive, high-risk NMIBC with CIS (with or without papillary) tumors (category 2A) or with BCG-unresponsive, high-risk NMIBC with high-grade papillary Ta/T1 only tumors without CIS (category 2B) who are ineligible for or have elected not to undergo cystectomy.
[t] Nadofaragene firadenovec-vncg may be considered for the treatment of patients with BCG-unresponsive, high-risk, NMIBC with CIS (with or without papillary) (category 2A) or with BCG-unresponsive, high-risk, NMIBC with high-grade papillary Ta/T1 only tumors without CIS (category 2B).
[u] Nogapendekin alfa inbakicept-pmln in combination with BCG may be considered for the treatment of patients with BCG-unresponsive, high-risk NMIBC with CIS (with or without papillary) tumors.

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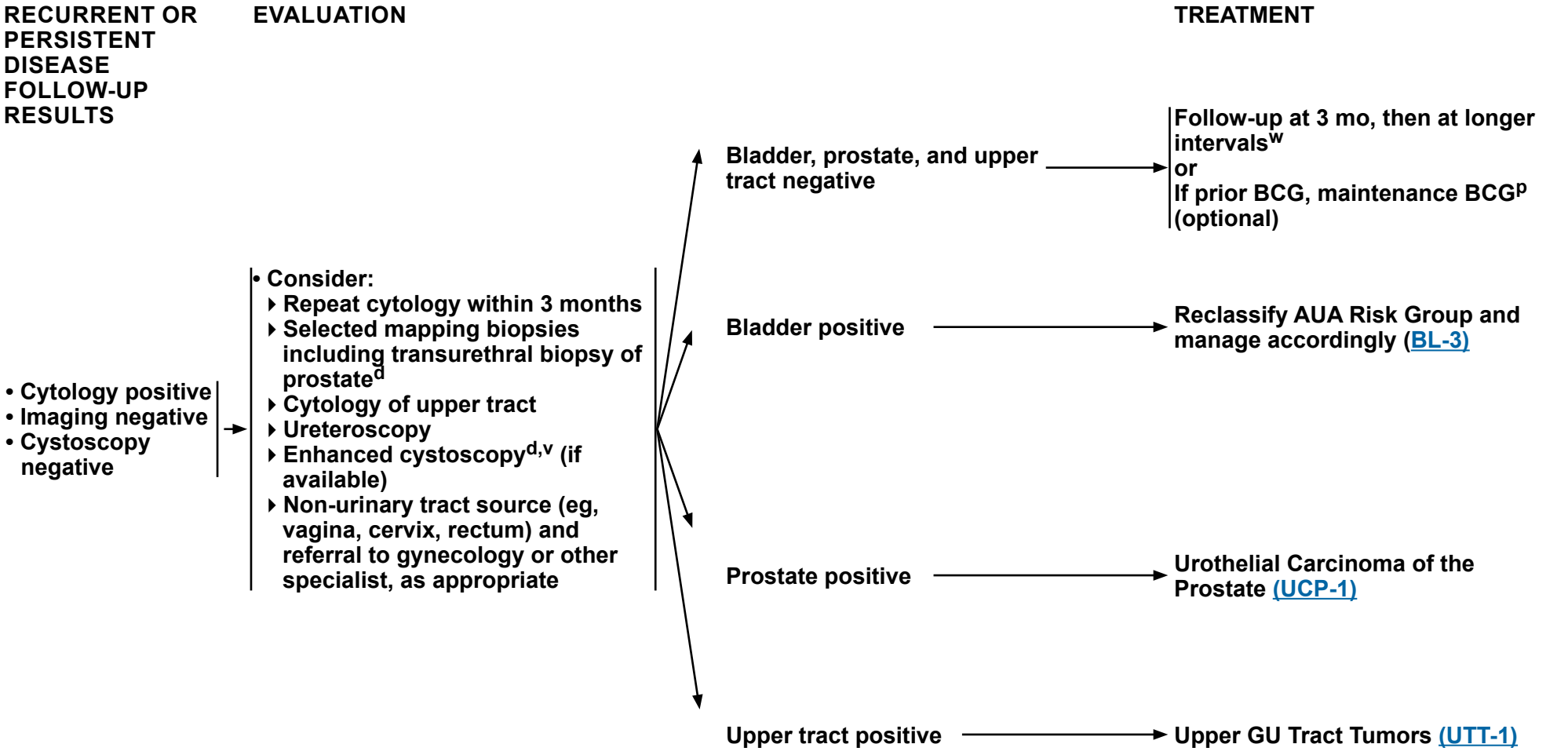
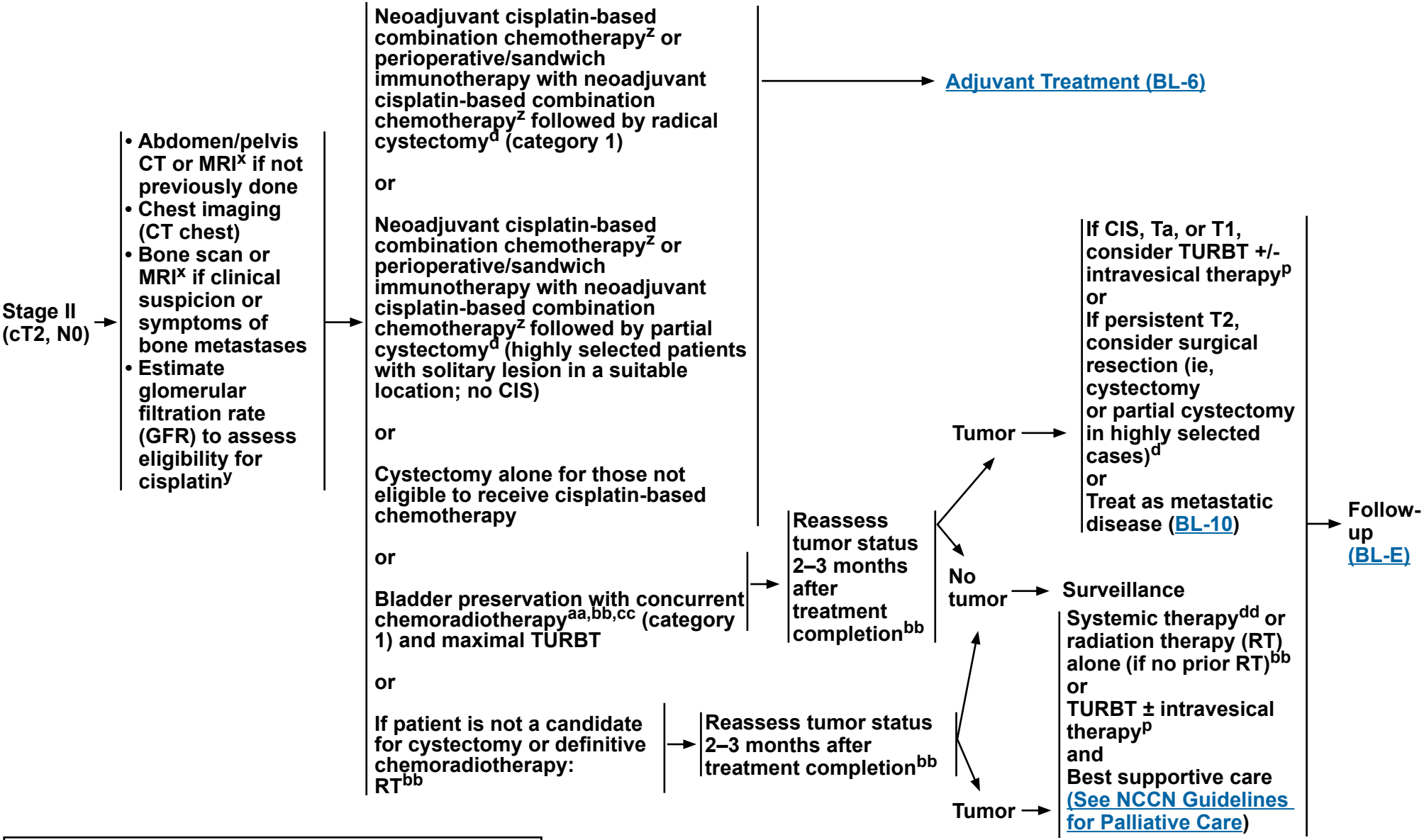



[d] Principles of Surgical Management (BL-B).
[p] Principles of Instillation Therapy (BL-F).
[v] If enhanced cystoscopy is not readily available, proceed to cystoscopy with bladder biopsies with or without uroscopy.
[w] Follow-up (BL-E).

**Note: All recommendations are category 2A unless otherwise indicated.**




**Note: All recommendations are category 2A unless otherwise indicated.**

Footnotes on BL-6

## ADJUVANT TREATMENT

**Following cystectomy** →

- **If gemcitabine + cisplatin + durvalumab given preoperatively, then durvalumab should be used postoperatively.**
- **Based on pathologic risk,**
  - **If no cisplatin neoadjuvant treatment given and pT3, pT4a, or pN+**
    - ◊ **Adjuvant cisplatin-based chemotherapy should be discussed (preferred)[z]**
      **or**
    - ◊ **Consider adjuvant nivolumab[ee] or pembrolizumab[z,ee]**

  **or**
  - **If cisplatin neoadjuvant chemotherapy given and ypT2–ypT4a or ypN+, consider nivolumab[ee] or pembrolizumab[z,ee]**

  **or**
  - **Consider adjuvant RT in selected patients (pT3–4, positive nodes/margins at the time of surgery)[bb] (category 2B)**

→ **Follow-up (BL-E)**

[c] Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
[d] Principles of Surgical Management (BL-B).
[h] The modifier “c” refers to clinical staging based on bimanual EUA, endoscopic surgery (biopsy or TUR), and imaging studies. The modifier “p” refers to pathologic staging based on cystectomy and lymph node dissection.
[p] Principles of Instillation Therapy (BL-F).
[x] Consider FDG-PET/CT scan (skull base to mid-thigh) (category 2B).
[y] For patients with borderline GFR, consider timed urine collection, which may more accurately determine eligibility for cisplatin.
[z] Principles of Systemic Therapy (BL-G 1 of 7).
[aa] Principles of Systemic Therapy (BL-G 5 of 7).
[bb] Principles of Radiation Management of Invasive Disease (BL-H).
[cc] Optimal candidates for bladder preservation with chemoradiotherapy include patients with tumors that present without moderate/severe hydronephrosis, are without concurrent extensive or multifocal CIS, and are <6 cm. Ideally, tumors should allow for a visually complete or maximally debulking TURBT. See Principles of Radiation Management of Invasive Disease (BL-H).
[dd] Principles of Systemic Therapy (BL-G 2 of 7).
[ee] Most appropriate for patients who value an opportunity to delay recurrence even if the chance of cure was not improved, and for whom the risk of side effects was acceptable.

**Note: All recommendations are category 2A unless otherwise indicated.**

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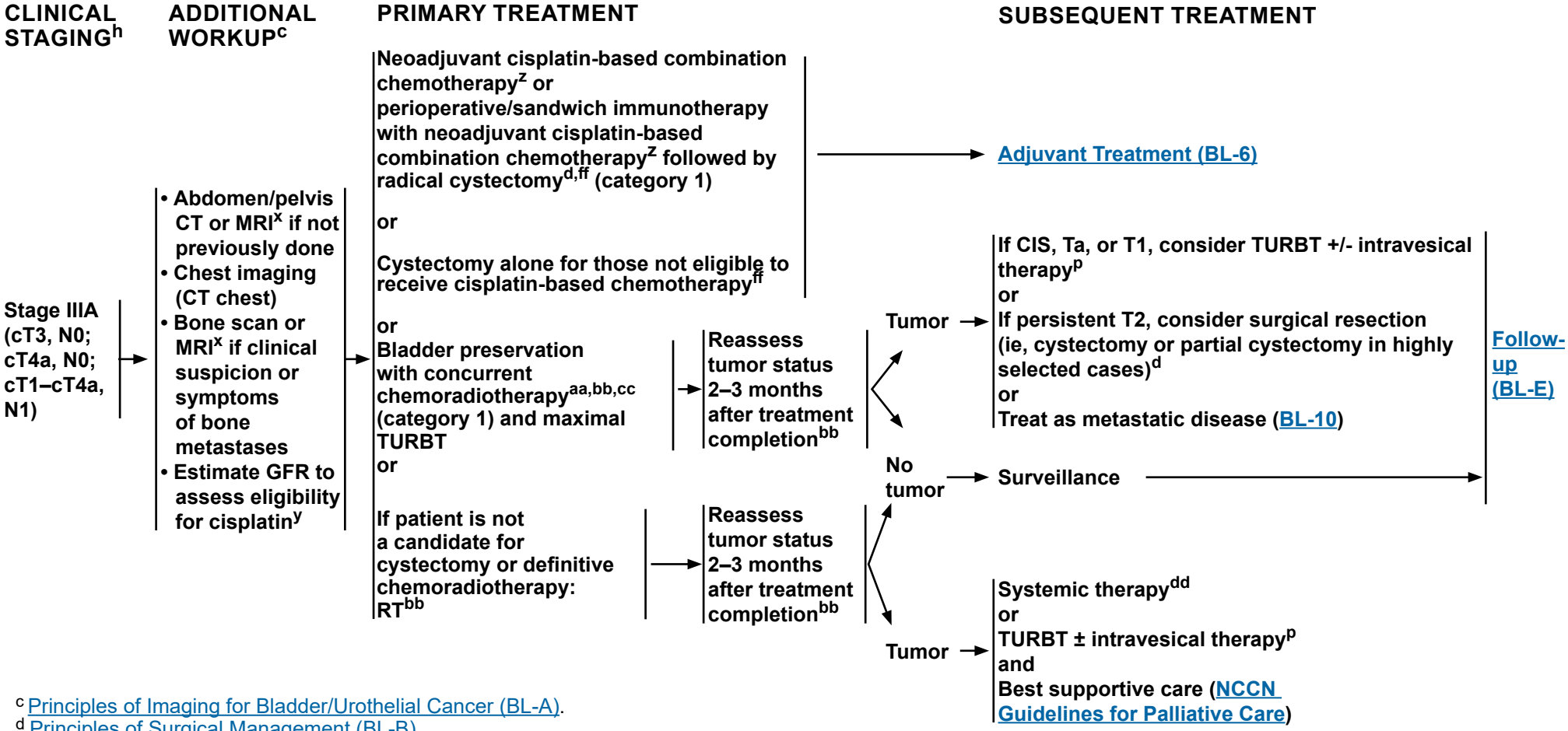


[c] Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
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[p] Principles of Instillation Therapy (BL-F).
[x] Consider FDG-PET/CT scan (skull base to mid-thigh) (category 2B).
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[dd] Principles of Systemic Therapy (BL-G 2 of 7).
[ff] Patients with cN1 disease have better outcomes if they are given neoadjuvant chemotherapy and have a response.

**Note: All recommendations are category 2A unless otherwise indicated.**

Recurrent or Persistent Disease (BL-11)

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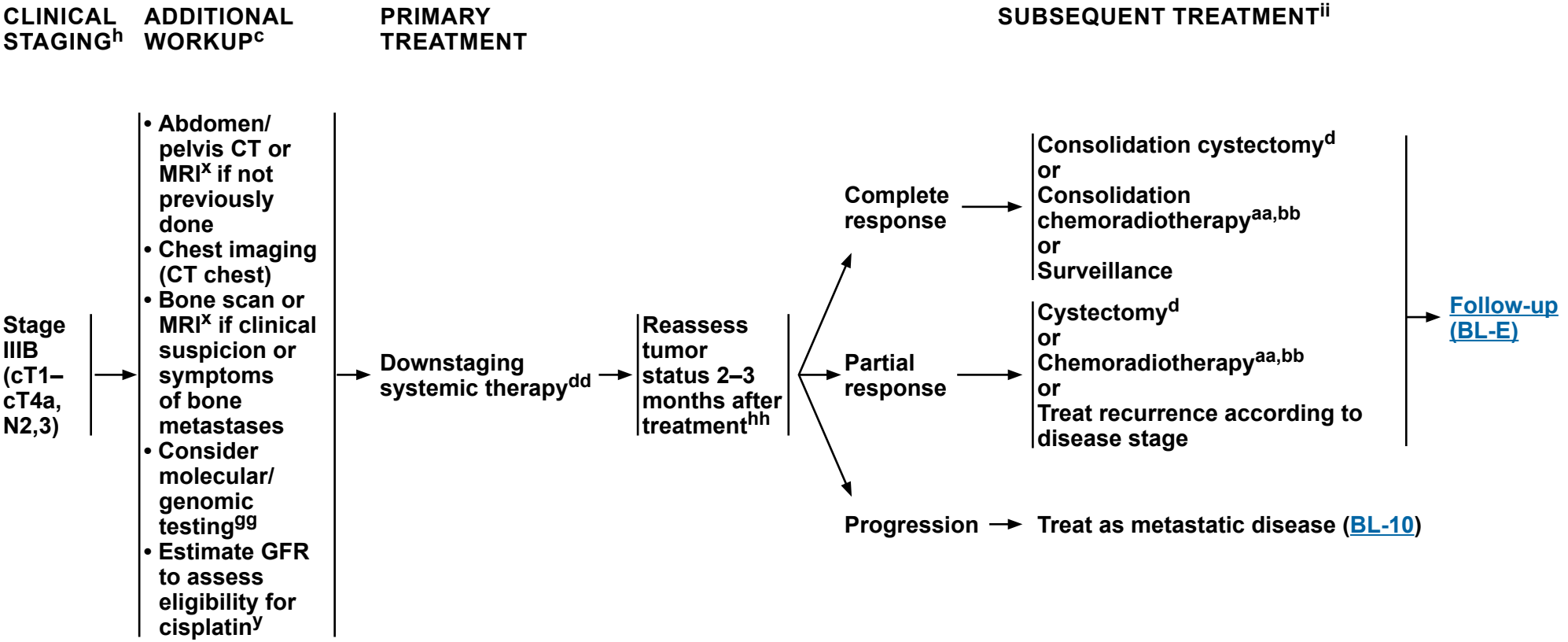


[c] Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
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[h] The modifier “c” refers to clinical staging based on bimanual EUA, endoscopic surgery (biopsy or TUR), and imaging studies. The modifier “p” refers to pathologic staging based on cystectomy and lymph node dissection.
[x] Consider FDG-PET/CT scan (skull base to mid-thigh) (category 2B).
[y] For patients with borderline GFR, consider timed urine collection, which may more accurately determine eligibility for cisplatin.
[aa] Principles of Systemic Therapy (BL-G 5 of 7).
[bb] Principles of Radiation Management of Invasive Disease (BL-H).
[dd] Principles of Systemic Therapy (BL-G 2 of 7).
[gg] See Principles of Alternative Risk Classifiers and Biomarkers (BL-I).
[hh] Imaging with CT of chest/abdomen/pelvis with contrast. If there is no evidence of distant disease on imaging reassessment, further cystoscopic assessment of tumor response in the bladder may be considered.
[ii] In the setting of previous complete response, if recurrence, treat according to stage of recurrent disease.

**Note: All recommendations are category 2A unless otherwise indicated.**

Recurrent or Persistent Disease (BL-11)

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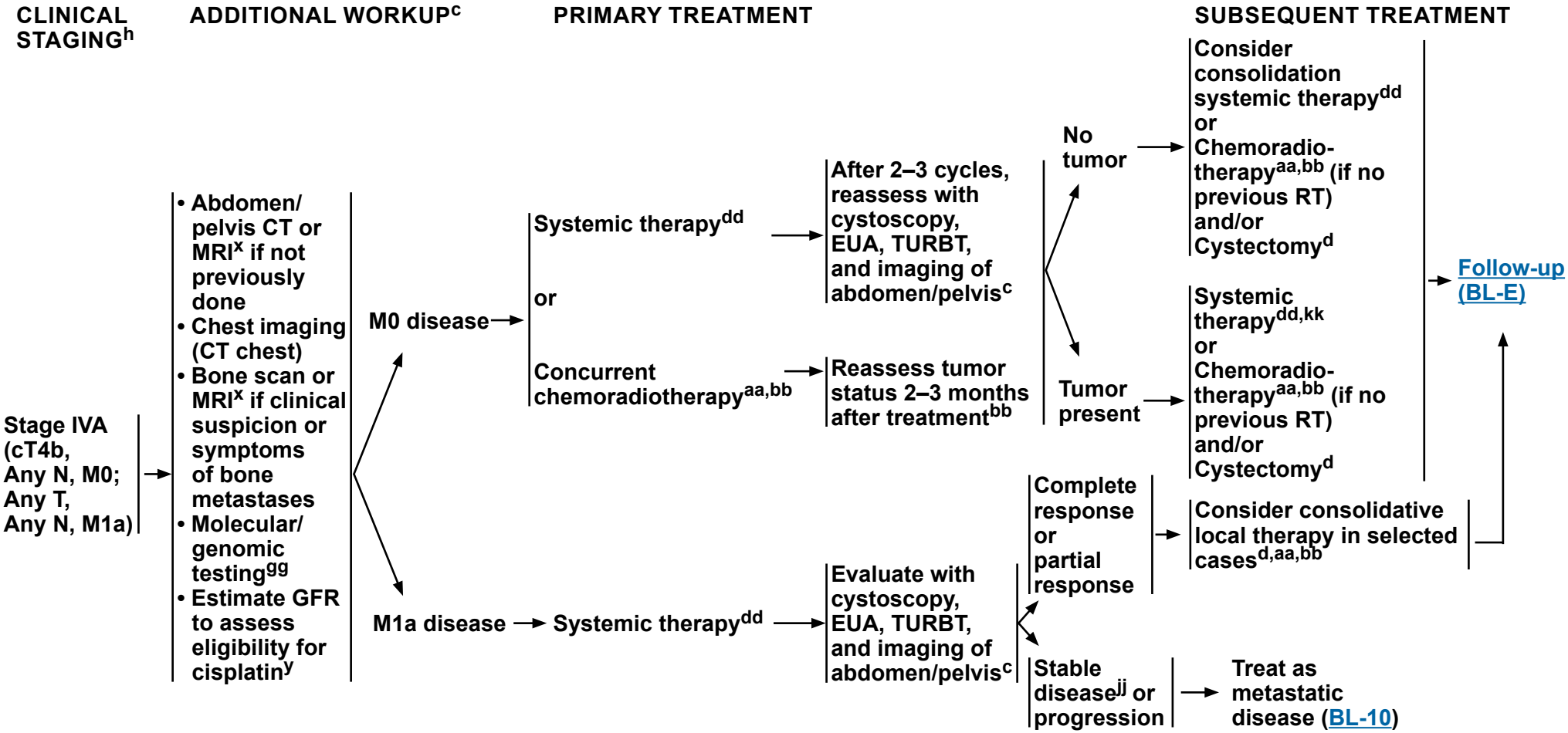
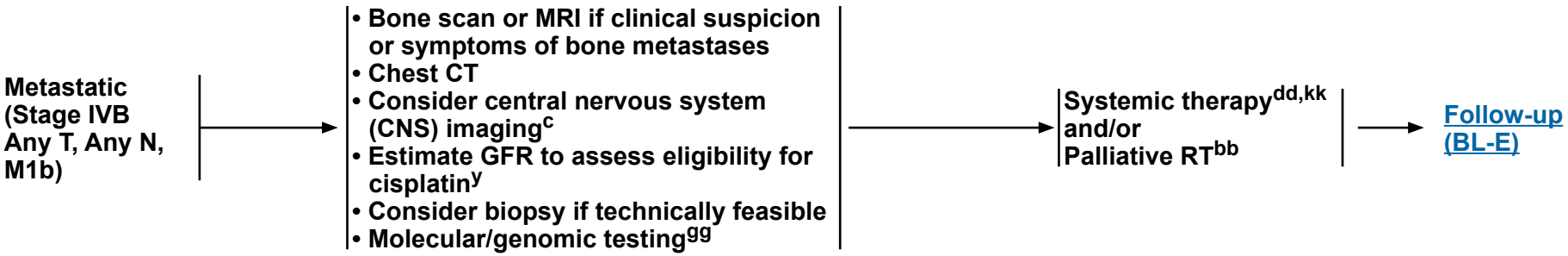



[c] Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
[d] Principles of Surgical Management (BL-B).
[h] The modifier "c" refers to clinical staging based on bimanual EUA, endoscopic surgery (biopsy or TUR), and imaging studies. The modifier "p" refers to pathologic staging based on cystectomy and lymph node dissection.
[x] Consider FDG-PET/CT scan (skull base to mid-thigh) (category 2B).

**Note: All recommendations are category 2A unless otherwise indicated.**

[y] For patients with borderline GFR, consider timed urine collection, which may more accurately determine eligibility for cisplatin.
[aa] Principles of Systemic Therapy (BL-G 5 of 7).
[bb] Principles of Radiation Management of Invasive Disease (BL-H).
[dd] Principles of Systemic Therapy (BL-G 2 of 7).
[gg] See Principles of Alternative Risk Classifiers and Biomarkers (BL-I).
[jj] Non-bulky disease and no significant clinical progression.
[kk] See Principles of Systemic Therapy (BL-G 3 of 7 and 4 of 7).

Recurrent or Persistent Disease (BL-11)




[c] Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
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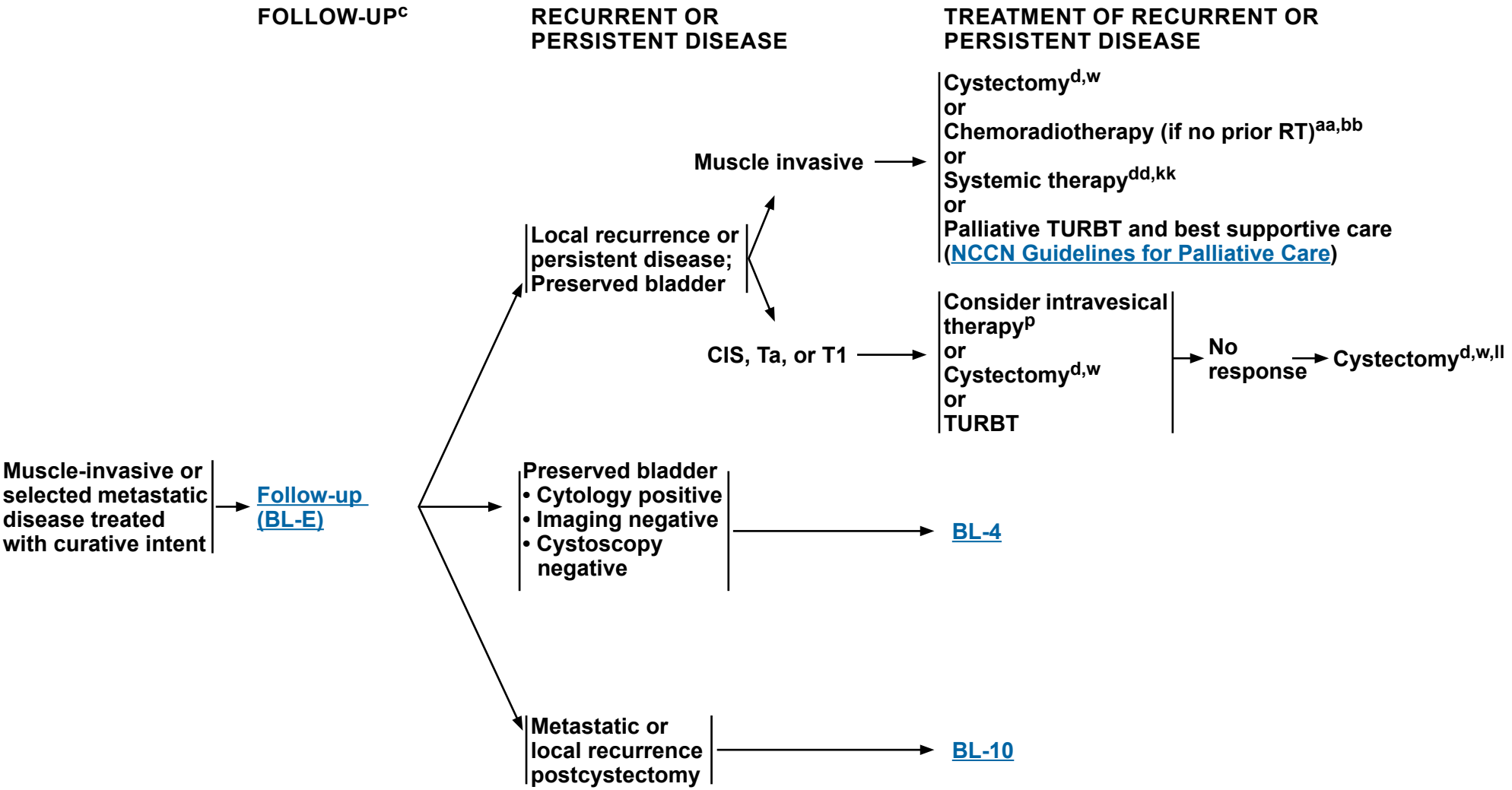
[y] For patients with borderline GFR, consider timed urine collection, which may more accurately determine eligibility for cisplatin.
[bb] Principles of Radiation Management of Invasive Disease (BL-H).
[dd] Principles of Systemic Therapy (BL-G 2 of 7).
[gg] See Principles of Alternative Risk Classifiers and Biomarkers (BL-I).
[kk] See Principles of Systemic Therapy (BL-G 3 of 7 and 4 of 7).

**Note: All recommendations are category 2A unless otherwise indicated.**




[c] Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
[d] Principles of Surgical Management (BL-B).
[p] Principles of Instillation Therapy (BL-F).
[w] Follow-Up (BL-E).
[aa] Principles of Systemic Therapy (BL-G 5 of 7).
[bb] Principles of Radiation Management of Invasive Disease (BL-H).
[dd] Principles of Systemic Therapy (BL-G 2 of 7).
[kk] See Principles of Systemic Therapy (BL-G 3 of 7 and 4 of 7).
[ll] If not a cystectomy candidate, consider concurrent chemoradiotherapy (BL-G 5 of 7) (if no prior RT), change in intravesical agent, or a clinical trial.

**Note: All recommendations are category 2A unless otherwise indicated.**

## 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]**

#### Abdomen and Pelvis Imaging

- **Staging:**
  - **CT urography (CTU) (CT of the abdomen and pelvis without and with intravenous (IV) contrast with excretory imaging).**
  - **MR urography (MRU) may be appropriate, especially 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: (BL-E)**
  - **Upper tract (CTU, MRU, IV pyelogram [IVP], or retrograde ureteropyelography with CT or US, or ureteroscopy) and abdomen/pelvis imaging at baseline. For patients with high-risk NMIBC, upper tract imaging also should be performed at 12 months 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.**

Continued
References

**Note: All recommendations are category 2A unless otherwise indicated.**

## 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.**

**Muscle-Invasive Bladder Cancer (MIBC)**

**Chest Imaging**

- **Staging[4]:**
  - **CT of the chest with or without contrast (preferred)[6]**
  - **Posteroanterior (PA) and lateral chest x-ray**
  - **FDG-PET/CT (category 2B) may be beneficial in selected patients with T2 (muscle-invasive disease) and in patients with ≥cT3 disease. This will also include abdomen and pelvis if performed.[7-10] FDG-PET/CT should not be used to delineate the anatomy of the upper urinary tract.**

- **Follow-up with or without cystectomy: (BL-E)**
  - **Chest CT with or without IV contrast (preferred)**
    - **◊ May be performed without contrast if IV contrast cannot be given.**
    - **◊ Consider performing with the abdomen and pelvis for a single exam in patients who also need imaging of the abdomen and pelvis.**
  - **PA and lateral chest x-ray**
  - **FDG-PET/CT (category 2B) may be performed if not previously done or if metastasis is suspected in selected patients. This examination will also include the abdomen and pelvis. FDG-PET/CT should not be used to delineate the anatomy of the upper urinary tract.**

- **Follow-up of cT4b (BL-E) and metastatic disease:**
  - **Chest CT with or without IV contrast (preferred)**
    - **◊ May be performed without contrast if IV contrast cannot be given.**
    - **◊ Consider performing with the abdomen and pelvis for a single exam in patients who also need imaging of the abdomen and pelvis.**
  - **PA and lateral chest x-ray**
  - **FDG-PET/CT (category 2B) may be performed if not previously done or in patients with high-risk MIBC in whom metastatic disease is suspected. This could also be used to guide biopsy in certain patients. FDG-PET/CT should not be used to delineate the anatomy of the upper urinary tract.**

**Note: All recommendations are category 2A unless otherwise indicated.**

Continued
References

## PRINCIPLES OF IMAGING FOR BLADDER/UROTHELIAL CANCER

**Muscle-Invasive Bladder Cancer (continued)**

**Abdomen and Pelvis Imaging**

- **Staging:**
  - **CTU (CT of the abdomen and pelvis without and with IV contrast with excretory imaging).[11]**
  - **MRU may be appropriate in patients with poor renal function or iodinated contrast allergy but with GFR >30 and no acute renal failure.**
  - **Renal US and CT without contrast (particularly when FDG-PET/CT is not utilized) may be utilized in conjunction with retrograde evaluation in patients who cannot receive either iodinated or gadolinium-based contrast material.**
  - **Ureteroscopy if suspected upper tract lesions.**
  - **FDG-PET/CT (category 2B) may be useful in selected patients with ≥cT2 disease and may change treatment in patients with ≥cT3 disease.[1] FDG-PET/CT should not be used to delineate the anatomy of the upper urinary tract.**
  - **CT or MRI of the abdomen and pelvis with IV contrast if not performed with initial evaluation.**
  - **MRI of the pelvis without and with IV contrast for local staging.**
    - **May be performed in addition to CTU.**
    - **May also be performed without contrast if there is a contraindication to contrast.[1]**
- **Follow-up (BL-E):**
  - **Upper tract and abdomen/pelvis imaging with contrast as defined previously at 3- to 6-month intervals for 2 years, then abdomen/pelvis imaging with contrast annually for up to 5 years and as indicated thereafter.**
  - **FDG-PET/CT (category 2B) may be performed if not previously done or in patients with high-risk MIBC in whom metastatic disease is suspected. This could also be used to guide biopsy in certain patients. FDG-PET/CT should not be used to delineate the anatomy of the upper urinary tract.**

**Evaluation for Suspected Bone Metastasis**

- **Symptomatic, or patients at high risk, or those with laboratory indicators of bone metastasis may be imaged with MRI, FDG-PET/CT (category 2B), or bone scan. FDG-PET/CT (category 2B) may also be considered in cases when additional sites of extraosseous metastatic disease are suspected or previously documented.**

**Metastatic Disease - Patients Being Observed**

- **See Follow-Up (BL-E 6 of 6)**

**Neurologic/Brain Imaging[4,5]**

- **Staging**
  - **Brain MRI without and with IV contrast is recommended only in symptomatic or selected patients at "high risk" (eg, small cell histology) .**
  - **CT with IV contrast is considered only when symptomatic patients cannot undergo MRI (ie, non-MRI–compatible cardiac pacer, implant or foreign body, end-stage renal disease).**

Continued
References

**Note: All recommendations are category 2A unless otherwise indicated.**

## PRINCIPLES OF IMAGING FOR BLADDER/UROTHELIAL CANCER

**Upper Tract (renal pelvis and urothelial carcinoma of the ureter)[12]**
- Staging and follow-up of ≤T1 disease (see recommendations for NMIBC bladder cancer).
- Staging and follow-up of ≥T2 disease (see recommendations for MIBC bladder cancer).

**Urothelial Carcinoma of the Prostate/Primary Carcinoma of the Urethra**
- Staging:
  - Chest CT (preferred) or PA and lateral chest x-ray.
  - Consider abdomen CT or MRI in high-risk T1 disease or patients with ≥T2 disease.[13]
  - MRI of the pelvis without and with IV contrast for local staging.

- Additional staging if urothelial carcinoma of prostate:
  - Imaging of upper tracts and collecting system.
  - CTU (CT of the abdomen and pelvis without and with IV contrast with excretory imaging).
  - MRU may be appropriate in patients with poor renal function or iodinated contrast allergy but with GFR >30 and no acute renal failure.
  - Ureteroscopy
  - Renal US or CT without contrast may be utilized in conjunction with retrograde evaluation in patients who cannot receive either iodinated or gadolinium-based contrast material.

- Additional staging if primary carcinoma of the urethra:
  - In the setting of palpable inguinal lymph nodes:
    - ◊ Biopsy of palpable nodes.
    - ◊ CT of the chest, abdomen, and pelvis for additional staging, if not yet performed.

- Follow-up:
  - Low-risk T1 or <T1 disease:
    - ◊ MRI or CT of pelvis with and without IV contrast.
  - High-risk T1 or ≥T2:
    - ◊ May consider more extensive follow-up based on risk factors; 3–6 months for 2 years and then yearly.
      - – Chest imaging with x-ray and/or CT as previously discussed.
      - – Imaging of abdomen and pelvis with MRI or CT with and without contrast.

References

Note: All recommendations are category 2A unless otherwise indicated.

## PRINCIPLES OF IMAGING FOR BLADDER/UROTHELIAL CANCER
## REFERENCES

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**Note: All recommendations are category 2A unless otherwise indicated.**

## PRINCIPLES OF SURGICAL MANAGEMENT

**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 CIS:
    - ◊ 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 multifocal lesions
      - Any T1 lesion
  - Transurethral resection (TUR) 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.

**TURBT/Maximal TURBT for Treatment**

- Maximally complete and safe TURBT is an essential part of bladder preservation. See Principles of Radiation Therapy (BL-H).
- TURBT alone can be considered for non-cystectomy candidates.
- A visually complete TURBT is associated with improved patient outcomes in non-metastatic settings.

Continued

Note: All recommendations are category 2A unless otherwise indicated.

## PRINCIPLES OF SURGICAL MANAGEMENT

**Transurethral Resection of the Prostate (TURP)**
- Primary treatment option for urothelial carcinoma of the prostate with ductal/acini or prostatic urethral pathology.
- Postsurgical intravesical BCG is recommended (Principles of Instillation Therapy [BL-F]).

**TUR of the Urethral Tumor**
- Primary treatment of CIS, Ta, T1 primary carcinoma of the urethra.
- Patients with a prior radical cystectomy and a cutaneous diversion should consider a total urethrectomy.
- Consider postsurgical intraurethral therapy (Principles of Instillation Therapy [BL-F]).

**Partial Cystectomy**
- May be used for cT2 muscle-invasive disease with solitary lesion in location amenable to segmental resection with adequate margins, in appropriately selected patients. May also be appropriate in other select situations including cancer in a bladder diverticulum.
- No CIS as determined by random biopsies.
- Bilateral pelvic lymphadenectomy should be performed.

**Radical Cystectomy/Cystoprostatectomy**
- In non–muscle-invasive disease, radical cystectomy is generally reserved for residual high-grade cT1, aggressive histopathologic subtypes, lymphovascular invasion, concomitant CIS, and BCG-unresponsive disease (Bladder Cancer: Non-Urothelial and Urothelial with Subtype Histology [BL-D]).
- Cystectomy should be done within 3 months of diagnosis if no therapy is 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.
- Bilateral pelvic lymphadenectomy should be performed.
- In appropriately selected patients, approaches that preserve the uterus, vagina, and/or ovaries should be employed when feasible.

**Radical Nephroureterectomy with Cuff of Bladder**
- Primary treatment option for non-metastatic high-grade upper GU tract tumors.

Continued

Note: All recommendations are category 2A unless otherwise indicated.

## PRINCIPLES OF SURGICAL MANAGEMENT

**Regional Lymphadenectomy**
- Endoscopic lymph node dissections should be equivalent to open dissection.
- For bladder, recommend pelvic lymph node dissection; for upper tract recommend regional lymph node dissection for high-grade tumors.

**Urethrectomy**
- Distal urethrectomy may include inguinal lymph node dissection in selected cases.
- Total urethrectomy may include inguinal lymphadenectomy in selected cases.
- 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 and cystectomy with organ-sparing approaches when feasible in appropriately selected cases.

**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.

NCCN recommendations have been developed to be inclusive of individuals of all sexual and gender identities to the greatest extent possible. On this page, the terms male and female refer to sex assigned at birth.

Continued

**Note: All recommendations are category 2A unless otherwise indicated.**

## PRINCIPLES OF SURGICAL MANAGEMENT

**Endoscopic Management of Upper Tract Urothelial Cancer (UTUC)**

- Favorable clinical and pathologic criteria for nephron preservation:
  - Low-grade tumor based on cytology and biopsy
  - Papillary architecture
  - Tumor size <1.5 cm
  - Unifocal tumor
  - Cross-sectional imaging showing no concern for invasive disease
- For favorable tumors - ureteroscopic and percutaneous management provide similar survival outcomes compared to nephroureterectomy
- Less favorable clinical and pathologic criteria for nephron preservation:
  - Multifocal tumors
  - Flat or sessile tumor architecture
  - Tumor size >1.5 cm
  - High-grade tumors
  - cT2–T4 tumors
  - Mid and proximal ureteral tumor due to technical challenges
  - Tumor crossing infundibulum or ureteropelvic junction
- Imperative indications for conservative therapy of UTUC
  - Bilateral renal pelvis and/or urothelial carcinoma of the ureter
  - Solitary or solitary functioning kidney
  - Chronic kidney disease/renal insufficiency
- Percutaneous or ureteroscopic surgical procedures
  - Tumor fulguration/cautery
  - Tumor resection incorporating electrical energy, baskets, or cold cup devices with fulguration of the tumor bed
  - Laser therapies Extirpative surgical procedures
  - Segmental ureterectomy ± ureteral reimplantation for distal ureteral tumors
  - Complete ureterectomy with ileal ureter replacement (proximal/mid-ureteral tumors)
- Topical immunotherapy and chemotherapy management (see Principles of Instillation Therapy [BL-F 3 of 4] for more information).Patients with renal pelvis and urothelial carcinoma of the ureter managed with nephron-preserving procedures and adjunctive therapies require long-term surveillance, including cross-sectional urography or endoscopic visualization. Treatment can be associated with patient anxiety, tumor seeding, and the need for multiple procedures and ultimate nephroureterectomy with bladder cuff. Clinical/pathologic understaging is problematic. Recurrence or tumor persistence might be life-threatening due to disease progression.

**Note: All recommendations are category 2A unless otherwise indicated.**

## PRINCIPLES OF PATHOLOGY MANAGEMENT
### 2022 WHO Classification of Tumors of the Urothelial Tract[1,2]

**Urothelial Tumors**
- Invasive urothelial carcinoma subtypes
  - Conventional urothelial carcinoma
  - Infiltrating urothelial carcinoma with squamous differentiation
  - Infiltrating urothelial carcinoma with glandular differentiation
  - Infiltrating urothelial carcinoma with trophoblastic differentiation
  - Nested urothelial carcinoma
  - Tubular and microcystic urothelial carcinoma
  - Micropapillary urothelial carcinoma
  - Lymphoepithelioma-like urothelial carcinoma
  - Plasmacytoid urothelial carcinoma
  - Sarcomatoid urothelial carcinoma
  - Giant cell urothelial carcinoma
  - Lipid-rich urothelial carcinoma
  - Clear cell (glycogen rich) urothelial carcinoma
  - Poorly differentiated urothelial carcinoma
- Noninvasive urothelial neoplasms
  - Urothelial CIS
  - Noninvasive papillary urothelial carcinoma, low grade
  - Noninvasive papillary urothelial carcinoma, high-grade
  - Papillary urothelial neoplasm of low malignant potential
  - Urothelial papilloma
  - Inverted urothelial papilloma
  - Urothelial proliferation of uncertain malignant potential
  - Urothelial dysplasia[a]

**Squamous Cell Neoplasms**
- Pure squamous cell carcinoma
- Verrucous carcinoma
- Squamous cell papilloma

**Glandular Neoplasms**
- Adenocarcinoma, NOS
  - Enteric
  - Mucinous
  - Mixed
- Villous adenoma

**Urachal Carcinoma**

**Tumors of Müllerian Type**
- Clear cell carcinoma
- Endometrioid carcinoma

**Neuroendocrine Tumors**
- Small cell neuroendocrine carcinoma
- Large cell neuroendocrine carcinoma
- Well-differentiated neuroendocrine tumor
- Paraganglioma

**Mesenchymal Tumors**
- Rhabdomyosarcoma
- Leiomyosarcoma
- Angiosarcoma
- Malignant inflammatory myofibroblastic tumor
- Malignant perivascular epithelioid cell tumor
- Malignant solitary fibrous tumor

**Urothelial Tract Hematopoietic and Lymphoid Tumors**

**Miscellaneous Tumors**
- Epithelial tumors of the upper urinary tract
- Tumors arising in a bladder diverticulum
- Urothelial tumors of the urethra
- Malignant melanoma
- Carcinoma of Skene, Cowper, and Littre glands
- Metastatic tumors and tumors extending from other organs

[a] The term “urothelial dysplasia” is very rarely used. Its morphologic features are poorly defined and interobserver reproducibility of this diagnosis is very low.

[1] Moch H, Amin MB, Berney DM, et al. The 2022 World Health Organization Classification of Tumours of the Urinary System and Male Genital Organs - Part A: Renal, Penile, and Testicular Tumours. Eur Urol 2022;82;458-468.
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Continued

**Note: All recommendations are category 2A unless otherwise indicated.**

## PRINCIPLES OF PATHOLOGY MANAGEMENT

- **The pathology report on biopsy/TURBT specimens should:**
  - **Include items listed in the College of American Pathologists (CAP) Cancer Protocol for reporting results (tumor site, histologic subtype, histologic grade, tumor extent, and lymphovascular invasion if present)[3]**
  - **Example:**
    - ◊ **Urinary bladder, tumor, TUR:**
      - – **High-grade urothelial carcinoma**
        - ▪ **Carcinoma infiltrates lamina propria**
        - ▪ **Muscularis propria present with invasion by tumor**
        - ▪ **Lymphovascular space invasion present**
        - ▪ **pT2**
  - **For tumors with intratumoral grade heterogeneity: tumors should be classified as high grade if the high-grade component represents >5% of the tumor. If the high-grade component is <5%, the tumor should be classified descriptively as "low grade with <5% high-grade component" as these may have a prognosis that is closer to low-grade tumors.[4]**
  - **Detail if muscularis propria (detrusor muscle) is present or absent (in addition to describing if invasion is present as per the reporting protocol).**
  - **Describe if adjacent urothelial CIS is present.**
  - **Urothelial carcinomas with an inverted growth pattern should be graded similar to the system for papillary tumors as described above.**
  - **Mixed neuroendocrine carcinoma of the bladder should specify the type(s) and percentage of the neuroendocrine component(s) present.**
  - **In addition to presence or absence of lamina propria invasion, the report should attempt to describe the extent of lamina propria invasion as early invasion/microinvasion or more extensive invasion. The exact method for characterizing early invasion versus more extensive invasion of lamina propria has not been defined/optimized; however, any of the following methods could be used as detailed in the 8th edition of the AJCC Cancer Staging Manual.[5]**
    - ◊ **<1 high power field or greatest invasive tumor diameter of ≤1 mm or invasive tumor above muscularis mucosae extending to a depth of ≤2 mm**
- **The pathology report on cystectomy specimens should:**
  - **Include items listed in the CAP Cancer Protocol for reporting results.[3]**
- **Consultation/re-review from an experienced genitourinary (GU) pathologist should be obtained as required for confirming clinically significant rare subtype histology, confirming metastatic carcinoma of urothelial origin, and in clinically discrepant scenarios.**

[3] CAP Cancer Protocol Templates (https://www.cap.org/protocols-and-guidelines/cancer-reporting-tools/cancer-protocol-templates).
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[5] Bochner BH, et al. Urinary Bladder. In: Amin MB, ed. AJCC Cancer Staging Manual. 8th Springer; 2017:757-765.

**Note: All recommendations are category 2A unless otherwise indicated.**

## BLADDER CANCER: NON-UROTHELIAL AND UROTHELIAL WITH SUBTYPE HISTOLOGY

**Mixed Histology:**
- Urothelial carcinoma plus squamous differentiation or adenocarcinoma differentiation should be identified because of the potential to have a more aggressive natural history.
- These are usually treated in a similar manner to pure urothelial carcinoma of the bladder.

**Aggressive Subtype Histologies:**
- Micropapillary,[1,2] plasmacytoid,[3] small cell/neuroendocrine, and sarcomatoid histologies (in pure or mixed form with associated urothelial carcinoma) are generally at higher risk for progression to muscle-invasive disease and a more aggressive approach should be considered.

**Pure Small Cell Carcinoma or Mixed Histology with Any Small Cell Component (or neuroendocrine features):**
- Neurologic/brain imaging is recommended (BL-A 3 of 5).
- Concurrent chemoradiotherapy or neoadjuvant systemic therapy followed by local treatment (cystectomy or RT) is recommended for any patient with small cell component histology with localized disease regardless of stage (including non–muscle-invasive disease).
- Neoadjuvant systemic therapy
  - Regimens recommended in the NCCN Guidelines for Small Cell Lung Cancer - Principles of Sytemic Therapy
    or
  - Alternating ifosfamide + doxorubicin with etoposide + cisplatin[4-6]
- Metastatic systemic therapy
  - Regimens recommended in the NCCN Guidelines for Small Cell Lung Cancer - Principles of Systemic Therapy or
  - Alternating ifosfamide + doxorubicin with etoposide + cisplatin[4-6]

**Pure Squamous Carcinoma:**
- There is no proven role for neoadjuvant/adjuvant chemotherapy for pure squamous cell carcinoma of the bladder.
- Local control with surgery or chemoradiotherapy and best supportive care (NCCN Guidelines for Palliative Care) are recommended.
- For advanced disease, clinical trial is preferred. For selected patients, combination chemotherapy with paclitaxel, ifosfamide, and cisplatin may be considered.[7]
- Consider postoperative RT in selected cases (positive margins).[8]

**Pure Adenocarcinoma Including Urachal Carcinoma:**
- There is no proven role for neoadjuvant/adjuvant chemotherapy for pure adenocarcinomas of the bladder, including urachal carcinoma.
- Local control with surgery or RT and best supportive care are recommended. See NCCN Guidelines for Palliative Care.
- For urachal carcinoma with localized disease, a partial or complete cystectomy with en bloc resection of the urachal ligament with umbilicus and lymph node dissection is recommended.
- Consider metastatic chemotherapy regimens seen in the NCCN Guidelines for Colon Cancer.
- For node-positive disease, consider regimens recommended for advanced or metastatic disease in the NCCN Guidelines for Colon Cancer or GemFLP [5-FU, leucovorin, gemcitabine, and cisplatin]). Consider post-chemotherapy surgical consolidation in responding disease.
- For advanced disease, clinical trial is preferred. For selected patients, regimens recommended for advanced or metastatic disease in the NCCN Guidelines for Colon Cancer, GemFLP, or ITP (paclitaxel, ifosfamide, and cisplatin), are options.
- For non-urachal pure adenocarcinoma, consider additional metastatic workup. See NCCN Guidelines for Occult Primary.

**Primary Bladder Sarcoma:**
- Treatment as per NCCN Guidelines for Soft Tissue Sarcoma.

**Note: All recommendations are category 2A unless otherwise indicated.**

References

## BLADDER CANCER: NON-UROTHELIAL AND UROTHELIAL WITH SUBTYPE HISTOLOGY
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**Note: All recommendations are category 2A unless otherwise indicated.**

## 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 |
|---|---|---|
| • Papillary urothelial neoplasm of low malignant potential<br>• Low-grade urothelial carcinoma<br>▸ Ta and<br>▸ ≤3 cm and<br>▸ Solitary | • Low-grade urothelial carcinoma<br>▸ T1 or<br>▸ >3 cm or<br>▸ Multifocal or<br>▸ Recurrence within 1 year<br>• High-grade urothelial carcinoma<br>▸ Ta and<br>▸ ≤3 cm and<br>▸ Solitary | • High-grade urothelial carcinoma<br>▸ CIS or<br>▸ T1 or<br>▸ >3 cm or<br>▸ Multifocal<br>• Very-high-risk features (any):<br>▸ BCG unresponsive[a]<br>▸ Certain histopathologic subtypes[b]<br>▸ Lymphovascular invasion<br>▸ Prostatic urethral invasion |

Adapted with permission from Chang SS, Boorjian SA, Chou R, et al. Diagnosis and treatment of non-muscle invasive bladder cancer: AUA/SUO guideline. J Urol 2016;196:1021-1029.

*Within each of these risk strata an individual patient may have more or less concerning features that can influence care.

**Table 2: Low-Risk,[c] Non–Muscle-Invasive Bladder Cancer**

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

Intermediate Risk, Non–Muscle Invasive (BL-E 2 of 6)
High-Risk, Non–Muscle Invasive (BL-E 2 of 6)
Post-Cystectomy Non–Muscle-Invasive Bladder Cancer (BL-E 3 of 6)
Post-Cystectomy Muscle-Invasive Bladder Cancer (BL-E 4 of 6)
Post-Bladder Sparing (BL-E 5 of 6)
Metastatic Disease: Surveillance (BL-E 6 of 6)
Recurrent or Persistent Disease (BL-11)

[a] Kamat AM, et al. J Clin Oncol 2016;34:1935-1944.
[b] See aggressive subtype histologies listed on Bladder Cancer: Non-Urothelial and Urothelial with Subytpe Histology (BL-D).
[c] See AUA Risk Stratification for Non–Muscle-Invasive Bladder Cancer definitions on BL-2.
[d] Principles of Imaging for Bladder/Urothelial Cancer (BL-A).

See NCCN Guidelines for Survivorship

**Note: All recommendations are category 2A unless otherwise indicated.**

## 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,[c] 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 and abdomen/pelvis imaging[d] | Baseline imaging | As clinically indicated | | | | | |
| Blood tests | N/A | | | | | | |
| Urine tests | Urine cytology 3, 6, 12 | Urine cytology every 6 mo | Annually | | | As clinically indicated | |

**Table 4: High-Risk,[c] 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 imaging[d] | Baseline imaging, and at 12 mo | Every 1–2 y | | | | | As clinically indicated |
| Abdomen/pelvis imaging[d] | Baseline imaging | As clinically indicated | | | | | |
| Blood tests | N/A | | | | | | |
| Urine tests | • Urine cytology every 3 mo<br>• Consider urinary urothelial tumor markers (category 2B) | | Urine cytology every 6 mo | | | Annually | As clinically indicated |

[c] See AUA Risk Stratification for Non–Muscle-Invasive Bladder Cancer definitions on BL-2.
[d] Principles of Imaging for Bladder/Urothelial Cancer (BL-A).

**Note: All recommendations are category 2A unless otherwise indicated.**

See NCCN Guidelines for Survivorship

## 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 5: Post-Cystectomy Non–Muscle-Invasive Bladder Cancer**

<table>
<tr><th rowspan="2">Test</th><th colspan="7">Year</th></tr>
<tr><th>1</th><th>2</th><th>3</th><th>4</th><th>5</th><th>5–10</th><th>>10</th></tr>
<tr><td>Cystoscopy</td><td colspan="7">N/A</td></tr>
<tr><td>Imaging[d]</td><td>• CTU or MRU (image upper tracts + axial imaging of abdomen/ pelvis) at 3 and 12 mo</td><td colspan="4">CTU or MRU (image upper tracts + axial imaging of abdomen/pelvis) annually</td><td>Renal US annually[e]</td><td>As clinically indicated</td></tr>
<tr><td>Blood tests</td><td>• Renal function testing (electrolytes and creatinine) every 3–6 mo<br>• LFT[f] every 3–6 mo<br>• CBC, CMP every 3–6 mo if received chemotherapy</td><td colspan="4">• Renal function testing (electrolytes and creatinine) annually<br>• LFT[f] annually<br>• $B_{12}$ annually based on clinical judgment</td><td colspan="2">$B_{12}$ annually based on clinical judgment</td></tr>
<tr><td>Urine tests</td><td colspan="2">• Consider urine cytology every 6–12 mo<br>• Consider urethral wash cytology every 6–12 mo[g]</td><td colspan="5">Urine cytology as clinically indicated<br>Urethral wash cytology as clinically indicated</td></tr>
</table>

Post-Cystectomy MIBC (BL-E 4 of 6)  Post-Bladder Sparing (BL-E 5 of 6)  Recurrent or Persistent Disease (BL-11)

[d] Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
[e] Renal US to look for hydronephrosis.
[f] Liver function testing (LFT) includes aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, and alkaline phosphatase.
[g] Urethral wash cytology is reserved for patients with high-risk disease. High-risk disease includes: positive urethral margin, multifocal CIS, and prostatic urethral invasion.

See NCCN Guidelines for Survivorship

**Note: All recommendations are category 2A unless otherwise indicated.**

## 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 6: Post-Cystectomy Muscle-Invasive Bladder Cancer**

<table>
<tr><th rowspan="2">Test</th><th colspan="7">Year</th></tr>
<tr><th>1</th><th>2</th><th>3</th><th>4</th><th>5</th><th>5–10</th><th>>10</th></tr>
<tr><td>Cystoscopy</td><td colspan="7">N/A</td></tr>
<tr><td>Imaging[d]</td><td colspan="2">• CTU or MRU (image upper tracts + axial imaging of abdomen/pelvis) every 3–6 mo<br>• CT chest (preferred) or chest x-ray every 3–6 mo<br>or<br>• FDG-PET/CT (category 2B) only if metastatic disease suspected</td><td colspan="3">• Abdomen/pelvis CT or MRI annually<br>• CT chest (preferred) or chest x-ray annually<br>or<br>• FDG-PET/CT (category 2B) only if metastatic disease suspected</td><td>Renal US annually[e]</td><td>As clinically indicated</td></tr>
<tr><td>Blood tests</td><td>• Renal function testing (electrolytes and creatinine) every 3–6 mo<br>• LFT[f] every 3–6 mo<br>• CBC, CMP every 3–6 mo if received chemotherapy</td><td colspan="4">• Renal function testing (electrolytes and creatinine) annually<br>• LFT[f] annually<br>• $B_{12}$ annually based on clinical judgment</td><td colspan="2">$B_{12}$ annually based on clinical judgment</td></tr>
<tr><td>Urine tests</td><td colspan="2">• Consider urine cytology every 6–12 mo<br>• Consider urethral wash cytology every 6–12 mo[g]</td><td colspan="5">Urine cytology as clinically indicated<br>Urethral wash cytology as clinically indicated</td></tr>
</table>

Post-Bladder Sparing (BL-E 5 of 6)

Recurrent or Persistent Disease (BL-11)

[d] Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
[e] Renal US to look for hydronephrosis.
[f] LFT includes AST, ALT, bilirubin, and alkaline phosphatase.
[g] Urethral wash cytology is reserved for patients with high-risk disease. High-risk disease includes: positive urethral margin, multifocal CIS, and prostatic urethral invasion.

See NCCN Guidelines for Survivorship

**Note: All recommendations are category 2A unless otherwise indicated.**

## 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 7: Post-Bladder Sparing (ie, Partial Cystectomy or Chemoradiation)[h]**

<table>
<tr><th rowspan="2">Test</th><th colspan="7">Year</th></tr>
<tr><th>1</th><th>2</th><th>3</th><th>4</th><th>5</th><th>5–10</th><th>>10</th></tr>
<tr><td>Cystoscopy</td><td colspan="2">Every 3 mo</td><td colspan="2">Every 6 mo</td><td colspan="2">Annually</td><td>As clinically indicated</td></tr>
<tr><td>Imaging[d]</td><td colspan="3">• CTU or MRU (image upper tracts + axial imaging of abdomen/pelvis) every 3–6 mo for MIBC<br>• CT chest (preferred) or chest x-ray every 3–6 mo for MIBC<br>or<br>• FDG-PET/CT (category 2B) only if metastatic disease suspected</td><td colspan="3">• Abdomen/pelvis CT or MRI annually<br>• CT chest (preferred) or chest x-ray annually<br>or<br>• FDG-PET/CT (category 2B) only if metastatic disease suspected[i]</td><td>As clinically indicated</td></tr>
<tr><td>Blood tests</td><td colspan="2">• Renal function testing (electrolytes and creatinine) every 3–6 mo<br>• LFT[f] every 3–6 mo<br>• CBC, CMP every 3–6 mo if received chemotherapy</td><td colspan="5">• Renal function testing (electrolytes and creatinine) as clinically indicated<br>• LFT[f] as clinically indicated</td></tr>
<tr><td>Urine tests</td><td colspan="3">Urine cytology every 6–12 mo</td><td colspan="4">Urine cytology as clinically indicated</td></tr>
</table>

[d] Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
[f] LFT includes AST, ALT, bilirubin, and alkaline phosphatase.
[h] For patients who are not eligible for aggressive therapy, less frequent surveillance may be warranted (eg, cystoscopy every 6 months, extended to annually over time).
[i] PET/CT not recommended for NMIBC.

**Note: All recommendations are category 2A unless otherwise indicated.**

## 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 8: Metastatic Disease: Surveillance**

| Test | Year | | | | | | |
|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 5–10 | >10 |
| Cystoscopy | • As clinically indicated | | | | | | |
| Imaging[d] | • CTU or MRU (image upper tracts + axial imaging of abdomen/pelvis) every 3–6 mo if clinically indicated and with any clinical change or new symptoms<br>• CT chest/abdomen/pelvis every 3–6 mo and with any clinical change or new symptoms<br>or<br>• FDG-PET/CT (category 2B) | | | | | | |
| Blood tests | • CBC, CMP every 1–3 mo<br>• B12 annually for patients who had undergone a cystectomy based on clinical judgment | | | | | | |
| Urine tests | • Urine cytology as clinically indicated | | | | | | |

[d] Principles of Imaging for Bladder/Urothelial Cancer (BL-A).

**Note: All recommendations are category 2A unless otherwise indicated.**

## PRINCIPLES OF INSTILLATION THERAPY

**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

- Clinical Presentation and Initial Evaluation (BL-1)
- A single instillation of chemotherapy is administered within 24 hours of surgery (ideally within 6 hours).
- Gemcitabine (category 1) (preferred)[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.
- Most efficacious in patients with low-grade, low-volume Ta urothelial cancer.
- Contraindications include: bladder perforation, known drug allergy.

#### Induction (Adjuvant) Intravesical Chemotherapy or BCG

- Treatment option for NMIBC.
- The most commonly used agents are BCG, mitomycin, and gemcitabine.
- 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]
- 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]

Continued
References

**Note: All recommendations are category 2A unless otherwise indicated.**

## PRINCIPLES OF INSTILLATION THERAPY

**Intravesical BCG Principles During Time of BCG Shortage:**

- **BCG induction and maintenance should be prioritized for patients at high risk for recurrence (eg, high-grade T1 and CIS), especially in the early maintenance period (ie, 3 and 6 months post-induction).**
- **BCG maintenance for patients with intermediate-risk NMIBC can be risk adapted to prioritize patients with high-risk NMIBC.**
- **BCG maintenance for patients with high-risk NMIBC should be stopped at 1 year.**
- **Consider induction with alternative agents if BCG is completely not available.**
  - **Alternative options include: sequential gemcitabine/docetaxel, mitomycin, gemcitabine, epirubicin, valrubicin, docetaxel, or sequential gemcitabine/mitomycin.**
- **Consider a clinical trial if available.**
- **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 (for induction or high-priority maintenance therapy).**

Continued
References

**Note: All recommendations are category 2A unless otherwise indicated.**

## PRINCIPLES OF INSTILLATION THERAPY

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

**Topical or Percutaneous Administration of Chemotherapy or BCG**

- Although the target site differs, the principles of this treatment are similar to intravesical therapy. Topical chemotherapeutic agents are delivered by instillation. Administration can be percutaneous or through a retrograde approach using a catheter. There is no standard regimen and patients should be referred to an institution with experience in this treatment or a clinical trial.
- Topical immunotherapy and chemotherapy management
  - BCG, mitomycin
  - Route of administration might include percutaneous antegrade (preferred) or retrograde ureteral catheters.
  - Induction and maintenance therapy regimens, similar to intravesical therapy, can be used.

**Postsurgical Intraprostatic BCG for Urothelial Carcinoma of the Prostate**

- Treatment for patients with ductal + acini, or prostatic urethra involvement. See Urothelial Carcinoma of the Prostate (UCP-1).
- Induction (adjuvant) therapy should be initiated 3–4 weeks after TURP.
- Induction BCG should be followed with maintenance BCG.
- Data indicate a reduction in recurrence in the prostate in patients with superficial disease.[5-11]

**Postsurgical Intraurethral Therapy for Primary Carcinoma of the Urethra**

- Consider as primary treatment for select patients with CIS, Ta, or T1 disease. See Primary Carcinoma of the Urethra (PCU-2).
- Induction (adjuvant) therapy should be initiated 3–4 weeks after TUR.
- The most commonly used agents are BCG, mitomycin, and gemcitabine.
- Role of maintenance in this context is uncertain.
- Efficacy of this treatment in primary carcinoma of the urethra has not been established.

**Intrapelvic and Intravesical Therapy for Upper Tract Tumors**

- Primary Therapy
  - Complete or near complete endoscopic resection or ablation is recommended prior to mitomycin ureteral gel application, which is most suitably indicated for a residual, low-grade, low-volume (5–15 mm), solitary tumor in the upper urinary tract for a patient who is not a candidate for or not seeking nephroureterectomy as a definitive treatment. Mitomycin for pyelocaliceal application may be administered via ureteral catheter or a nephrostomy tube.
- Postsurgical Therapy
  - Consider intrapelvic therapy for patients with non-metastatic, low-grade tumors of the renal pelvis. See Upper GU Tract Tumors: Renal Pelvis (UTT-1).
    - ◊ Intrapelvic induction (adjuvant) therapy should be initiated 3–4 weeks after endoscopic resection.
    - ◊ The most commonly used agents for intrapelvic therapy are BCG, mitomycin C, and gemcitabine.
    - ◊ Role of maintenance following intrapelvic therapy in this context is uncertain.
    - ◊ Efficacy of intrapelvic therapy in upper urinary tract cancer has not been established.[12-14]
  - Perioperative intravesical chemotherapy should be strongly considered following nephroureterectomy with cuff of bladder resection as randomized trials have shown a decrease in intravesical recurrence.[15-18]

References

**Note: All recommendations are category 2A unless otherwise indicated.**

## PRINCIPLES OF INSTILLATION THERAPY – REFERENCES

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**Note: All recommendations are category 2A unless otherwise indicated.**

## PRINCIPLES OF SYSTEMIC THERAPY

| Neoadjuvant Chemotherapy (preferred for bladder) |
|---|
| **Preferred regimen**<br>• DDMVAC (dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin) with growth factor support for 3–6 cycles[1,2]<br>**Useful in certain circumstances**<br>• Gemcitabine and cisplatin for 4 cycles[3,4] |

| Perioperative/Sandwich Therapy |
|---|
| **Preferred regimen**<br>• Gemcitabine + cisplatin + durvalumab prior to cystectomy, then durvalumab after cystectomy[5] (for bladder cancer only) (category 1) |

| Adjuvant Therapy | |
|---|---|
| **No previous platinum-based neoadjuvant therapy (pT3, pT4a, pN+)** | **Previous platinum-based neoadjuvant therapy (ypT2–ypT4a or ypN+)** |
| **Preferred regimen**<br>• DDMVAC with growth factor support for 3–6 cycles[1,2]<br>**Other recommended regimens**<br>• Gemcitabine and cisplatin for 4 cycles[3,4]<br>• Nivolumab[6]<br>• Pembrolizumab[7] | **Other recommended regimen**<br>• Nivolumab[6]<br>• Pembrolizumab[7] |

- 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) for MIBC.[1,8,9]
- Meta-analysis suggests overall survival benefit with adjuvant cisplatin-based chemotherapy for pathologic T3, T4 or N+ disease at cystectomy, if it was not given as neoadjuvant.[9]
- 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 for metastatic disease showing DDMVAC to be better tolerated and more effective than conventional MVAC in advanced disease.[2,10] 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 for metastatic disease showing equivalence to conventional MVAC in the setting of advanced disease.[4,11]
- For gemcitabine/cisplatin, a 21-day cycle is preferred. Better dose adherence may be achieved with fewer delays in dosing using the 21-day schedule.[12]
- Neoadjuvant chemotherapy is preferred for patients with UTUC, particularly for higher stage and/or grade tumors or concerning radiographic findings, as renal function will decline after nephroureterectomy and may preclude adjuvant therapy.
  - Multicenter data support the use of neoadjuvant, split-dose cisplatin-based chemotherapy (gemcitabine and cisplatin) for patients with high-grade UTUC.[13] Staging for UTUC is less precise than for bladder cancers and understaging is common, necessitating discussion on the risk of under- versus over-treatment.
  - Adjuvant therapy should be considered if neoadjuvant therapy was not given for UTUC.[14]
- Carboplatin should not be substituted for cisplatin in the perioperative bladder cancer 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. Consider timed urine collection, which may more accurately determine eligibility for cisplatin.
- Nivolumab and hyaluronidase-nvhy subcutaneous injection may be substituted for IV nivolumab. Nivolumab and hyaluronidase-nvhy has different dosing and administration instructions compared to IV nivolumab.

Continued

References

**Note: All recommendations are category 2A unless otherwise indicated.**

## PRINCIPLES OF SYSTEMIC THERAPY

| First-Line Systemic Therapy for Locally Advanced or Metastatic Disease (Stage IV) | | |
|---|---|---|
| **Preferred regimen**<br>• Enfortumab vedotin-ejfv[15,16] and pembrolizumab (category 1) | **Other recommended regimens**<br>• Gemcitabine and cisplatin[4] (category 1) followed by avelumab maintenance therapy (category 1)[a,17]<br>• Gemcitabine, cisplatin, and nivolumab (category 1) followed by nivolumab maintenance therapy[18] (category 1)<br>• DDMVAC with growth factor support[2,10] (category 1) followed by avelumab maintenance therapy (category 1)[a,17] | **Useful in certain circumstances (cisplatin-ineligible)**<br>• Gemcitabine and carboplatin[19] followed by avelumab maintenance therapy (category 1)[a,17]<br>• Pembrolizumab (for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for any platinum-containing chemotherapy)[20]<br>• Atezolizumab[21] (only for patients whose tumors express PD-L1[b] or who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression) (category 2B) |

- Atezolizumab and hyaluronidase-tqjs subcutaneous injection may be substituted for IV atezolizumab. Atezolizumab and hyaluronidase-tqjs has different dosing and administration instructions compared to atezolizumab for IV infusion.
- Nivolumab and hyaluronidase-nvhy subcutaneous injection may be substituted for IV nivolumab. Nivolumab and hyaluronidase-nvhy has different dosing and administration instructions compared to IV nivolumab.

[a] Maintenance therapy with avelumab only if there is no progression on first-line platinum-containing chemotherapy.
[b] Atezolizumab: SP142 assay, PD-L1–stained tumor-infiltrating immune cells covering ≥5% of the tumor area.

**Note: All recommendations are category 2A unless otherwise indicated.**

Continued
References

## PRINCIPLES OF SYSTEMIC THERAPY

### Second-Line Systemic Therapy for Locally Advanced or Metastatic Disease (Stage IV)

#### Previous immunotherapy and enfortumab vedotin-ejfv (no previous chemotherapy)

| Preferred regimens | Other recommended regimens | Useful in certain circumstances |
|---|---|---|
| • DDMVAC with growth factor support[2]<br>• Gemcitabine and cisplatin[4]<br>• Gemcitabine and carboplatin (category 2B)<br>• Biomarker-directed therapy (see biomarker-directed therapy table, BL-G 4 of 7) | • Paclitaxel[22] or docetaxel[23]<br>• Gemcitabine[24] | • Gemcitabine, cisplatin, and nivolumab (category 2B) |

#### Previous chemotherapy (no previous immunotherapy or enfortumab vedotin-ejfv)[c]

| Preferred regimens | Other recommended regimens | Useful in certain circumstances |
|---|---|---|
| • Pembrolizumab (category 1 post-platinum)[25]<br>• Enfortumab vedotin-ejfv and pembrolizumab[16]<br>• Enfortumab vedotin-ejfv[26]<br>• Nivolumab[27] (category 2B)<br>• Avelumab[28,29] (category 2B)<br>• Biomarker-directed therapy (see biomarker-directed therapy table, BL-G 4 of 7) | • Paclitaxel[22] or docetaxel[23]<br>• Gemcitabine[24] | • DDMVAC with growth factor support[2] (category 2B)<br>• Ifosfamide, doxorubicin, and gemcitabine[30] (category 2B)<br>• Gemcitabine and paclitaxel[31] (category 2B)<br>• Gemcitabine and cisplatin[4] (category 2B) |

#### Previous immunotherapy (no previous chemotherapy or enfortumab vedotin-ejfv)

| Preferred regimens | Other recommended regimens | Useful in certain circumstances |
|---|---|---|
| • Enfortumab vedotin-ejfv[26]<br>• Enfortumab vedotin-ejfv and pembrolizumab<br>• Gemcitabine and carboplatin<br>• Gemcitabine and cisplatin[4]<br>• DDMVAC with growth factor support[2]<br>• Biomarker-directed therapy (see biomarker-directed therapy table, BL-G 4 of 7) | • Paclitaxel[22] or docetaxel[23]<br>• Gemcitabine[24] | • Gemcitabine, cisplatin, and nivolumab (category 2B)<br>• Ifosfamide, doxorubicin, and gemcitabine[30](category 2B)<br>• Gemcitabine and paclitaxel[31] (category 2B) |

#### Previous chemotherapy and immunotherapy (no previous enfortumab vedotin-ejfv)[d,e]

| Preferred regimens | Other recommended regimens | Useful in certain circumstances |
|---|---|---|
| • Enfortumab vedotin-ejfv[32,33](category 1)<br>• Biomarker-directed therapy (see biomarker-directed therapy table, BL-G 4 of 7) | • Enfortumab vedotin-ejfv and pembrolizumab<br>• Paclitaxel[22] or docetaxel[23]<br>• Gemcitabine[24]<br>• Gemcitabine and cisplatin[4]<br>• DDMVAC with growth factor support[2]<br>• Ifosfamide, doxorubicin, and gemcitabine[30] (category 2B)<br>• Gemcitabine and paclitaxel[31] (category 2B) | • Sacituzumab govitecan-hziy[34] |

• Nivolumab and hyaluronidase-nvhy subcutaneous injection may be substituted for IV nivolumab. Nivolumab and hyaluronidase-nvhy has different dosing and administration instructions compared to IV nivolumab.

**Note: All recommendations are category 2A unless otherwise indicated.**

Footnotes References

## PRINCIPLES OF SYSTEMIC THERAPY

| Subsequent-Line Systemic Therapy for Locally Advanced or Metastatic Disease (Stage IV)[d,e] | | |
|---|---|---|
| **Previous chemotherapy, immunotherapy, and enfortumab vedotin-ejfv** | | |
| **Preferred regimen**<br>• Biomarker-directed therapy Biomarker-directed therapy (see biomarker-directed therapy table) | **Other recommended regimens**<br>• Gemcitabine[24]<br>• Paclitaxel[22] or docetaxel[23]<br>• Ifosfamide, doxorubicin, and gemcitabine[30](category 2B)<br>• Gemcitabine and paclitaxel[31] (category 2B) | **Useful in certain circumstances**<br>• Sacituzumab govitecan-hziy[34] |

| Biomarker-Directed Therapy (regardless of previous therapy) (pan-cancer tumor-agnostic treatments can be considered for patients with actionable mutations) |
|---|
| • Erdafitinib (susceptible *FGFR3* genetic alterations)[f,35]<br>• Fam-trastuzumab deruxtecan-nxki (HER2-positive, IHC 3+)[36] |

[c] If progression-free survival >12 months after platinum (eg, cisplatin or carboplatin), consider re-treatment with platinum if the patient is still platinum eligible.
[d] Patient should have already received platinum and a checkpoint inhibitor, if eligible.
[e] These therapies are appropriate for patients who received a first-line platinum-containing chemotherapy followed by checkpoint inhibitor maintenance therapy or first-line therapy containing both platinum chemotherapy and an immune checkpoint inhibitor.
[f] Category 1 for patients who have already received platinum and a checkpoint inhibitor if eligible.

**Note: All recommendations are category 2A unless otherwise indicated.**

## PRINCIPLES OF SYSTEMIC THERAPY

| Radiosensitizing Chemotherapy Regimens[g] | | |
|---|---|---|
| **Preferred regimens**<br>• Cisplatin[h] alone[37,38]<br>• Low-dose gemcitabine[39-41]<br>• 5-FU and mitomycin[42] | **Other recommended regimens**<br>• Cisplatin and 5-FU[39,43]<br>• Cisplatin and paclitaxel[39,44] | **Useful in certain circumstances (not generally used for curative-intent chemoradiotherapy for organ preservation)**<br>• Taxane (docetaxel or paclitaxel) (category 2B)<br>• 5-FU (category 2B)<br>• Capecitabine (category 3) |

[g] In select cases these regimens may be used with palliative intent.
[h] 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;20:3061-3071).

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**Note: All recommendations are category 2A unless otherwise indicated.**

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**Note: All recommendations are category 2A unless otherwise indicated.**

## PRINCIPLES OF RADIATION MANAGEMENT OF INVASIVE DISEASE

**Carcinoma of the Bladder: Unless otherwise stated, doses are 1.8–2.0 Gy daily fractionation.**

- **Precede RT 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 RT prior to segmental cystectomy (category 2B).**
- **Concurrent chemoradiotherapy or RT alone is most successful for patients without moderate/severe hydronephrosis and without extensive CIS associated with their muscle-invading tumor.**
- **For patients with stage Ta, T1, or CIS, external beam RT (EBRT) alone is rarely appropriate. For patients with recurrent Ta–T1 disease usually following BCG therapy but without extensive CIS 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 RT 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 dose-volume histogram (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 recommended for added tumor cytotoxicity, and can be given without significant increased toxicity over RT alone. Concurrent 5-FU and mitomycin C or low-dose gemcitabine can be used instead of cisplatin-containing regimens in patients with low or moderate renal function. Such therapy is optimally given by dedicated multidisciplinary teams.**
- **Concurrent chemoradiotherapy (preferred) or RT alone should be considered as potentially curative therapy for patients who are medically inoperable. Concurrent chemoradiotherapy or RT alone should be considered 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 5 of 7 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 a 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 RT (category 2B). 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.**
- **Conduct tumor status assessment after completion of full-dose primary chemoradiotherapy. See Table 7 on BL-E 5 of 6.**
- **In highly selected T4b tumor cases, may consider intraoperative RT.**
- **Concurrent chemoradiotherapy is generally most suitable for patients with solitary tumors, negative nodes, no extensive or multifocal CIS, no moderate/severe tumor-related hydronephrosis, and good pre-treatment bladder function.**
- **For palliative RT, consider a dose of 30 Gy in 10 fractions or 21 Gy in 3 fractions.**
- **A meta-analysis of individual patient data from two randomized phase III studies (BC2001 and BCON) found that a hypofractionated schedule of 55 Gy in 20 fractions over 4 weeks is noninferior to the standard fractionation schedule of 64 Gy in 32 fractions over 6.5 weeks for both invasive local control and toxicity and that the hypofractionated schedule is superior regarding invasive local control.**

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References

**Note: All recommendations are category 2A unless otherwise indicated.**

## PRINCIPLES OF RADIATION MANAGEMENT OF INVASIVE DISEASE

**Carcinoma of the Urethra: Unless otherwise stated, doses are 1.8–2.0 Gy daily fractionation.**

- **Data support the use of RT 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**
    - ◊ **66–70 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**
    - ◊ **45–50.4 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 66–70 Gy and gross nodal disease to 54–66 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 RT**
    - ◊ **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 45–50.4 Gy EBRT. Involved resection margins and areas of extranodal extension should be boosted to 54–60 Gy if feasible based on normal tissue constraints. Areas of gross residual disease should be boosted to 66–70 Gy, if feasible based on normal tissue constraints. Concurrent chemotherapy with regimens used for bladder cancer should be considered for added tumor cytotoxicity.**
  - **Recurrent disease**
    - ◊ **Clinical target volume (CTV) should include gross disease in any suspected areas of spread at 66–74 Gy (higher dose up to 74 Gy for larger tumor and non-urothelial histology) and consideration can be given to elective regional-nodal basins (45–50.4 Gy) as discussed above, if feasible based on normal tissue constraints.**

NCCN recommendations have been developed to be inclusive of individuals of all sexual and gender identities to the greatest extent possible. On this page, the terms male and female refer to sex assigned at birth.

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**Note: All recommendations are category 2A unless otherwise indicated.**

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**Note: All recommendations are category 2A unless otherwise indicated.**

## PRINCIPLES OF ALTERNATIVE RISK CLASSIFIERS AND BIOMARKERS

- **A physician's expertise and patient's preferences are critical when considering the diagnosis of bladder cancer, frequency of surveillance, and treatment intensification or deintensification decisions. The NCCN Guidelines provide an evidence-based expert consensus that applies to most patients, but cannot capture all the nuances of any individual patient case. The NCCN Bladder Cancer Panel acknowledges that risk classifiers may provide additional prognostic information for estimating the risk of various outcomes after diagnosis or treatment. These risk classifiers include, but are not limited to, staging systems derived from routinely available clinical information and nomograms, commercially available molecular tests, radiologic evaluations, and emerging artificial intelligence models. These risk classifiers should be restricted to use in cases where there is concern that delivering guideline-directed practices or therapy may lead to over- or under-treatment or unacceptable toxicity.**

### Prognostic Biomarkers

- **Since prognostic biomarkers are agnostic to the treatments received, evidence supporting their use may be derived from retrospective studies, prospective registries, or prospective clinical trials. The NCCN Bladder Cancer Panel has elected not to list all the available and emerging prognostic risk classifiers, regardless of the evidence level. The Panel encourages physicians and patients to carefully weigh the quality and size of the studies that led to their development and validation when using them as clinical tools to aid in determining the frequency of surveillance monitoring, treatment intensification, or deintensification decisions. To be clinically useful, the test should inform the patient of the absolute risk of the event of interest (eg, metastasis or progression). Prognostic biomarkers may be used in considering treatment intensification or deintensification decisions.**

### Predictive Biomarkers

- **Predictive biomarkers inform decisions on whether specific interventions may be beneficial, futile, or harmful, regardless of the absolute risk. To be classified as a predictive biomarker, a risk classifier must prove that a change in management alters the risk of an outcome of interest. To do so, the risk classifier must be tested in data derived from prospectively randomized trials, where the randomization question was the management change, and the pre-specified endpoints of the trial were the outcome of interest.**

**Note: All recommendations are category 2A unless otherwise indicated.**

## PRINCIPLES OF ALTERNATIVE RISK CLASSIFIERS AND BIOMARKERS

**Disease Contexts**

- **Germline Testing**
  - **The Panel recommends inquiring about the family and personal history of cancer and known germline variants at the time of initial diagnosis. The criteria for germline testing should be reviewed at the time of the initial diagnosis and, if relevant, at recurrence.**

- **Non–Muscle-Invasive Bladder Cancer (NMIBC)**
  - **Biomarkers have a limited role in the initial evaluation and management of NMIBC. Any suspected patient with bladder cancer should undergo cystoscopy, TURBT, and EUA for diagnosis/disease risk stratification, which will drive subsequent treatment options offered to patients.**
  - **Office cystoscopy at recommended intervals is a critical diagnostic and surveillance tool for NMIBC. Omission or delay of cystoscopy is acceptable only if a predictive biomarker has been tested and found to be non-inferior in a prospective randomized clinical trial.**
  - **Currently, there is no routine role for obtaining urine cytology or other urinary biomarkers in low-risk NMIBC.[a]**
  - **The ability of biomarkers to replace urine voided cytology, most notably in the surveillance of NMIBC (in the intermediate or greater risk stratification groups), remains uncertain, and randomized clinical trials are required to conclusively address such questions.**
  - **The use of certain biomarkers can be considered in the evaluation and workup of gross hematuria, but this is outside the scope of this guideline.**
  - **Biomarkers have the greatest clinical value in the further evaluation of patients with subjective findings at the time of office cystoscopy (eg, focal or diffuse redness raising concern most notably in a patient with previous intravesical treatment that could explain such findings) or in the context of abnormal voided cytology (most notably when the upper tract diagnostic imaging evaluation is negative). However, we leave this to the discretion and clinical judgment of board-certified practicing urologists to determine if and when such biomarkers may be clinically used in their practice.**

- **Muscle-Invasive Bladder Cancer (MIBC)/Resectable:**
  - **The Panel does not recommend routine somatic tumor testing unless it enables a patient to be considered for an available clinical trial.**
  - **The Panel recognizes that some ultrasensitive circulating tumor DNA (ctDNA) assays may have prognostic value after cystectomy. However, to date, the Panel has concluded that there are insufficient data for ctDNA results to determine the course of surveillance or therapy after complete surgical resection.**

[a] See AUA Risk Stratification for Non–Muscle-Invasive Bladder Cancer definitions on BL-2.

**Note: All recommendations are category 2A unless otherwise indicated.**

## PRINCIPLES OF ALTERNATIVE RISK CLASSIFIERS AND BIOMARKERS

**Disease Contexts (cont.)**

- **Locally Advanced Unresectable/Metastatic Bladder Cancer:**
  - **The Panel recommends somatic tumor testing[b] for all patients with unresectable or metastatic bladder cancer at the time of initial diagnosis and, if relevant, at recurrence. Somatic tumor testing assays should cover *FGFR3* alterations. A larger panel may be preferred to identify rare mutations that may have approved therapies or allow for clinical trial eligibility.**
  - **The Panel recommends evaluation of microsatellite instability-high (MSI-H) and/or mismatch repair (MMR) status.**
  - **The Panel recommends immunohistochemistry (IHC) testing for HER2.**

- **Advanced Disease**
  - **Studies have demonstrated that ultrasensitive ctDNA assays may track the response to therapy and progression. However, there are insufficient data that changes in therapy based on ctDNA significantly improve outcomes. Additionally, there are no data to date that ctDNA clearance should be used to make decisions to alter or discontinue therapy.**

[b] Molecular/genomic testing in a Clinical Laboratory Improvement Amendments (CLIA)-approved laboratory, including FGFR RGQ reverse transcriptase polymerase chain reaction (RT-PCR) for *FGFR3* genetic alterations and IHC for HER2 overexpression.

**Note: All recommendations are category 2A unless otherwise indicated.**

# NCCN Guidelines Version 1.2025
# Upper GU Tract Tumors

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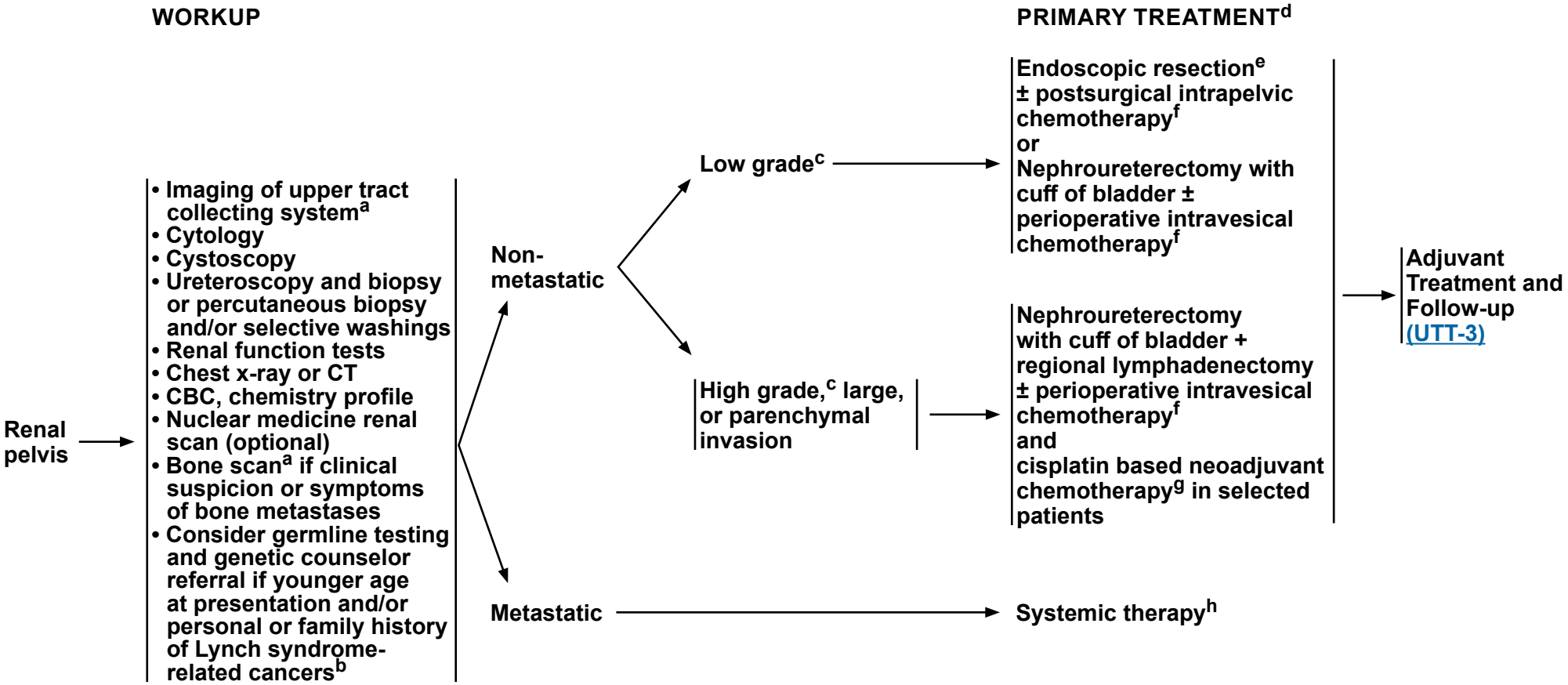
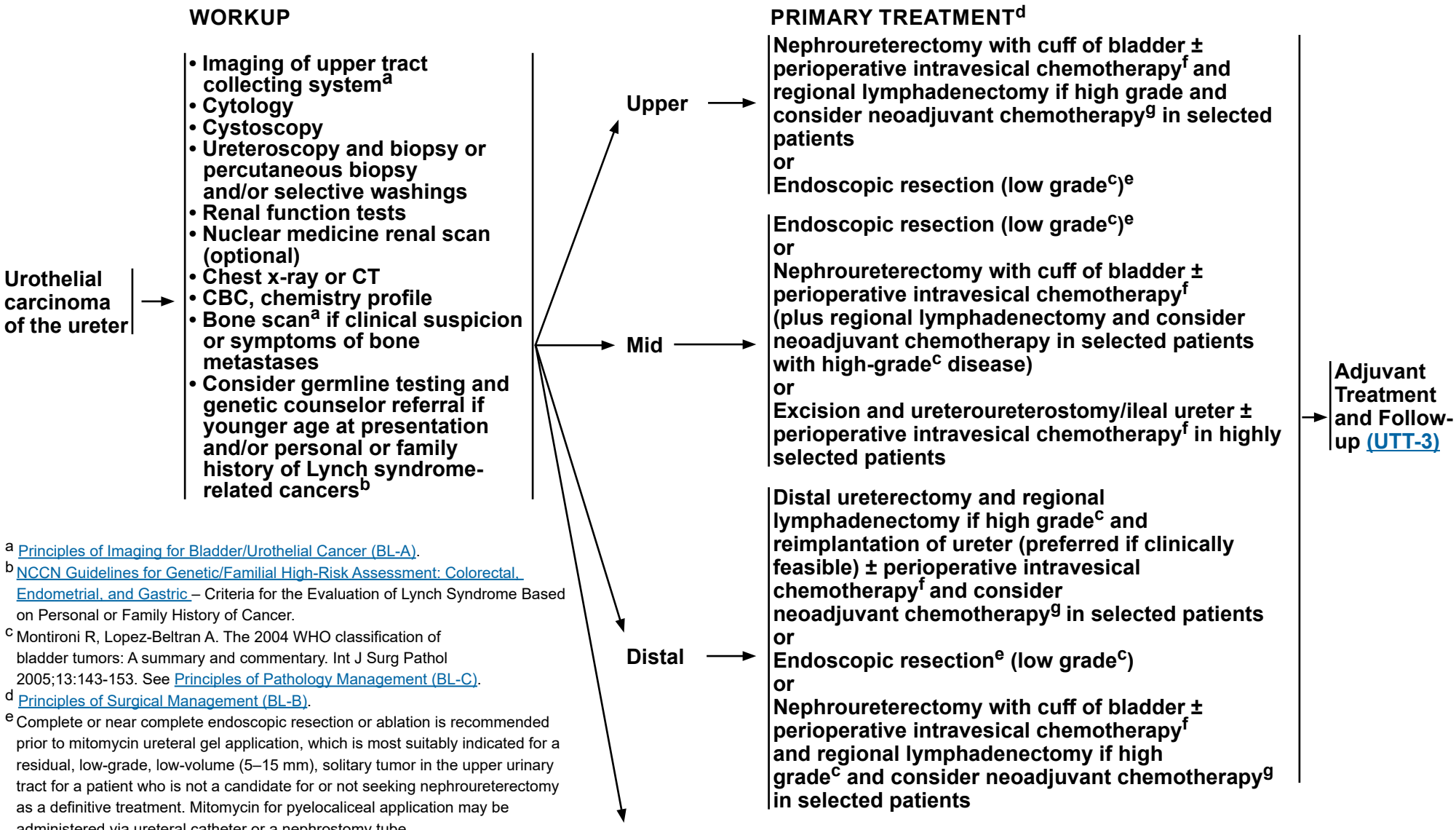



[a] Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
[b] NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric – Criteria for the Evaluation of Lynch Syndrome Based on Personal or Family History of Cancer.
[c] Montironi R, Lopez-Beltran A. The 2004 WHO classification of bladder tumors: A summary and commentary. Int J Surg Pathol 2005;13:143-153. See Principles of Pathology Management (BL-C).
[d] Principles of Surgical Management (BL-B).
[e] Complete or near complete endoscopic resection or ablation is recommended prior to mitomycin ureteral gel application, which is most suitably indicated for a residual, low-grade, low-volume (5–15 mm), solitary tumor in the upper urinary tract for a patient who is not a candidate for or not seeking nephroureterectomy as a definitive treatment. Mitomycin for pyelocaliceal application may be administered via ureteral catheter or a nephrostomy tube.
[f] Principles of Instillation Therapy (BL-F).
[g] Principles of Systemic Therapy (BL-G 1 of 7).
[h] See Principles of Systemic Therapy (BL-G 2 of 7, 3 of 7, and 4 of 7).

**Note: All recommendations are category 2A unless otherwise indicated.**




a Principles of Imaging for Bladder/Urothelial Cancer (BL-A).

b NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric – Criteria for the Evaluation of Lynch Syndrome Based on Personal or Family History of Cancer.

c 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).

d Principles of Surgical Management (BL-B).

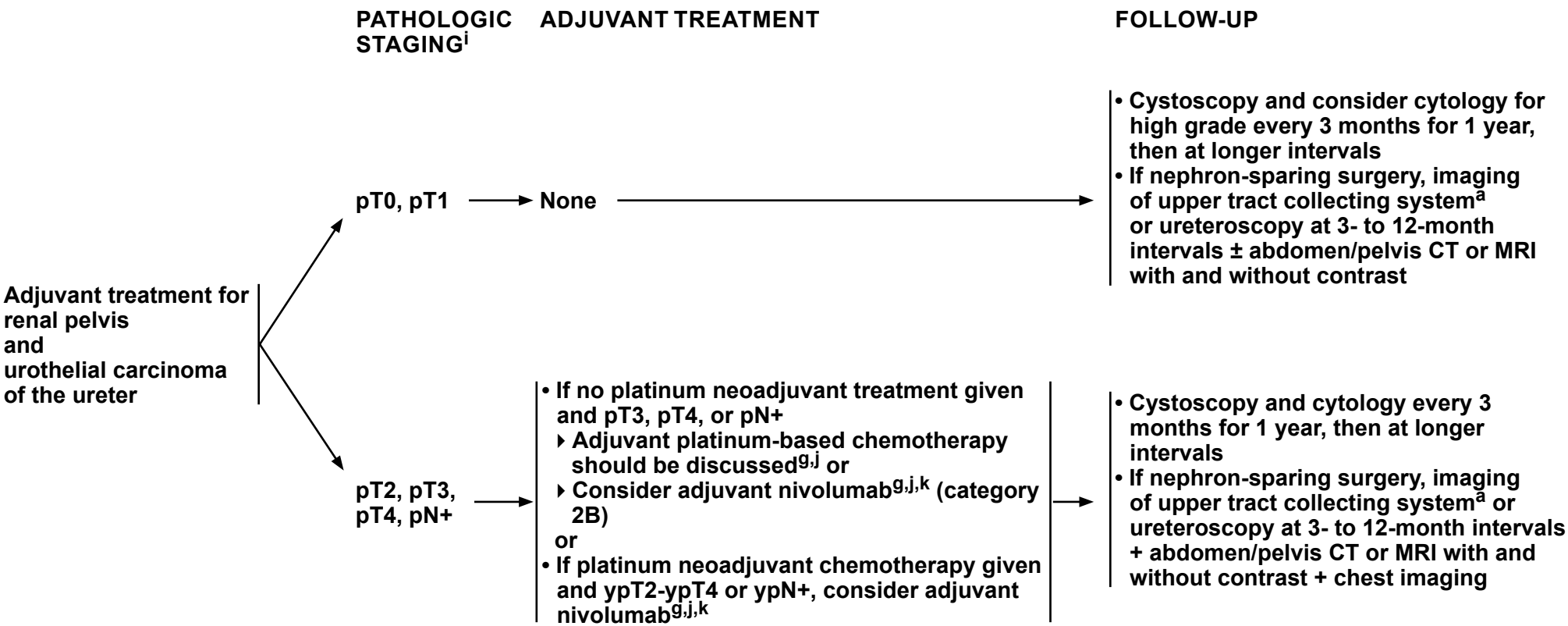
e Complete or near complete endoscopic resection or ablation is recommended prior to mitomycin ureteral gel application, which is most suitably indicated for a residual, low-grade, low-volume (5–15 mm), solitary tumor in the upper urinary tract for a patient who is not a candidate for or not seeking nephroureterectomy as a definitive treatment. Mitomycin for pyelocaliceal application may be administered via ureteral catheter or a nephrostomy tube.

f Principles of Intravesical Treatment Instillation Therapy (BL-F).

g Principles of Systemic Therapy (BL-G 1 of 7).

h See Principles of Systemic Therapy (BL-G 2 of 7, 3 of 7, and 4 of 7).

**Note: All recommendations are category 2A unless otherwise indicated.**




[a] Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
[g] Principles of Systemic Therapy (BL-G 1 of 7).
[i] The modifier “p” refers to pathologic staging based on surgical resection and lymph node dissection.
[j] Follow recommendations for adjuvant chemotherapy after ensuring that patient is fully staged to rule out metastatic disease.
[k] Most appropriate for patients who value an opportunity to delay recurrence even if the chance of cure was not improved, and for whom the risk of side effects was acceptable.

**Note: All recommendations are category 2A unless otherwise indicated.**

National Comprehensive Cancer Network®

# NCCN Guidelines Version 1.2025
# Urothelial Carcinoma of the Prostate

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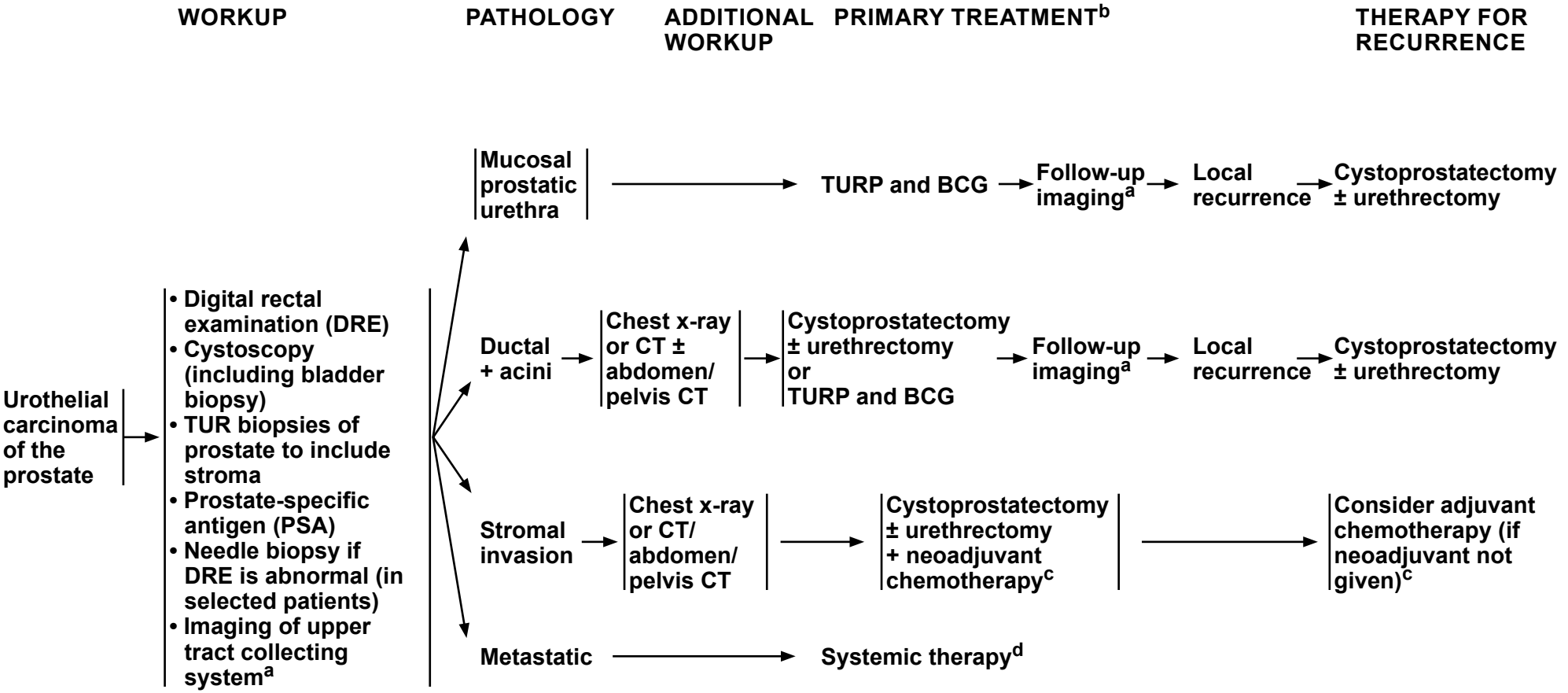
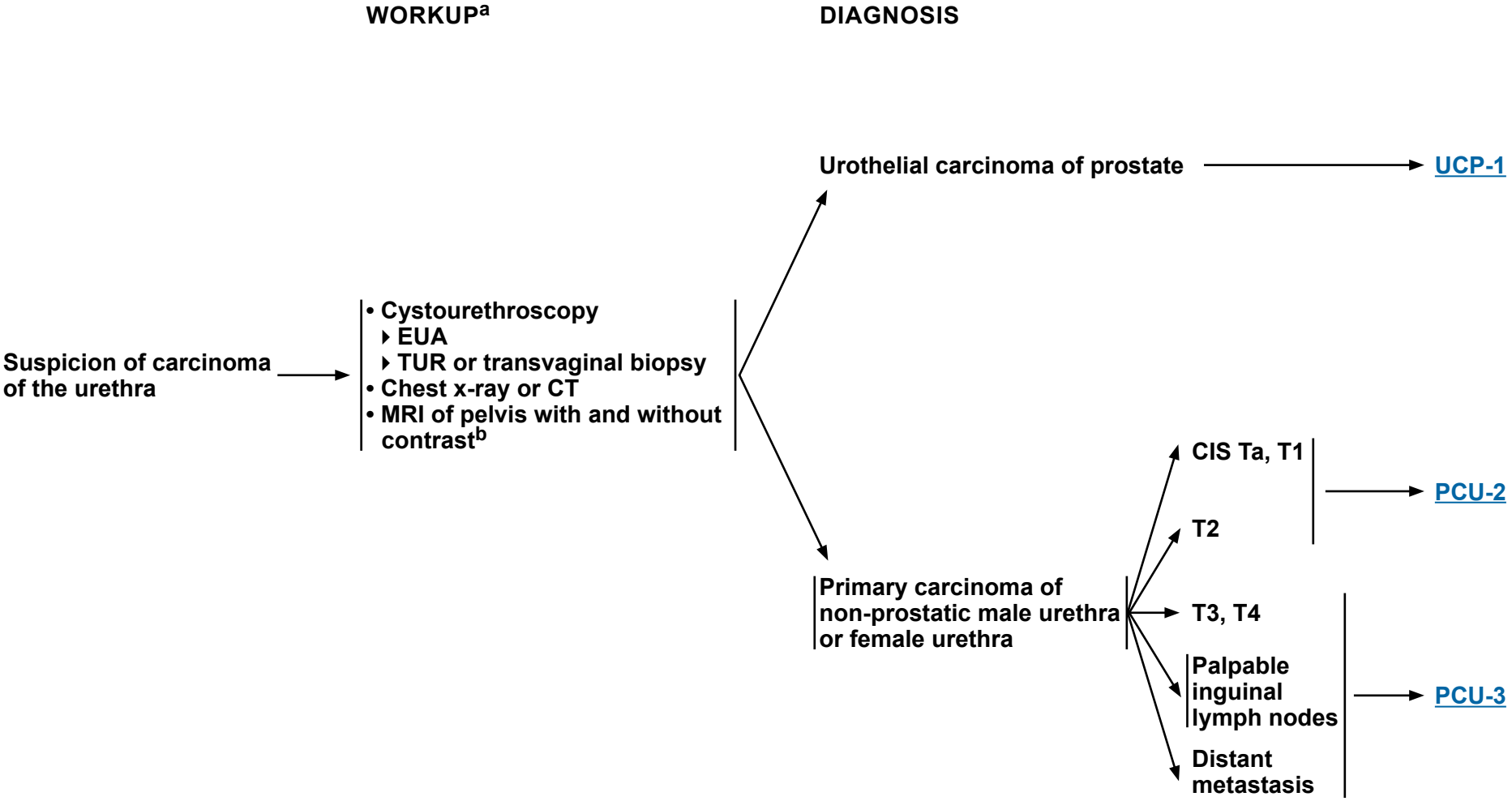



[a] Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
[b] Principles of Surgical Management (BL-B).
[c] Principles of Systemic Therapy (BL-G 1 of 7).
[d] See Principles of Systemic Therapy (BL-G 2 of 7, 3 of 7, and 4 of 7).

**Note: All recommendations are category 2A unless otherwise indicated.**




[a] Referral to a specialized center is recommended.
[b] Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
NCCN recommendations have been developed to be inclusive of individuals of all sexual and gender identities to the greatest extent possible. On this page, the terms male and female refer to sex assigned at birth.

**Note: All recommendations are category 2A unless otherwise indicated.**

# NCCN Guidelines Version 1.2025
# Primary Carcinoma of the Urethra

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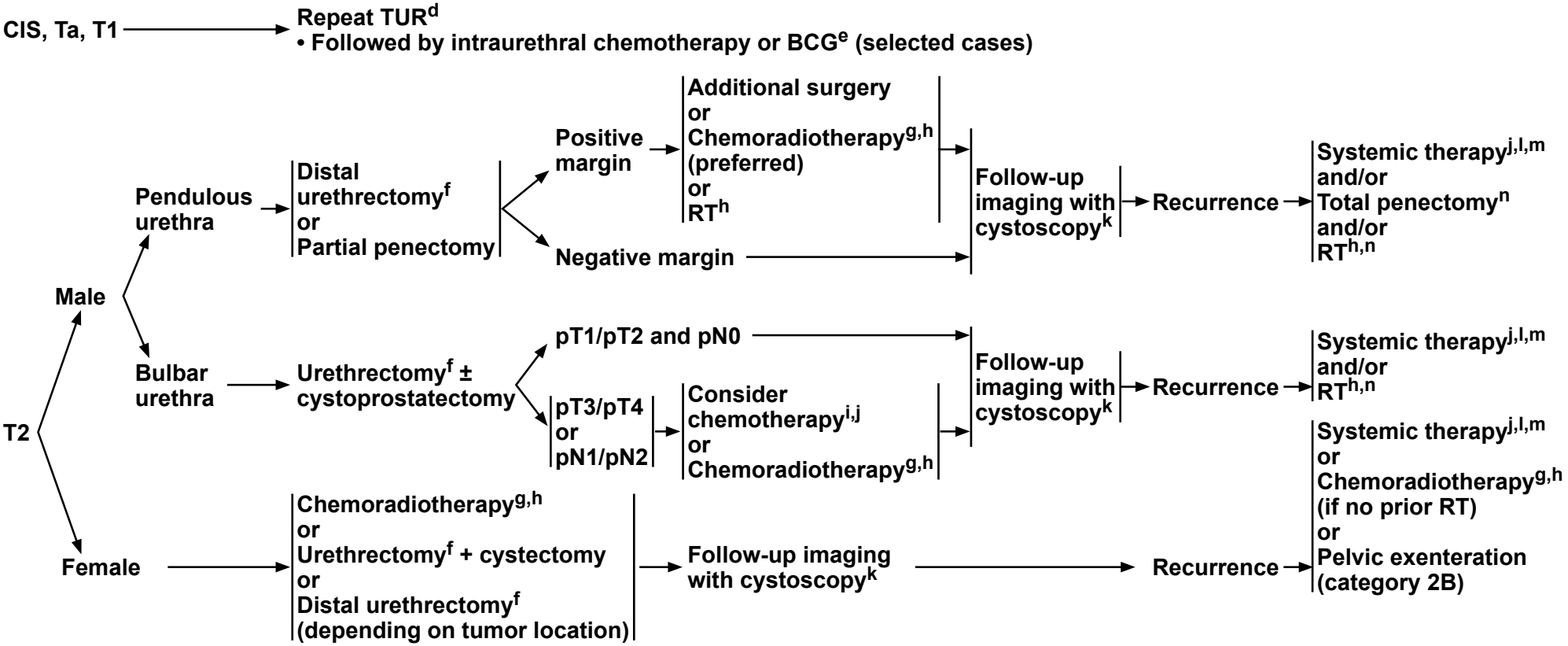


[c] Principles of Surgical Management (BL-B).
[d] In patients with a prior radical cystectomy and a cutaneous diversion, consider a total urethrectomy.
[e] Principles of Instillation Therapy (BL-F).
[f] Consider neoadjuvant chemotherapy (category 2B) or chemoradiation.
[g] Principles of Systemic Therapy (BL-G 5 of 7).
[h] Principles of Radiation Management of Invasive Disease - Carcinoma of the Urethra (BL-H 2 of 3).
[i] Principles of Systemic Therapy (BL-G 1 of 7).
[j] Chemotherapy regimen based on histology (Dayyani F, et al. Urol Oncol 2013;31:1171-1177). Also see Non-Urothelial Cell and Urothelial with Subtype Histology (BL-D).
[k] Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
[l] Principles of Systemic Therapy (BL-G 2 of 7).
[m] See Principles of Systemic Therapy (BL-G 3 of 7 and 4 of 7).
[n] Consider for local recurrence (± chemotherapy).

NCCN recommendations have been developed to be inclusive of individuals of all sexual and gender identities to the greatest extent possible. On this page, the terms male and female refer to sex assigned at birth.

**Note: All recommendations are category 2A unless otherwise indicated.**

# NCCN Guidelines Version 1.2025
# Primary Carcinoma of the Urethra

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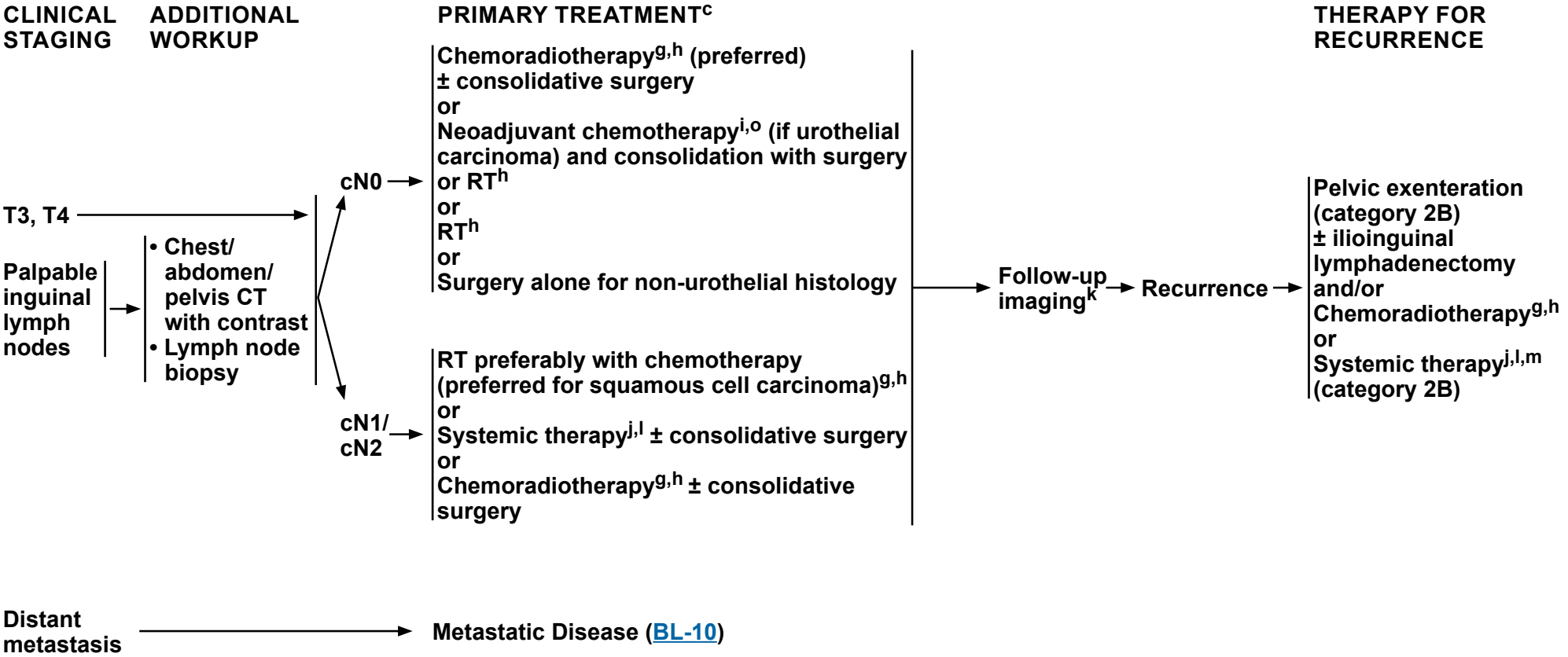


[c] Principles of Surgical Management (BL-B).
[g] Principles of Systemic Therapy (BL-G 5 of 7).
[h] Principles of Radiation Management of Invasive Disease - Carcinoma of the Urethra (BL-H 2 of 3).
[i] Principles of Systemic Therapy (BL-G 1 of 7).
[j] Chemotherapy regimen based on histology (Dayyani F, et al. Urol Oncol 2013;31:1171-1177). Also see Non-Urothelial Cell and Urothelial with Subtype Histology (BL-D).
[k] Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
[l] Principles of Systemic Therapy (BL-G 2 of 7).
[m] See Principles of Systemic Therapy (BL-G 3 of 7 and 4 of 7).
[o] Data support neoadjuvant chemotherapy only for urothelial carcinoma.

**Note: All recommendations are category 2A unless otherwise indicated.**

***Table 1.*** **American Joint Committee on Cancer (AJCC) TNM Staging System for Bladder Cancer 8th ed., 2017)**

| | |
|---|---|
| **T** | **Primary Tumor** |
| **TX** | Primary tumor cannot be assessed |
| **T0** | No evidence of primary tumor |
| **Ta** | Noninvasive papillary carcinoma |
| **CIS (Tis)** | Urothelial carcinoma in situ: “flat tumor” |
| **T1** | Tumor invades lamina propria (subepithelial connective tissue) |
| **T2** | Tumor invades muscularis propria |
| pT2a | Tumor invades superficial muscularis propria (inner half) |
| pT2b | Tumor invades deep muscularis propria (outer half) |
| **T3** | Tumor invades perivesical tissue |
| pT3a | Microscopically |
| pT3b | Macroscopically (extravesical mass) |
| **T4** | Extravesical tumor directly invades any of the following: prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall |
| T4a | Extravesical tumor invades prostatic stroma, seminal vesicles, uterus, vagina |
| T4b | Extravesical tumor invades pelvic wall, abdominal wall |

| | |
|---|---|
| **N** | **Regional Lymph Nodes** |
| **NX** | Lymph nodes cannot be assessed |
| **N0** | No lymph node metastasis |
| **N1** | Single regional lymph node metastasis in the true pelvis (perivesical, obturator, internal and external iliac, or sacral lymph node) |
| **N2** | Multiple regional lymph node metastasis in the true pelvis (perivesical, obturator, internal and external iliac, or sacral lymph node metastasis) |
| **N3** | Lymph node metastasis to the common iliac lymph nodes |

| | |
|---|---|
| **M** | **Distant Metastasis** |
| **M0** | No distant metastasis |
| **M1** | Distant metastasis |
| M1a | Distant metastasis limited to lymph nodes beyond the common iliacs |
| M1b | Non-lymph-node distant metastases |

**Histologic Grade (G)**

For urothelial histologies, a low- and high-grade designation is used to match the current World Health Organization/International Society of Urological Pathology (WHO/ISUP) recommended grading system:

| | |
|---|---|
| **LG** | Low-grade |
| **HG** | High-grade |

For squamous cell carcinoma and adenocarcinoma, the following grading schema is recommended:

| | |
|---|---|
| **GX** | Grade cannot be assessed |
| **G1** | Well differentiated |
| **G2** | Moderately differentiated |
| **G3** | Poorly differentiated |

***Table 2.*** **AJCC Prognostic Groups**

| | T | N | M |
|---|---|---|---|
| **Stage 0a** | Ta | N0 | M0 |
| **Stage 0is** | CIS (Tis) | N0 | M0 |
| **Stage I** | T1 | N0 | M0 |
| **Stage II** | T2a | N0 | M0 |
| | T2b | N0 | M0 |
| **Stage IIIA** | T3a | N0 | M0 |
| | T3b | N0 | M0 |
| | T4a | N0 | M0 |
| | T1-T4a | N1 | M0 |
| **Stage IIIB** | T1-T4a | N2,N3 | M0 |
| **Stage IVA** | T4b | Any N | M0 |
| | Any T | Any N | M1a |
| **Stage IVB** | Any T | Any N | M1b |

Continued

Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing.

***Table 3.*** **American Joint Committee on Cancer (AJCC)**
**TNM Staging System for Renal Pelvis and Ureter Cancer (8th ed., 2017)**

| **T** | **Primary Tumor** |
|---|---|
| **TX** | Primary tumor cannot be assessed |
| **T0** | No evidence of primary tumor |
| **Ta** | Papillary noninvasive carcinoma |
| **CIS (Tis)** | Carcinoma *in situ* |
| **T1** | Tumor invades subepithelial connective tissue |
| **T2** | Tumor invades the muscularis |
| **T3** | For renal pelvis only: Tumor invades beyond muscularis into peripelvic fat or the renal parenchyma.<br>For ureter only: Tumor invades beyond muscularis into periureteric fat. |
| **T4** | Tumor invades adjacent organs, or through the kidney into the perinephric fat. |

| **N** | **Regional Lymph Nodes** |
|---|---|
| **NX** | Regional lymph nodes cannot be assessed |
| **N0** | No regional lymph node metastasis |
| **N1** | Metastasis ≤2 cm in greatest dimension, in a single lymph node |
| **N2** | Metastasis >2 cm in a single lymph node; or multiple lymph nodes |

| **M** | **Distant Metastasis** |
|---|---|
| **M0** | No distant metastasis |
| **M1** | Distant metastasis |

**Histologic Grade (G)**
For urothelial histologies, a low- and high-grade designation is used to match the current WHO/ISUP recommended grading system:

| | |
|---|---|
| **LG** | Low-grade |
| **HG** | High-grade |

For squamous cell carcinoma and adenocarcinoma, the following grading schema is recommended.

| | |
|---|---|
| **GX** | Grade cannot be assessed |
| **G1** | Well differentiated |
| **G2** | Moderately differentiated |
| **G3** | Poorly differentiated |

***Table 4.*** **AJCC Prognostic Groups**

| | **T** | **N** | **M** |
|---|---|---|---|
| **Stage 0a** | Ta | N0 | M0 |
| **Stage 0is** | CIS (Tis) | N0 | M0 |
| **Stage I** | T1 | N0 | M0 |
| **Stage II** | T2 | N0 | M0 |
| **Stage III** | T3 | N0 | M0 |
| **Stage IV** | T4 | NX, N0 | M0 |
| | Any T | N1 | M0 |
| | Any T | N2 | M0 |
| | Any T | Any N | M1 |

Continued

Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing.

***Table 5.*** **American Joint Committee on Cancer (AJCC) TNM Staging System for Urethral Carcinoma (8th ed., 2017)**

**Male Penile Urethra and Female Urethra**

| T | Primary Tumor |
|---|---|
| **TX** | Primary tumor cannot be assessed |
| **T0** | No evidence of primary tumor |
| **Ta** | Non-invasive papillary carcinoma |
| **CIS (Tis)** | Carcinoma *in situ* |
| **T1** | Tumor invades subepithelial connective tissue |
| **T2** | Tumor invades any of the following: corpus spongiosum, periurethral muscle |
| **T3** | Tumor invades any of the following: corpus cavernosum, anterior vagina |
| **T4** | Tumor invades other adjacent organs (e.g., invasion of the bladder wall) |

**Prostatic Urethra**

| T | Primary Tumor |
|---|---|
| **TX** | Primary tumor cannot be assessed |
| **T0** | No evidence of primary tumor |
| **Ta** | Non-invasive papillary carcinoma |
| **CIS (Tis)** | Carcinoma in situ involving the prostatic urethra or periurethral or prostatic ducts without stromal invasion |
| **T1** | Tumor invades urethral subepithelial connective tissue immediately underlying the urothelium |
| **T2** | Tumor invades the prostatic stroma surrounding ducts either by direct extension from the urothelial surface or by invasion from prostatic ducts |
| **T3** | Tumor invades the periprostatic fat |
| **T4** | Tumor invades other adjacent organs (e.g., extraprostatic invasion of the bladder wall, rectal wall) |

| N | Regional Lymph Nodes |
|---|---|
| **NX** | Regional lymph nodes cannot be assessed |
| **N0** | No regional lymph node metastasis |
| **N1** | Single regional lymph node metastasis in the inguinal region or true pelvis [perivesical, obturator, internal (hypogastric) and external iliac], or presacral lymph node |
| **N2** | Multiple regional lymph node metastasis in the inguinal region or true pelvis [perivesical, obturator, internal (hypogastric) and external iliac], or presacral lymph node |

| M | Distant Metastasis |
|---|---|
| **M0** | No distant metastasis |
| **M1** | Distant metastasis |

**Histologic Grade (G)**

Grade is reported by the grade value. For urothelial histology, a low- and high-grade designation is used to match the current WHO/ISUP recommended grading system:

| | |
|---|---|
| **LG** | Low grade |
| **HG** | High grade |

For squamous cell carcinoma and adenocarcinoma, the following grading schema is recommended:

| | |
|---|---|
| **GX** | Grade cannot be assessed |
| **G1** | Well differentiated |
| **G2** | Moderately differentiated |
| **G3** | Poorly differentiated |

***Table 6.*** **AJCC Prognostic Groups**

| | T | N | M |
|---|---|---|---|
| **Stage 0is** | CIS (Tis) | N0 | M0 |
| **Stage 0a** | Ta | N0 | M0 |
| **Stage I** | T1 | N0 | M0 |
| **Stage II** | T2 | N0 | M0 |
| **Stage III** | T1 | N1 | M0 |
| | T2 | N1 | M0 |
| | T3 | N0 | M0 |
| | T3 | N1 | M0 |
| **Stage IV** | T4 | N0 | M0 |
| | T4 | N1 | M0 |
| | Any T | N2 | M0 |
| | Any T | Any N | M1 |

Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing.

## ABBREVIATIONS

| | |
|---|---|
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| BCG | Bacillus Calmette-Guérin |
| CAP | College of American Pathologists |
| CBC | complete blood count |
| CIS | carcinoma in situ |
| CLIA | Clinical Laboratory Improvement Amendments |
| CMP | comprehensive metabolic panel |
| CNS | central nervous system |
| ctDNA | circulating tumor DNA |
| CTU | computed tomography urography |
| CTV | clinical target volume |
| DRE | digital rectal examination |
| DVH | dose-volume histogram |
| EBRT | external beam radiation therapy |
| EUA | examination under anesthesia |
| FDG | fluorodeoxyglucose |
| GFR | glomerular filtration rate |
| GU | genitourinary |
| H&P | history and physical |
| IHC | immunohistochemistry |
| IVP | intravenous pyelogram |
| LFT | liver function test |
| MIBC | muscle-invasive bladder cancer |
| MMR | mismatch repair |
| MRU | magnetic resonance urography |
| MSI-H | microsatellite instability-high |
| NMIBC | non–muscle-invasive bladder cancer |
| NOS | not otherwise specified |
| PA | posteroanterior |
| PSA | prostate-specific antigen |
| RT-PCR | reverse transcriptase polymerase chain reaction |
| TUR | transurethral resection |
| TURBT | transurethral resection of bladder tumor |
| TURP | transurethral resection of the prostate |
| UTUC | upper tract urothelial cancer |

| NCCN Categories of Evidence and Consensus | |
|---|---|
| **Category 1** | Based upon high-level evidence (≥1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate. |
| **Category 2A** | Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate. |
| **Category 2B** | Based upon lower-level evidence, there is NCCN consensus (≥50%, but <85% support of the Panel) 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 indicated.

| NCCN Categories of Preference | |
|---|---|
| **Preferred intervention** | Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability. |
| **Other recommended intervention** | Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes. |
| **Useful in certain circumstances** | Other interventions that may be used for selected patient populations (defined with recommendation). |

All recommendations are considered appropriate.

 

# Discussion

This discussion corresponds to the NCCN Guidelines for Bladder Cancer. All sections, excluding muscle invasive urothelial bladder cancer, were last updated on February 28, 2025. The section on muscle invasive urothelial bladder cancer was last updated January 17, 2025.

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## Overview

An estimated 83,190 new cases of urinary bladder cancer (63,070 males and 20,120 females) will be diagnosed in the United States in 2024 with approximately 16,840 deaths (12,290 males and 4550 females) occurring during this same period.[1] Bladder cancer, the sixth most common cancer in the United States, is rarely diagnosed in individuals <40 years. Given that the median age at diagnosis is 73 years,[2] and the associated risk factors, comorbid medical conditions are a frequent consideration in comprehensive care of patients with bladder cancer.

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 medications, chronic infection or irritation of the urinary tract, and certain medical conditions including obesity and diabetes.[3-6] While 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.[7] Certain genetic syndromes, most notably Lynch syndrome, may also predispose an individual to urothelial carcinoma.[8]

The clinical spectrum of bladder cancer can be divided into three categories that differ in prognosis, management, and therapeutic aims. The first category consists of non–muscle-invasive bladder cancer (NMIBC), for which treatment is directed at reducing recurrences and preventing progression to a more advanced stage, while minimizing adverse events (AEs) related to treatment. The second group encompasses muscle invasive, non-metastatic disease. Unlike NMIBC, muscle invasive disease poses a much greater risk for progression and requires more aggressive therapy, often a multidisciplinary approach including a combination of systemic therapy, surgery, and/or radiation.

The critical concern for the third group, consisting of metastatic lesions, is how to prolong survival and maintain quality of life. Numerous agents with different mechanisms of action have antitumor effects on this disease. The goal is to use these agents to increase survival and quality of life.

## Guidelines Update Methodology

The complete details of the Development and Update of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are available at www.NCCN.org.

## Literature Search Criteria

Prior to the update of this version of the NCCN Guidelines® for Bladder Cancer, an electronic search of the PubMed database was performed to obtain key literature using the following search terms: bladder cancer OR urothelial carcinoma of the ureter OR urothelial carcinoma of the prostate OR primary carcinoma of the urethra. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.[9]

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Meta-Analysis; Randomized Controlled Trials; Systematic Reviews; and Validation Studies. The data from key PubMed articles as well as articles from additional sources deemed as relevant to these Guidelines as discussed by the panel during the Guidelines update have been included in this version of the Discussion section. Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

## Sensitive/Inclusive Language Usage

NCCN Guidelines strive to use language that advances the goals of equity, inclusion, and representation.[10] NCCN Guidelines endeavor to use language that is person-first; not stigmatizing; anti-racist, anti-classist, anti-misogynist, anti-ageist, anti-ableist, and anti-weight-biased; and inclusive of individuals of all sexual orientations and gender identities. NCCN Guidelines incorporate non-gendered language, instead focusing on organ-specific recommendations. This language is both more accurate and more inclusive and can help fully address the needs of individuals of all sexual orientations and gender identities. NCCN Guidelines will continue to use the terms men, women, female, and male when citing statistics, recommendations, or data from organizations or sources that do not use inclusive terms. Most studies do not report how sex and gender data are collected and use these terms interchangeably or inconsistently. If sources do not differentiate gender from sex assigned at birth or organs present, the information is presumed to predominantly represent cisgender individuals. NCCN encourages researchers to collect more specific data in future studies and organizations to use more inclusive and accurate language in their future analyses.

## 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 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. Enhanced cystoscopy may be used if available. If a lesion is documented, the 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. Because smoking is a major risk factor for bladder cancer,[11] screening for smoking and initiation of treatment for smoking cessation, if appropriate, is recommended during the initial evaluation (see NCCN Guidelines for Smoking Cessation).

Evidence has suggested that bladder cancer has a substantial hereditary component, including a high prevalence of Lynch syndrome in patients with urothelial carcinoma.[8,12] Therefore, it is recommended to take a thorough family history for all patients with bladder cancer and consider germline testing and referral to a genetic counselor for those who are at higher risk of Lynch syndrome based on younger age at presentation and/or a personal or family history of Lynch syndrome-related cancers (see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal for information on the criteria and strategies for evaluation of Lynch syndrome).

A CT scan or MRI of the abdomen and pelvis is recommended before the TURBT, as long as it is logistically feasible, to allow for better anatomical characterization of the lesion and possible delineation of the 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 (EUA) is performed to resect visible tumor and to sample muscle within the area of the tumor to assess invasion. In a case where the tumor is clearly not invasive (eg, multiple small papillary tumors), EUA would not be

necessary. 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 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)*. Existing data support this approach largely for low-volume, low-grade disease.[13-15]

Mapping or random biopsies of normal-appearing urothelium rarely yield positive results and lack sensitivity for CIS, especially for low-risk tumors.[16-19] In addition, these biopsies often cause additional damage to the bladder without benefit to the patient. Therefore, mapping biopsies of normal-appearing urothelium are not recommended 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) must be evaluated and ureteroscopy may be considered.

Clinical investigation of the specimen obtained by TURBT or biopsy 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 EUA, 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[20] (see *Staging* in the algorithm). The NCCN Guidelines® for Bladder Cancer divide treatment recommendations for urothelial carcinoma of the bladder according to non-muscle invasive disease (Ta, T1, and CIS) 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%).[21] 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 either be at the same stage as the initial tumor or at a more advanced stage. While not fully endorsed by the AJCC staging system, there are data to support that pT1 sub-staging may have prognostic value, with microscopic or focal invasion into the lamina propria showing better outcomes than more extensive pT1 disease.[22-24] If feasible, pT1 sub-staging may be useful for prognostication, although it is currently not widely utilized and relies on specialized pathology review, which may not be available at all centers.

Papillary tumors confined to the mucosa or submucosa are generally managed endoscopically with complete resection. Progression to a more advanced stage may result in local symptoms or, less commonly, symptoms related to metastatic disease. An estimated 31% to 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.[25] 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 while 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 for localized bladder cancer.

The 8th edition of the AJCC Cancer Staging Manual includes 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).[20] 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.[20,26] 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*).

### Enhanced Cystoscopy

White light cystoscopy (WLC) is the current standard in the evaluation and staging of bladder cancer. While 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 expertise; however, data are still limited for both methods and WLC remains the mainstay of bladder cancer staging.

#### *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 the heme biosynthesis pathway. 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 fluoresce with a red emission in the presence of blue light. Earlier studies used the photosensitizer 5-aminolevulinic acid (5-ALA), although more recent studies use only the U.S. Food and Drug Administration (FDA)-approved photosensitizer hexyl-aminolevulinate (HAL).

Several prospective clinical studies have evaluated BLC in conjunction with WLC and found higher detection rates of non-muscle invasive lesions with BLC.[27-32] Particularly CIS, which is often missed by WLC, was detected at a higher rate. A meta-analysis of BLC TURBT in NMIBC included 12 randomized controlled trials with a total of 2258 patients.[33] A lower recurrence rate was observed (overall response [OR], 0.5; $P < .00001$) with a delayed time to first recurrence by 7.39 weeks ($P < .0001$). Recurrence-free survival (RFS) 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,[34] 1345 patients with Ta, T1, or CIS disease showed improved detection of bladder tumors and a reduction in recurrence.[34] Compared to 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-ALA, 15 studies with HAL, and two studies that used both methodologies. The results from this review also support greater detection and reduced recurrence but no reduction in disease progression.[35]

Although most studies have found no significant reduction in disease progression, a recent analysis reported a trend towards a lower rate with the use of BLC compared to WLC (12.2% vs. 17.6%, respectively; *P* = .085) with a longer time to progression (*P* = .05).[36] Although BLC has demonstrated improved detection and reduced recurrence, the value of this technique in reducing disease progression remains less established. Therefore, 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.[35] The limitations of BLC require judicious application of this additional diagnostic tool.

***Narrow-Band Imaging***

NBI uses two narrow bands of light at 415 nanometers and 540 nanometers 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 positives is higher.[37-41]

A systematic review and meta-analysis including seven prospective studies and 1040 patients with non-muscle invasive disease evaluated the accuracy of NBI compared to WLC. In total, 1476 tumors were detected by 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 to the 16 patients by WLC. Similarly, 276 additional tumors were reported in five studies using NBI versus 13 additional tumors by WLC. Although individual studies demonstrated an increase in the rate of false positives, 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 of NBI, as measured by a reduction in recurrence or progression.

A randomized prospective trial followed 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 to WLC (32.9% vs. 51.4%, respectively; OR, 0.62).[42] 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 NMIBC. This study found that while recurrence rates were similar between the two groups in the study population overall, NBI-guided TUR significantly reduced the likelihood of disease recurrence at 1 year in patients with low-risk disease (5.6% for NBI vs. 27.3% for WLC; $P = .002$).[43] These results are supported by the systemic reviews and meta-analyses that have also shown reduced recurrence rates following NBI-guided TUR compared to WLC-guided TUR.[44,45]

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.[43-46]

## 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 cytologic and architectural atypia.

Non-muscle invasive urothelial tumors may have flat and/or papillary histology. Flat urothelial lesions may be classified as urothelial CIS, a type of high-grade noninvasive urothelial carcinoma. The term urothelial dysplasia may be used in rare circumstances where the morphologic features fall short for a diagnosis of CIS. Papillary lesions may be benign (ie, urothelial papilloma, inverted papilloma) or malignant. The latter group includes papillary urothelial neoplasms of low malignant potential (PUNLMP) and papillary urothelial carcinoma (low and high grade). In some cases, a Ta or T1 NMIBC will have an associated urothelial CIS component.

Urothelial (transitional cell) carcinoma is the most common histologic subtype of bladder cancer in the United States and Europe and may develop anywhere urothelium is present, from the renal pelvis to the ureter, bladder, and proximal two thirds of the urethra. The fifth edition of the World Health Organization (WHO) Classification of Tumors of the Urinary System and Male Genital Organs, published in November 2022, provided new information into the grading of invasive urothelial carcinomas, as well as noninvasive urothelial neoplasms, and the definition of precursor lesions.[47]

Subtype (variant) histology is common with higher grades. The fifth edition of the WHO Classification included the adoption of a modified terminology where the designation of “subtype” was adopted to replace “variant” histology when referring to distinct morphologic categories within a given tumor type.[48,49] The reasoning behind this change is that the term “variant” has increasingly been used to describe genomic, rather than morphologic alterations, and therefore the WHO Classification system reserves “variant” for this purpose to avoid confusion. The presence of histologic subtypes of urothelial carcinoma should be documented as data suggest that the subtype may help define the natural history and inherent risk of progression, reflect different genetic etiology, and subsequently determine whether a more aggressive treatment approach should be considered (see *Bladder Cancer: Non-Urothelial and Urothelial with Subtype Histology* in the algorithm).[50-52] In some cases with a mixed histology, systemic treatment may only target cells of urothelial origin and the non-urothelial component can remain.

Squamous cell neoplasms of the urothelial tract 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.[53] Squamous cell carcinoma of the bladder is

morphologically indistinguishable from squamous cell carcinoma of other sites and generally presents at an advanced stage. The three 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 non-urothelial tumors, most commonly adenocarcinomas, which arise from the urachal ligament and secondarily involve the midline/dome of the bladder.[54] Tumors arising within the genitourinary tract but that are not of urothelial origin (eg, tumors of Müllerian type, melanocytic tumors, mesenchymal tumors) are beyond the scope of these guidelines.

## 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. Treatment for non-muscle invasive disease often includes intravesical therapy or, for those with particularly high-risk disease, 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 following TURBT to TURBT alone, although the instillation did not prolong the time to progression or time to death from bladder cancer.[15] This study also found that the instillation did not reduce recurrences in patients who had a prior recurrence rate of greater than one recurrence per year or with a European Organization for Research and Treatment of Cancer (EORTC) recurrence score greater than or equal to 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 NMIBC based on cystoscopic appearance showed that immediate post-TURBT instillation of gemcitabine reduced the rate of recurrence compared to saline instillation (placebo).[13] In the intention to treat (ITT) 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).[13] Intravesical therapy for a previous NMIBC was allowed in the study if received at least 6 months prior to enrollment. Another phase III, prospective, multicenter, randomized study of 2844 patients with NMIBC 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.[14] Previous intravesical chemotherapy was permitted in study participants as long as it was received at least 3 years prior to participation. For both studies, the rate of AEs did not significantly differ between the treatment and control groups, indicating that immediate intravesical instillation of gemcitabine or mitomycin was well tolerated.[13,14] Gemcitabine is preferred over mitomycin based on toxicity

profiles and lower cost.[55] 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 concern for 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 NMIBC.[56] The most commonly used chemotherapy agents are mitomycin C and gemcitabine, although gemcitabine is preferred over mitomycin due to better tolerability and cost. In addition, in systematic reviews and meta-analyses, gemcitabine has shown superior efficacy compared to mitomycin, in that it demonstrated reduced rates of recurrence and progression.[57,58]

Induction BCG has been shown to decrease the risk of bladder cancer recurrence following 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.[59] There are several meta-analyses demonstrating that BCG after TURBT is superior to TURBT alone, or TURBT and chemotherapy in preventing recurrences of high-grade Ta and T1 tumors.[60-63] A meta-analysis including nine trials of 2820 patients with NMIBC reported that mitomycin C was superior to BCG without maintenance in preventing recurrence, but inferior to BCG in trials using BCG maintenance.[64] Using the SEER database, a reduction in mortality of 23% was reported in patients receiving BCG therapy.[65] Other studies have also reported that BCG was better at reducing recurrence in intermediate- and high-risk NMIBC when compared to mitomycin C.[66,67]

BCG has also been compared to 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.[68] There were more frequent local and systemic side effects 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 to 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.[69] Long-term data comparing BCG to epirubicin in combination with interferon[69,70] in patients with T1 disease showed a better reduction in recurrence with BCG; however, no differences in progression or AEs were seen.[70] Patients in both studies received 2 to 3 years of maintenance therapy.

***Maintenance Therapy***

Maintenance intravesical therapy may be considered following 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 NMIBC 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 as well as 3- 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.[71] The 3-week timing of BCG has shown improved outcomes compared with epirubicin[70] or isoniazid.[69] 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.[72] A study of 1355 patients with a median follow-up of 7.1 years found no benefit in 3 years of

maintenance BCG compared to 1 year for patients with intermediate-risk disease.[73] Conversely, 3-year maintenance BCG reduced recurrence compared to 1-year maintenance but did not impact progression or survival in patients with high-risk disease. These data suggest that 1 year may be suitable for patients at intermediate risk while 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 the 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.[56,60,61,71,74,75]

***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.[76] Installation of BCG into the bladder can mimic a urinary tract infection and may produce intense local discomfort. The side effects of treatment have translated to discontinuation of BCG therapy. Dysuria has been reported in 60% of patients in clinical trials.[76] However, the side effects are treatable in almost all cases[77] 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.[78,79]

A reduced (one-third) dose of BCG was evaluated for the possible reduction of side effects. In a phase III study, 1316 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.[80] Among all four groups, the percentage of patients with greater than or equal to one 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.[81-83] 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.

A reduction in the frequency of BCG instillations with the goal of reducing treatment-related AEs was tested in the phase III NIMBUS trial.[84] In this trial, 345 patients with NMIBC were randomized to receive standard-dose BCG for 6 weeks of induction, followed by 3 weeks of maintenance at 3, 6, and 12 months (15 total instillations) or standard-dose BCG for 3 weeks of induction, followed by 2 weeks of maintenance at 3, 6, and 12 months (9 total instillations). After 12 months of follow-up the ITT population showed a higher number of recurrences in the reduced frequency treatment group (46/170) compared to the standard treatment group (21/175) and a safety analysis HR of 0.40, with the upper part of the one-sided 95% CI of 0.68, meeting the predefined criteria for immediately stopping the trial due to inferiority of the reduced frequency arm.

**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 approaches for some patients with NMIBC.[85] 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 NMIBC in the context of this shortage.[86] NCCN 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 NMIBC (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[55,87] and mitomycin.[88] Two separate meta-analyses of randomized trials reported that there were no differences in risk of recurrence between BCG and mitomycin,[56,89] although BCG may show more favorable outcomes from maintenance regimens.[56] Other options include epirubicin,[69,90] valrubicin,[91] docetaxel,[92] sequential gemcitabine/docetaxel,[93] or gemcitabine/mitomycin.[94] Another alternative to intravesical BCG for patients with NMIBC at high risk of recurrence and, particularly, at high risk of progression, is initial radical cystectomy.[95]

Another option during a shortage is splitting the dose of BCG so that multiple patients may be treated using a single vial. While several randomized trials have reported that one-third-dose BCG showed similar outcomes when compared to full-dose BCG,[82,96,97] a phase 3 trial of 1355 patients with intermediate- or high-risk NMIBC reported that patients receiving the full dose of BCG show a longer disease-free interval, compared with those receiving the one-third dose.[73] In this study, the 5-year disease-free rate was 58.5% for the one-third dose compared to 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 there were no differences in progression or survival rates.[73] Based on these data, the panel recommends that one-half or one-third dose may be considered for BCG induction during a shortage and should be used for BCG maintenance, if supply allows. Maintenance BCG should be prioritized for patients with high-risk NMIBC (cT1 high grade and/or CIS) in the early maintenance period (eg, 3 and 6 months post-induction), although in cases of shortage, BCG induction therapy should be prioritized over maintenance BCG.

### Treatments for BCG-Unresponsive or BCG-Intolerant NMIBC

***Nadofaragene Firadenovec-vncg***

Nadofaragene firadenovec is a non-replicating adenoviral vector-based gene therapy that is indicated for the treatment of patients with high-risk, BCG-unresponsive NMIBC with CIS, with or without papillary tumors. A phase III, open-label, multicenter study evaluated nadofaragene firadenovec in 157 patients with BCG-unresponsive NMIBC.[98] Of the 103 patients on the study with CIS, with or without a high-grade Ta or T1 tumor, 25 remained free of high-grade recurrence at 12 months (24.3% 12-month complete response rate; 95% CI, 16.4-33.7). Urinary urgency was the most common grade ≥3 treatment-related AE (1% of patients). A longer-term follow-up from this same cohort of patients was reported on in a 2021 AUA Conference abstract with a mean follow-up of 23.5 months.[99] Twenty-four months after the first dose, 19.4% of patients remained free of high-grade recurrence, with a median duration of high-grade RFS of 12.2 months. Of the 55 patients who achieved a complete response, 20 (36.4%) remained free of high-grade recurrence at 24 months. By 24 months, cystectomy-free survival was 64.6% and OS was 94.4%. The most common drug-related AEs were instillation site discharge (24.3%), fatigue (23.4%), bladder spasm (17.8%), and urinary urgency (16.8%), with most AEs being grades 1–2. Two patients discontinued treatment due to drug-related AEs.

A second cohort of the same phase III trial detailed above included 48 patients with BCG-unresponsive NMIBC, high-grade Ta/T1 tumors only. A 2021 AUA Conference abstract reported on 2-year follow-up results from this cohort.[100] Of the 48 patients in this cohort, 72.9%, 43.8%, and 33.3% were high-grade recurrence-free at 3, 12, and 24 months, respectively. Of those who were free of high-grade recurrence at 3 months, 45.7% were high-grade recurrence-free at 24 months, with a median duration of high-grade RFS of 19.8 months. As estimated at 24 months, cystectomy-free survival was 69.8% and OS was 93.2%.

***Nogapendekin alfa inbakicept-pmln (N-803)***

N-803 is an immune cell-activating interleukin-15 superagonist that was studied in combination with BCG for patients with BCG-unresponsive, high-risk NMIBC in the phase II/III QUILT-3.032 study.[101] QUILT-3.032 included three cohorts of patients: those with bladder CIS, with or without Ta/T1 papillary disease, who were treated with N-803 plus BCG (cohort A); those with high-grade papillary Ta/T1 only disease who were treated with N-803 plus BCG (cohort B); and those with bladder CIS, with or without Ta/T1 papillary disease, who were treated with N-803 alone (cohort C). In cohort A, complete response was reported in 71% of 82 patients, with a median duration of complete response of 26.6 months. For the 72 patients in cohort B, DFS was 55.4% at 12 months, with a median DFS of 19.3 months. For cohort C, only 2 of 10 patients showed complete response after 3 months and cohort C was ultimately discontinued approximately 6 months into the study due to futility. Most treatment-related AEs for N-803 plus BCG were grade 1-2 (86%), 2% of patients treated with the combination reported at least one grade 3 immune-related treatment-emergent AE. A study on patient-reported outcomes in the QUILT-3.032 study concluded that the combination of N-803 and BCG had a favorable risk to benefit ratio and quality of life following treatment.[102]

***Pembrolizumab for NMIBC***

Pembrolizumab is a programmed cell death protein 1 (PD-1) inhibitor that has been evaluated as systemic therapy for BCG-unresponsive NMIBC with CIS in the single-arm, phase II KEYNOTE-057 study (pembrolizumab is also indicated for treatment of metastatic urothelial carcinoma; see section on *Metastatic (Stage IVB) Urothelial Bladder Cancer,* below). In the KEYNOTE-057 study, 101 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.[103] Ninety-six patients were eligible for inclusion in the efficacy analysis. The 12-month complete response rate was 19% (18 of 96 total patients on the study), and the median duration of response (DOR) from time of onset was 16.2 months (95% CI, 6.7–36.2). Grade ≥3 treatment-related AEs were reported in 13% of patients, with arthralgia and hyponatremia being the most common. Serious treatment-related AEs occurred in 8% of patients.

Cohort B of the KEYNOTE-057 study included 132 patients with high-risk, BCG-unresponsive NMIBC with high-grade Ta or any-grade T1 papillary tumors (without CIS). A 2023 ASCO Genitourinary Cancers Symposium abstract reported efficacy data after a median follow-up of 45.4 months.[104] Median high-risk disease-free survival (DFS) was 7.7 months and progression-free survival (PFS) to worsening of grade, stage, or death was 44.5 months. Thirty-one patients (23.5%) underwent radical cystectomy after discontinuation of pembrolizumab. Twelve-month OS was 96.2%.

## NCCN Recommendations for Treatment of NMIBC

The NCCN Panel recommends management of NMIBC based on AUA/SUO risk stratification,[105] with the caveat that an individual patient within each of the risk strata may have more or less concerning features that can influence care decisions (see *AUA Risk Stratification for Non-*

*Muscle Invasive Bladder Cancer* in the algorithm). Retrospective reviews have shown that the AUA/SUO risk classification accurately stratifies patients with NMIBC by the likelihood of recurrence and progression.[106]

After the initial TURBT shows NMIBC, a repeat TURBT is recommended for visually incomplete or high-volume tumors and for high-grade NMIBC, which is found to be T1 on the initial TURBT.[107] 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.[108] 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. Similarly, a randomized 10-year extension trial of 210 patients with pT1 NMIBC found that patients who underwent repeat TURBT had a significantly higher 5-, 7-, and 10-year RFS and PFS and, in addition, the 10-year OS rate was significantly higher in patients with repeat TURBT (59.1% vs. 40.8%; $P = .004$).[109] Repeat TURBT was found to be an independent determinant of prolonged OS on multivariate analysis.

Repeat TURBT may also be considered for select patients with high-grade Ta on initial TURBT, particularly if the tumor is large and/or there was no muscle present in the initial TURBT specimen. Restaging TURBT detected residual disease in 27% of Ta patients when muscle was present in the original TURBT.[110] 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.[111]

If muscle invasive disease is found during repeat TURBT, then additional staging for muscle invasive disease and appropriate treatment depending on stage should be followed.

***Treatment of Low-Risk NMIBC***

By the AUA/SUO risk stratification, low-risk NMIBC includes PUNLMP and low-grade urothelial carcinoma that is a solitary Ta and less than or equal to 3 cm.[105] For these tumors, risk of recurrence or progression is low following TURBT and no further treatment is necessary,[112] although a single instillation of intravesical chemotherapy immediately post-TURBT can be helpful in reducing the risk of recurrence.[15] An appropriate surveillance schedule is recommended for early detection of disease recurrence.

***Treatment of Intermediate-Risk NMIBC***

Intermediate-risk NMIBC includes low-grade urothelial carcinoma that has any of the following characteristics: T1, size greater than 3 cm, multifocal, or recurrence within 1 year. In addition, high-grade urothelial carcinoma that is solitary, Ta, and less than or equal to 3 cm is also considered intermediate risk.[105] Although a complete TURBT alone can eradicate intermediate-risk NMIBC, there is a relatively high risk for recurrence. Therefore, after TURBT and immediate intravesical chemotherapy, the panel recommends a 6-week induction course of intravesical therapy. Options for intravesical therapy for intermediate-risk NMIBC include BCG or chemotherapy. The availability of BCG should be considered in decision-making as it may be prioritized for treatment of higher risk disease. A systematic review and meta-analysis has reported that intravesical treatment with BCG does not appear superior to chemotherapy for reduction of disease recurrence in patients with intermediate-risk NMIBC.[113] If maintenance BCG is given following the induction course, data support limiting maintenance BCG to one year for intermediate-risk disease since no additional benefit is derived from the full 3 years.[73] While an induction course of intravesical therapy is preferred, surveillance is also an option for intermediate-risk disease.

The value of an induction course of intravesical therapy depends on the patient's prognosis and likelihood of disease recurrence. Factors to consider include the size, number, T category, and grade of the tumor(s), as well as concomitant CIS and prior recurrence.[25] Meta-analyses have confirmed the efficacy of adjuvant (induction) intravesical chemotherapy in reducing the risk of recurrence.[114,115] In the literature, there are four meta-analyses confirming that BCG after TURBT is superior to TURBT alone, or TURBT and chemotherapy in preventing recurrences of Ta and T1 tumors.[60-63] Close follow-up of all patients is needed, although the risk for progression to a more advanced stage is low (see *Surveillance* in the discussion and algorithm).

***Treatment of High-Risk NMIBC***

High-risk NMIBC has a relatively high risk for recurrence and progression towards more invasiveness. According to the AUA/SUO risk stratification, high-risk NMIBC includes high-grade urothelial carcinoma that has any of the following characteristics: CIS, T1, size greater than 3 cm, or multifocal. In addition, a subgroup of very-high-risk features includes BCG unresponsiveness, variant histologies, lymphovascular invasion, and prostatic urethral invasion.[105] 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 CIS component. The presence of CIS is associated with an increased risk of invasive disease, including increased cancer progression rates and worse cancer-specific outcomes.[20] If untreated, 50% of CIS progresses to muscle invasive disease within 5 years and, even with treatment, 30% to 40% progresses within 10 years.[116]

Treatment options for high-risk NMIBC depend on whether the tumor has previously been shown to be unresponsive or intolerant to BCG. For BCG-naïve NMIBC, the options are cystectomy or BCG. When very high-risk features are present, cystectomy is preferred because of the high risk for progression to a more advanced stage,[117,118] while BCG is preferred when these are not present. BCG is also a category 1 recommendation for BCG-naïve, high-risk NMIBC without very-high-risk features. A prospective study including 50 patients with high-risk, BCG-naïve NMIBC randomized patients to either radical cystectomy or induction, then maintenance, BCG.[119] During follow-up, two (10%) of 23 patients in the BCG arm developed metastatic bladder cancer, while all participants in the cystectomy arm remained disease-free.

For some patients, BCG is not an option due to side effects or a tumor that is BCG-resistant. For these patients, cystectomy is preferred although other intravesical chemotherapy, N-803, pembrolizumab, or nadofaragene firadenovec are other options (see *Treatments for BCG-Unresponsive or BCG-Intolerant Disease* for patient and disease characteristics for which these treatment options would be appropriate). Non-cystectomy candidates with recurrent or persistent high-grade cTa or cT1 disease may also consider concurrent chemoradiotherapy as an option (category 2A for cT1, category 2B for cTa). Valrubicin is approved for CIS that is refractory to BCG, although panelists disagree on its value.[91]

**Surveillance**

For intermediate and high-risk NMIBC, 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* in the algorithm). Urine molecular tests for urothelial tumor markers are now available.[120] 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 NMIBC. However, it remains unclear whether these tests offer additional useful information 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 NMIBC, 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 NMIBC.

### Posttreatment of Recurrent or Persistent Disease

#### *Treatment of Patients with Positive Cystoscopy*

Patients under surveillance after initial TURBT, who show a documented recurrence by positive cystoscopy, should undergo another TURBT to reclassify the AUA/SUO risk group. Patients should be treated and followed as indicated based on the risk of their recurrent disease.

#### *Treatment of Patients with Positive Cytology*

In patients without a documented recurrence but with initial positive cytology and negative cystoscopy and imaging, it may be appropriate to repeat the cytology test within 3 months. If subsequent cytology tests are positive, selected mapping biopsies including transurethral resection of the prostate (TURP) may be considered. In addition, the upper tract must be evaluated and ureteroscopy may be considered for detecting tumors of the upper tract. If available, enhanced cytoscopy should be considered (see *Enhanced Cystoscopy*, above). With persistent positive cytology and no demonstrable clinical disease in the urinary tract, evaluation of the contiguous organs (eg, vagina, cervix, uterus, or anorectum) via referral to an appropriate specialist may be warranted. Several case reports have described the detection of urothelial carcinoma spread to the vagina, cervix, or vulva.[121-123] It has also been reported that as many as 14% of patients with a positive urine cytology and no visible disease in the bladder had tumors in contiguous organs as the source of the positive cytology finding.[124] If the bladder, prostate, and upper tract continue to show negative results on further evaluation, additional follow-up is indicated after 3 months, then at longer intervals. If BCG was given previously, maintenance BCG may be considered.

If transurethral biopsy of the prostate is positive, treatment of the prostate should be initiated as described below (see *Urothelial Carcinomas of the Prostate*). If upper tract urothelial carcinoma (UTUC) is identified, then the treatment described below should be followed (see *Upper Tract Urothelial Carcinoma)*.

If the selected mapping biopsy of the bladder is positive, then the AUA risk group should be reclassified and the tumor managed according to *NCCN Recommendations for Treatment of NMIBC*, above.

In a phase II multicenter study of NMIBC that recurred following two courses of BCG, intravesical gemcitabine demonstrated activity that was relegated to high-risk NMIBC.[125] In the 47 patients with evaluable response, 47% had DFS at 3 months. The 1-year RFS was 28% with all cases except for two 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.[126] Surveillance

may be reasonable in highly select cases where low-grade, small-volume tumors had limited lamina propria invasion and no CIS.[127,128] Further investigation and validation of results is warranted for establishing the efficacy of alternative agents for BCG-unresponsive or -refractory disease.[129] Recurrences that are found to be muscle invasive or metastatic disease should be treated as described in the appropriate section below.

## Muscle Invasive Urothelial Bladder Cancer

### Additional Workup

Several workup procedures are recommended to accurately determine clinical staging of muscle invasive disease. Laboratory studies, such as a complete blood count (CBC) and chemistry profile, including alkaline phosphatase, must be performed. Since cisplatin-based chemotherapy is a preferred approach both for neoadjuvant therapy prior to cystectomy and as part of trimodal therapy for bladder preservation, 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.[130]

Patients should also be assessed for regional or distant metastases. This evaluation should include chest imaging (CT [preferred], x-ray, or fluorodeoxyglucose [FDG]-PET/CT [category 2B]) and evaluation for suspected bone metastasis in patients with symptoms or clinical suspicion of bone metastasis (eg, elevated alkaline phosphatase, focal bone pain). Chest imaging with CT is preferred over chest x-ray based on studies showing better sensitivity of CT for detection of metastatic disease.[131,132] Bone imaging may include a bone scan, MRI, or FDG-PET/CT (category 2B). Imaging studies help assess the extent of tumor spread to lymph nodes or distant organs.[133,134] An abdominal/pelvic CT or MRI is used to assess the local and regional extent of disease.[135,136] 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 TURBT is often required for muscle invasive tumors, although select patients may be treated with TURBT alone.[137,138] Different treatment modalities are discussed below. These include radical cystectomy, partial cystectomy, neoadjuvant or adjuvant therapy, bladder-preserving approaches, and systemic therapy for advanced disease.

### Cystectomy

#### *Radical Cystectomy*

Radical surgical treatment of bladder cancer involves a cystoprostatectomy or a cystectomy and commonly a hysterectomy for those with a uterus, followed by the formation of a urinary diversion, although in appropriately selected patients, approaches that preserve the uterus, vagina, fallopian tubes, and/or ovaries may be used.[139,140] This surgery can be performed in an open or robotic manner.[141-144] 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 CIS 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, EUA, and TURBT is modest, even when combined with cross-sectional imaging and when understaging is frequently encountered. A retrospective study of 778 patients with bladder cancer found that 42% of patients were upstaged following cystectomy.[145] 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.[146-150] Conversely, a 2019 prospective, randomized trial concluded that an extended LND did not show a significant advantage over limited LND for RFS, cancer-specific survival, or OS.[151] However, differing definitions of "extended" versus "limited" LND between studies and specifics on how the study was powered complicate these results. Therefore, additional information will be needed to determine whether extended LND leads to improved outcomes. Results from the SWOG-1011 trial, which is fully accrued but not yet reported, may help to further answer this question.[152] Patient factors that may preclude a PLND include severe scarring secondary to previous treatments or surgery, advanced age, or severe comorbidities.

***Partial Cystectomy***

In fewer than 5% of cases, an initial invasive tumor develops in an area of the bladder where an adequate margin of soft tissue and an adequate 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 CIS 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. Outcomes data on partial cystectomy are varied and, in general, partial cystectomy is not considered the standard surgical treatment of muscle invasive bladder cancer. 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 done laparoscopically. If the intraoperative findings preclude a partial cystectomy, a radical cystectomy is performed. The decision to recommend adjuvant radiation or systemic therapy 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 the treatment of bladder cancer is the optimal use of perioperative chemotherapy for muscle invasive disease. Data support the role of neoadjuvant chemotherapy before cystectomy for stage II and IIIA lesions.[153-158] In a SWOG randomized trial of 307 patients with muscle invasive disease, 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.[153] In a meta-analysis of 11 trials involving 3005 patients, cisplatin-based multiagent neoadjuvant chemotherapy was associated with improved 5-year OS and DFS (5% and 9% absolute improvement, respectively).[157] The randomized, phase III JCOG0209 study comparing neoadjuvant MVAC to no neoadjuvant chemotherapy also found no difference in health-related quality of life

after cystectomy, further supporting the use of neoadjuvant chemotherapy in all patients who are eligible to receive it.[159] A review of the National Cancer Database (NCDB) supports initiation of neoadjuvant chemotherapy as soon as possible, but not more than 8 weeks after diagnosis to prevent upstaging after radical cystectomy.[160]

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 rate compared to standard (28-day) dosing of MVAC (11% vs. 25%; 2-sided *P* = .006).[161] 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 muscle invasive bladder cancer (n = 44) were given 3 cycles of ddMVAC with pegfilgrastim followed by radical cystectomy and lymph node dissection.[162] ddMVAC was anticipated to have a safer profile, a shorter time to surgery, and a similar pathologic complete response rate compared to 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 the start of chemotherapy.[162] A separate single-arm phase II study also reported pathologic downstaging in 49% of patients receiving neoadjuvant ddMVAC with a similar safety profile.[163] An additional neoadjuvant clinical trial of ddMVAC with bevacizumab reported 5-year survival outcomes of 63% and 64% (OS and DSS, respectively; median follow-up, 49 months), with pT0N0 and less than or equal to pT1N0 downstaging rates of 38% and 53%, respectively.[164] Bevacizumab had no definitive impact on overall outcomes.

Gemcitabine and cisplatin (GC) has also been evaluated for neoadjuvant therapy of muscle invasive bladder cancer, albeit mainly in smaller phase II or retrospective studies. Overall, these studies showed that GC is effective and well-tolerated when used as neoadjuvant therapy for muscle invasive bladder cancer,[165-169] although some of the studies report lower pathologic response compared to MVAC[168] and lack of a demonstrated OS benefit due to short follow-up or small study size.[166,167] More recently, the phase II COXEN trial has evaluated ddMVAC and GC as neoadjuvant therapy for muscle invasive bladder cancer with the aim of validating scoring from a coexpression extrapolation algorithm-generated gene expression model.[170,171] In the ITT population of 227 patients, pT0 rates for ddMVAC and GC were 28% and 30% (*P* = .75) and downstaging was 47% and 40% (*P* = .27), respectively.[170] No significant difference between ddMVAC and GC was reported for OS or event-free survival.[171] Dose-dense GC has been evaluated as neoadjuvant therapy in a prospective, phase II trial including 46 evaluable patients.[172] The primary endpoint of this trial was met as 57% of patients had their disease downstaged to NMIBC (less than pT2, N0). Pathologic response also correlated with improved RFS and OS. Thirty-nine percent of patients experienced dose modifications due to treatment toxicity, but no patients were unable to undergo cystectomy due to treatment-related AEs. The most frequent treatment-related AE was anemia (12% grade 3).

The randomized phase III GETUG/AFU V05 VESPER trial compared the efficacy of ddMVAC to GC in the perioperative setting for 500 patients with muscle invasive bladder cancer.[173,174] Of the 437 patients who received neoadjuvant chemotherapy, organ-confined response (less than ypT3, N0) was observed more frequently with ddMVAC than GC (77% vs. 63%; *P* = .001).[173] PFS at 3 years was also significantly higher among those who received neoadjuvant ddMVAC compared to neoadjuvant GC (66% vs. 56%; HR, 0.70; 95% CI, 0.51–0.96; *P* =

.025). An analysis comparing secondary endpoints of the VESPER trial also reported a higher complete pathologic response rate for neoadjuvant ddMVAC compared to GC (42% vs. 36%).[174] Reported toxicity was similar between the therapies, with 52% of patients experiencing grade 3 or higher AEs with ddMVAC compared to 55% with GC. Grade 3 or higher AEs that were more frequently observed with ddMVAC included gastrointestinal disorders ($P$ = .003) and asthenia ($P$ = .001). A systematic review and meta-analysis similarly showed a significantly higher rate of pathologic complete response and OS for neoadjuvant therapy with ddMVAC compared to GC.[175]

In an international, multicenter, randomized trial (BA06 30894) that investigated the effectiveness of neoadjuvant cisplatin, methotrexate, and vinblastine (CMV) in 976 patients, neoadjuvant CMV resulted in a 16% reduction in mortality risk (HR, 0.84; 95% CI, 0.72–0.99; $P$ = .037) at a median follow-up of 8 years.[158] However, based on NCCN Panel consensus that this regimen is not used in their practices, CMV is no longer recommended as an option for neoadjuvant or adjuvant therapy.

The NCCN Panel recommends neoadjuvant chemotherapy followed by radical cystectomy for patients with stage II or IIIA bladder cancer. Neoadjuvant chemotherapy followed by radical cystectomy is a category 1 recommendation based on high-level data supporting its use. For highly select patients with stage II disease who receive a partial cystectomy, neoadjuvant chemotherapy is a category 2A recommendation. Patients with hearing loss or neuropathy, poor performance status, or renal insufficiency may not be eligible for cisplatin-based chemotherapy. If cisplatin-based chemotherapy cannot be given, neoadjuvant chemotherapy is not recommended. Carboplatin has not demonstrated a survival benefit and should not be substituted for cisplatin in the perioperative setting. Cystectomy alone is an appropriate option for these patients. Based on results of the VESPER trial, ddMVAC is the preferred regimen for perioperative treatment of muscle invasive bladder cancer. 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 Systemic Therapy

Data are less clear regarding the role of adjuvant systemic therapy in invasive bladder cancer. Studies have shown that adjuvant chemotherapy may delay recurrences and improve OS[176-178]; however, no randomized comparisons of adequate sample size have definitively shown a survival benefit, in large part due to poor accrual.[179] 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.[180-182] However, methodologic issues 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.[183] Interestingly, the follow-up analysis included 3 more studies for a total of 9 trials (N = 945 patients).[178] 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.[178] An observational study evaluated 5653 patients of which 23% received adjuvant chemotherapy

post-cystectomy.[177] Patients who received adjuvant chemotherapy had an improved OS (HR, 0.70; 95% CI, 0.06–0.76).[177] Other studies have reported similar results.[184] Although evidence for adjuvant therapy is not as strong as for neoadjuvant therapy, the growing body of data support the administration of adjuvant therapy for certain patients with a high risk for relapse.

The VESPER trial, described in detail above, included a subgroup of 55 patients who were treated with either ddMVAC or GC as adjuvant therapy.[173,174] While results were not conclusive due to small sample size for the adjuvant group, 3-year PFS was improved in the ddMVAC group compared to the GC group for all patients who received perioperative therapy (64% vs. 56%; HR, 0.77; 95% CI, 0.57–1.02; *P* = .066) as was time to progression (3-year rate 69% vs. 58%; HR, 0.68; 95% CI, 0.50–0.93; *P* = .014). Based on these results, ddMVAC is preferred over GC for adjuvant chemotherapy.

Checkpoint inhibitors have also been investigated in the adjuvant setting, with the phase 3 CheckMate 274 trial of adjuvant nivolumab reporting positive results for its primary endpoints across the entire study population, although the authors note the possibility of a larger effect size for bladder compared to UTUC (see *Adjuvant Treatment and Follow-up* under *UTUC*, below, for more discussion on these data).[185] In the ITT population of 709 patients with muscle invasive urothelial carcinoma treated with radical surgery on CheckMate 274, DFS was 20.8 months with nivolumab compared to 10.8 months with placebo (HR, 0.70; 98.22% CI, 0.55–0.90; *P* < .001). For patients with a programmed death-ligand 1 (PD-L1) expression level of 1% or more, DFS was 74.5% with nivolumab and 55.7% with placebo (HR, 0.55; 98.72% CI, 0.35–0.85; *P* < .001). Importantly, adjuvant nivolumab was tested both in patients who had received neoadjuvant therapy as well as those who did not; 43.4% of the trial participants had received previous cisplatin-based neoadjuvant therapy. Treatment-related AEs of grade 3 or higher occurred in 17.9% of those treated with nivolumab and 7.2% of those treated with placebo. Further follow-up is ongoing to assess OS outcomes. While atezolizumab has also been tested in the adjuvant setting for patients with high-risk muscle invasive urothelial carcinoma in the phase 3 IMvigor010 study, this study did not meet its primary endpoint of improved DFS with adjuvant atezolizumab compared to observation.[186] Median DFS was 19.4 months with atezolizumab compared to 16.6 months with observation (HR, 0.89; 95% CI, 0.74–1.08; *P* = .24).

The NCCN Guidelines suggest that adjuvant systemic therapy should be discussed with patients with high-risk pathology after cystectomy. If cisplatin-based neoadjuvant therapy was not given and the tumor is found to be pT3, pT4, or pN+ following resection, adjuvant cisplatin-based chemotherapy is the preferred approach, although adjuvant nivolumab may also be considered. If cisplatin-based neoadjuvant therapy was given and the tumor is ypT2–ypT4a or ypN+, nivolumab may be considered, although consideration of this approach should balance its effect at delaying progression of disease with the risk of side effects. A minimum of 3 cycles of a cisplatin-based combination, such as ddMVAC (preferred) or GC, may be used in patients undergoing perioperative chemotherapy. Chemotherapy regimen and dosing recommendations are mainly based on studies in advanced disease.[153,165,187,188] 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 or less and have no nodal involvement or lymphovascular invasion after cystectomy are considered to have lower risk and are not recommended to receive adjuvant therapy.

### Adjuvant Radiation

Patients with locally advanced disease (pT3–4) have high rates of pelvic recurrence and poor OS after radical cystectomy, PLND, and perioperative chemotherapy (pelvic failure 20%–45% and survival 10%–50% at 5 years, depending on risk factors).[189-192] 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 to surgery alone.[193] A more recent randomized phase II trial compared adjuvant sequential chemotherapy and radiation versus adjuvant chemotherapy alone in 120 patients with locally advanced disease with one or more risk factors (≥pT3b, grade 3, or node-positive), in a study population with a high proportion of squamous cell carcinoma. This study demonstrated a significant improvement in local control for chemoradiation (3-year local control of 96% vs. 69%; $P <$ .01) and marginal improvements in DFS and OS. Late-grade ≥3 gastrointestinal toxicity on the chemoradiation arm was low (7% of patients).[194] A 2019 systematic review evaluating the oncologic efficacy of adjuvant radiation for bladder cancer or UTUC concluded that there was no clear benefit of adjuvant radiation following radical surgery (eg, cystectomy), although the combination of adjuvant radiation with chemotherapy may be beneficial in locally advanced disease.[195]

While there are no conclusive data demonstrating improvements in OS, it is reasonable to consider adjuvant radiation in patients with pT3/pT4 urothelial bladder cancer with positive nodes or margins at the time of surgery, although this approach has been evaluated in only a limited number of studies, reflected by the category 2B designation. Patients meeting these characteristics with positive surgical margins and/or lymph nodes identified in the pelvic dissection have especially high pelvic recurrence rates (40%–45% by 5 years), and adjuvant radiation is reasonably well tolerated and improves local control. 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.[194] 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. In fact, a meta-analysis of 73 studies comprising 9110 patients reported that only 19.2% of patients who initially receive bladder-preserving therapy for muscle invasive bladder cancer eventually require radical cystectomy due to recurrence or lack of response.[196] Another multicenter retrospective analysis of 287 patients with cN+ M0 bladder cancer showed no difference in OS (HR, 0.94; 95% CI, 0.63–1.41; $P = .76$) or PFS (HR, 0.74; 95% CI, 0.50–1.08; $P = .12$) between radical cystectomy versus organ preservation with radical dose radiotherapy.[197] Receiving radical cystectomy or bladder-sparing trimodality therapy was, however, associated with improved OS compared to palliative treatment ($P < .001$).

Bladder-preserving approaches are reasonable alternatives to cystectomy for patients who are medically unfit for surgery and those seeking an alternative to radical cystectomy.[198,199] Combined modality chemoradiation therapy as an alternative to immediate cystectomy for muscle invasive bladder cancer 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.[200-202] There is an apparent underutilization of aggressive bladder-preserving therapies for non-cystectomy candidates, especially in patients who are older and Black patients.[203,204] Between 23% and 50% of patients with muscle invasive bladder cancer who are ≥65 years receive no treatment or non-aggressive therapy, despite prospective, phase II data showing that bladder preservation with trimodality therapy has positive outcomes and an acceptable toxicity profile for patients ≥65 years, with a 2-year OS of 94.4% and 2-year DFS of 72.6%.[205] For tools to aid in the optimal assessment and care of older adults with cancer, see the NCCN Guidelines for Older Adult Oncology.

With any of the alternatives to cystectomy, there is 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.[204,206,207] Conversely, one series reported that all patients who achieved a complete response after radiotherapy with concurrent cisplatin and fluorouracil (5-FU) were pT0 on immediate cystectomy.[208] 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 than with 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 extensive or multifocal CIS, no tumor-related moderate or severe hydronephrosis, and good pre-treatment bladder function. Patients who are medically fit for radical cystectomy but who have hydronephrosis are poor candidates for bladder-sparing procedures.[209,210] Maximal TURBT with concurrent chemoradiotherapy should be given as primary treatment for these patients, with radiotherapy alone or TURBT alone reserved for select patients (see *TURBT Alone as Primary Treatment for Muscle Invasive Bladder Cancer* below for more information). When possible, bladder-sparing options should be chosen in the context of clinical trials.

***Radiotherapy with Concurrent Chemotherapy Following TURBT as Primary Treatment for Muscle Invasive Bladder Cancer***

Several groups have investigated the combination of concurrent or sequential chemotherapy and radiotherapy 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.[211-213]

Radiation Therapy Oncology Group (RTOG) protocol 89-03 compared concurrent cisplatin and radiotherapy with or without 2 cycles of induction MCV (methotrexate, cisplatin, and vinblastine) chemotherapy.[210] 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 (RT).[212,214]

In the phase 3 RTOG 89-03 trial in which 123 patients with clinical stage T2–T4a were treated with radiotherapy plus concurrent cisplatin, with or without induction MCV chemotherapy, 5-year OS was approximately 49% in both arms.[210] 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 of 83%.[215] The RTOG 97-06 trial treated 47 patients with twice-daily irradiation and concurrent cisplatin; patients also received adjuvant chemotherapy with CMV.[216] Three-year OS was 61%. In the RTOG 99-06 study, 80 patients received twice-daily irradiation plus cisplatin and paclitaxel, followed by adjuvant cisplatin and gemcitabine. Five-year OS was 56%.[217] In RTOG 0233, 97 patients received twice-daily radiation with concurrent paclitaxel plus cisplatin or 5-FU plus cisplatin. Five-year OS was 73%.[218] RTOG 0712 investigated 5-FU plus cisplatin with twice-daily radiation or gemcitabine with once-daily radiation, with 33 patients eligible for analysis on each arm. Three-year distant metastasis-free survival rates were 78% and 84%, respectively.[219] Taken together, the complete response rates ranged from 59% to 88%.

Up to approximately 80% of long-term survivors maintain an intact bladder, while other patients ultimately require radical cystectomy.[209-217] A combined analysis of survivors from four of these trials, with a median follow-up of 5.4 years, showed that combined-modality therapy was associated with low rates of late grade 3 toxicities (5.7% genitourinary and 1.9% gastrointestinal).[220] No late grade 4 toxicities or treatment-related deaths were recorded.

Based on the trials described above, as well as the phase 3 BC2001 trial that demonstrated a locoregional DFS benefit for those treated with 5-FU and mitomycin concurrently with radiotherapy compared to radiotherapy alone, with no significant increase in AEs,[221] bladder preservation with concurrent chemoradiotherapy was given a category 1 designation for primary treatment of stage II or IIIA bladder cancer.

A meta-analysis of individual patient data from two randomized, phase III studies (BC2001 and BCON) compared two radiotherapy fractionation schedules that are commonly used in treatment of locally advanced bladder cancer, a standard schedule of 64 Gy in 32 fractions over 6.5 weeks and a hypofractionated schedule of 55 Gy in 20 fractions over 4 weeks.[222] This analysis found that the hypofractionated schedule is noninferior to the standard fractionation schedule for both invasive local control and toxicity and that the hypofractionated schedule is superior regarding invasive local control.

***Chemotherapy Following TURBT as Primary Treatment for Muscle Invasive Bladder Cancer***

Chemotherapy alone is considered to be inadequate without additional treatment to the bladder and it remains investigational. Studies showed that the proportions of complete pathologic response in the bladder using neoadjuvant chemotherapy alone were only up to 38%.[153] A higher proportion of bladders can be rendered tumor-free and therefore preserved when chemotherapy is combined with concurrent radiotherapy.

***Radiotherapy Following TURBT as Primary Treatment for Muscle Invasive Bladder Cancer***

Radiotherapy alone is inferior to radiotherapy combined with chemotherapy for patients with an invasive bladder tumor, and is not considered standard for patients who can tolerate combined therapy.[221,223] In a randomized trial of 360 patients, radiotherapy with concurrent mitomycin C and 5-FU improved 2-year locoregional DFS from 54% (radiotherapy alone) to 67% ($P$ = .01), and 5-year OS from 35% to 48% ($P$ = .16), without increasing grade 3–4 acute or late toxicities.[221] Hence, radiotherapy alone is only indicated for those who cannot tolerate a cystectomy or chemotherapy because of medical comorbidities.

***TURBT Alone as Primary Treatment for Muscle Invasive Bladder Cancer***

TURBT alone may be an option for patients with stage II disease who are not candidates for cystectomy. TURBT alone may be curative in selected cases that include solitary lesions less than 2 cm in size that

have minimally invaded the muscle. These cases should also have no associated in situ component, palpable mass, or associated hydronephrosis.[224]

If primary treatment consists of 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, treatment 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.

### NCCN Recommendations for Treatment of Muscle Invasive Bladder Cancer

#### *Treatment of Stage II and IIIA Tumors*

The critical issues in the care 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, stage II) 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 stage II and IIIA disease is a radical cystectomy and pelvic lymphadenectomy. Neoadjuvant chemotherapy is recommended (category 1). Partial cystectomy along with neoadjuvant cisplatin-based chemotherapy can be considered for stage II (cT2, N0) disease with a single tumor in a suitable location and no presence of CIS. Partial cystectomy is not an option for patients with stage III disease. If cisplatin-based neoadjuvant therapy was not given and the tumor is found to be pT3, pT4, or pN+ following resection, adjuvant cisplatin-based chemotherapy is the preferred approach, although adjuvant nivolumab may also be considered. If cisplatin-based neoadjuvant therapy was given and the tumor is ypT2–ypT4a or ypN+, nivolumab may be considered. Adjuvant RT is another option for patients with tumors that are pT3–4, with positive nodes or margins, at the time of surgery (category 2B).

Bladder preservation with maximal TURBT followed by concurrent chemoradiotherapy is another category 1 primary treatment option for these patients. Candidates for this bladder-sparing approach include patients with tumors that present without moderate or severe hydronephrosis and tumors that allow a visibly complete or a maximally debulking TURBT. Radiotherapy with concurrent cisplatin-based chemotherapy or 5-FU plus mitomycin as a radiosensitizer is the most common and well-studied chemoradiation method used to treat muscle invasive bladder cancer.[208-212,221,223,225] Therefore, based on clinical practice and strength of the data, the following radiosensitizing regimens are preferred for organ-preserving chemoradiation: 5-FU plus mitomycin C, cisplatin alone, or low-dose gemcitabine. Cisplatin plus 5-FU or cisplatin plus paclitaxel may be considered as alternative regimens. Other radiosensitizing chemotherapy regimens that may be used with palliative intent, but would rarely be appropriate for curative-intent chemoradiotherapy for organ preservation, are docetaxel (category 2B), paclitaxel (category 2B), 5-FU (category 2B), or capecitabine (category 3) monotherapies.

The overall tumor status should be reassessed 2 to 3 months after treatment completion. If no residual tumor is detected, surveillance is appropriate. If residual disease is present, surgical consolidation of bladder-only residual disease or treatment as metastatic disease may be appropriate. If residual disease is CIS, Ta, or T1, TURBT with or without intravesical therapy may be considered.

In patients with extensive comorbid disease or poor performance status who are not candidates for cystectomy or definitive chemoradiotherapy,

treatment options include radiotherapy alone or TURBT. The overall tumor status should be reassessed 2 to 3 months after treatment completion. If no tumor is evident, the patient should be observed. If tumor is observed, systemic therapy, radiotherapy (if no prior radiotherapy), TURBT with or without intravesical therapy, or best supportive care may be given.

***Treatment of Stage IIIB Tumors***

Primary treatment for stage IIIB (cT1–T4a, N2–3) disease can include either downstaging systemic therapy or concurrent chemoradiotherapy.[226,227] A population-based study of 659 patients with cT1–T4a, node-positive urothelial bladder cancer tested the effectiveness of induction chemotherapy for pathologic downstaging.[227] For cN1 disease, complete pathologic downstaging was achieved in 39% of patients who received induction chemotherapy compared to 5% of patients who did not receive induction chemotherapy. For cN2–3, the rate of pathologic downstaging was 27% versus 3% for these two groups. OS was also improved in patients who received induction chemotherapy ($P < .001$), although the nature of the study limits interpretation of the OS results.[227] Another study used the NCDB to analyze outcomes of 1783 patients with clinically node-positive bladder cancer who were treated with chemotherapy alone (n = 1388) or chemoradiotherapy (n = 395).[226] This study found that patients treated with chemoradiotherapy had a higher median OS than those treated with chemotherapy (19.0 vs. 13.8 months; $P < .001$). The improvement in outcome with chemoradiotherapy persisted upon evaluation of propensity-matched populations ($P < .001$).[226] Cystectomy as primary treatment or for surgical palliation may be appropriate in very select situations, such as in patients with limiting local symptoms and/or those with comorbidities that prevent administration of chemotherapy.

Tumor status should be reassessed 2 to 3 months after treatment by imaging of the chest, abdomen, and pelvis using CT with contrast. If there is no evidence of distant disease on imaging reassessment, further cystoscopic assessment of tumor response in the bladder may be considered.

Subsequent disease management depends on the response to primary treatment. Patients who received downstaging systemic therapy and had a complete disease response may then be subsequently treated with cystectomy or chemoradiotherapy or may be observed until disease relapse, depending on patient-specific features. Patients who received downstaging systemic therapy and showed a partial response may be treated with cystectomy or chemoradiotherapy (for persistent disease confined to the bladder) or treated as with metastatic disease with additional lines of systemic therapy (for distant disease). Patients who had disease progression following primary downstaging systemic therapy may be treated as with metastatic disease, with additional lines of systemic therapy.

Patients with complete disease response following concurrent chemoradiotherapy should be observed until disease relapse. Disease with partial responses to concurrent chemoradiotherapy may be subsequently treated with surgical consolidation (for residual disease confined to the bladder), with consideration of intravesical BCG (for CIS, Ta, or T1 residual disease), or as metastatic disease with systemic therapy (for remaining disease outside the bladder). Progression following concurrent chemoradiotherapy may be treated as metastatic disease with systemic therapy.

***Treatment of Stage IVA Tumors***

Stage IVA includes patients with cT4b, any N, M0 or any T, any N, M1a disease.[20] For patients with stage IVA disease, treatment options differ depending on the presence of distant metastasis (M0 vs. M1a).

Primary treatment recommendations for patients with M0 disease include systemic therapy or concurrent chemoradiotherapy followed by evaluation with cystoscopy, EUA, TURBT, and imaging of the abdomen and pelvis. If no evidence of tumor is present after primary treatment, the patient may be treated with consolidation systemic therapy or adjuvant treatment with chemoradiotherapy may be initiated if the patient did not receive prior radiotherapy. In general, stage IVA 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 on evaluation after primary therapy, systemic therapy or cystectomy is recommended. Systemic therapy may include targeted therapy, chemoradiotherapy (if no prior radiotherapy), or chemotherapy. Cystectomy, if feasible, is an option.

Patients with M1a disease should receive systemic therapy as primary treatment. Those select patients with metastatic disease treated with curative intent should be evaluated with cystoscopy, EUA, TURBT, and abdominal/pelvic imaging. If a complete or partial response is noted following primary treatment of metastatic disease, consolidative local therapy with concurrent chemoradiotherapy or cystectomy may be considered in select cases. If the disease remains stable or progresses following primary therapy, these patients should follow treatment for metastatic 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.[228] Surveillance by urine cytology or upper tract imaging detected recurrences in 7% and 30% of cases, respectively.

Follow-up after a cystectomy should include urine cytology, liver function tests, creatinine, and electrolytes. Imaging of the chest, upper tract abdomen, and pelvis should be conducted at intervals based on the risk of recurrence. 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 CIS was found within the bladder or prostatic urethra. For details of follow-up recommendations, see *Follow-up* in the algorithm.

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.

### Recurrent or Persistent Disease

A positive cytology with no evidence of disease in the bladder following imaging and cystoscopy should be managed as described in the *Posttreatment of Recurrent or Persistent Disease* under *Non-Muscle Invasive Urothelial Bladder Cancer*, above.

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, CIS, Ta, or T1 tumors are generally

managed with intravesical therapy, cystectomy, or TURBT. If no response is noted, 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 EBRT and has bulky residual disease. For these patients, systemic therapy or palliative TURBT and best supportive care is advised.

Subsequent-line therapy for metastatic disease or local recurrence following cystectomy generally would include systemic therapy. Radiotherapy alone can also be considered as a subsequent-line therapy for patients with metastatic disease or local recurrence following cystectomy, especially in selected cases with regional-only recurrence or with clinical symptoms.

## Metastatic (Stage IVB) Urothelial Bladder Cancer

Approximately 5% of patients have metastatic disease at the time of diagnosis.[2] Additionally, approximately 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 (CNS) imaging should be considered. An estimated 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.[130] If the evidence of spread is limited to nodes and biopsy is technically feasible, nodal biopsy should be considered and patients' disease 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*, below).

Patients who present with disseminated metastatic disease are generally treated with systemic therapy. Metastasectomy and/or palliative radiotherapy may also be useful for select patients.[229]

### Metastasectomy for Oligometastatic Disease

Highly select patients with oligometastatic disease who are without evidence of rapid progression may benefit from metastasectomy following 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 two 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.[230] Another phase II trial of 70 patients who underwent complete surgical resection of bladder cancer metastases investigated survival, performance status, and quality of life following surgery. This study reported no survival

advantage from surgery, although the quality of life and performance status were improved for symptomatic patients.[231]

Beyond these prospective data, several retrospective studies have demonstrated a survival advantage following metastasectomy.[232-235] A retrospective series of 55 patients with bladder primary urothelial carcinoma metastatic to the pelvic or retroperitoneal lymph nodes, who underwent post-chemotherapy 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 were similar for cN1–3 versus cM1.[236] 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 to non-surgical treatment of metastatic lesions. Five-year survival in these studies ranged from 28% to 72%.[237] Another population-based analysis of 497 patients ≥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.[238] Conversely, a study that queried the NCDB database from 2004 to 2016 reported no difference in OS between propensity score-matched patients with urothelial carcinoma who had undergone metastasectomy compared with those who had not (HR, 0.94; 95% CI, 0.83–1.07; *P* = .38).[239] This study found that 7% of metastatic urothelial carcinoma patients were treated with metastasectomy and, on average, patients treated with metastasectomy were younger, had greater than cT3 disease, had radical surgery on the primary tumor, and received systemic therapy.

Due to the limited and somewhat conflicting 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.[240] The NCCN Bladder Cancer Panel recommends that molecular/genomic testing be conducted 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 approvals for erdafitinib and fam-trastuzumab deruxtecan, molecular testing should include analysis for *FGFR3* genetic alterations and HER2 overexpression by immunohistochemistry (IHC). For certain patients who are ineligible to receive cisplatin, the checkpoint inhibitor atezolizumab may be considered for first-line therapy based on PD-L1 testing results (see *Checkpoint Inhibitor Monotherapy as First-line Treatment*, below).

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.[241,242] 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 one 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 *CDKN2A* (34%), *FGFR3* (21%), *PIK3CA* (20%), and *ERBB2* (17%).[243]

### First-Line Systemic Therapy for Metastatic Disease

The specific systemic therapy regimen recommended partially depends on the presence or absence of medical comorbidities, such as cardiac disease, autoimmune disease, peripheral neuropathy, diabetes, and renal dysfunction, along with the risk classification of the patient based on disease extent. In general, long-term survival with combination platinum-based chemotherapy has been reported only in patients with more favorable prognosis, defined as those with good performance status, no visceral (ie, liver, lung) nor bone disease, and normal alkaline phosphatase or lactic dehydrogenase levels. Patients with disease with poor prognostic features, defined as those with poor performance status or visceral disease, have consistently shown higher discontinuation rates with multiagent platinum-based combination chemotherapy regimens and few complete remissions, which are prerequisites for durable responses. An assessment of clinical application is currently underway to better determine how “platinum-ineligible” may be defined.[244] Newer combinations with better clinical utility, such as the immune checkpoint inhibitors, antibody-drug conjugates, and targeted therapies, provide other treatment options for these patients who are not candidates for cisplatin-based chemotherapy.

For patients with metastatic disease treated with chemotherapy, disease status should be re-evaluated after two to three cycles of chemotherapy, and treatment is continued for two more cycles in patients whose disease responds or remains stable. Chemotherapy may be continued for a maximum of six cycles in most cases, depending on response and tolerance. If no response is noted after two cycles or if significant morbidities are encountered, a change in therapy is advised, considering the patient’s current performance status, extent of disease, and specific prior therapy.

Surgery or radiotherapy may be feasible in highly select metastatic 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. If disease is completely resected, two additional cycles of chemotherapy can be considered, depending on patient tolerance.

***Platinum-Based Chemotherapy Regimens (ddMVAC or GC)***

GC[245,246] and ddMVAC[161,187] are commonly used combination chemotherapy regimens 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.[188] At a median follow-up of 19 months, OS and time to progression were similar in the two arms. Fewer toxic deaths were recorded among patients receiving GC compared to 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%; PFS, 9.8% vs. 11.3%, respectively).[246] Another large, randomized, phase III trial compared ddMVAC to standard (28-day) MVAC.[161,187] 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 to 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.

The performance status of the patient is a major determinant in the selection of a regimen and can often limit the use of cisplatin-containing

regimens such as ddMVAC or GC. 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, 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 two carboplatin-containing regimens in medically unfit patients (performance status 2).[247] 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).

Avelumab maintenance therapy is recommended following cisplatin- or carboplatin-based first-line therapy if there is no progression on first-line platinum-containing chemotherapy (see *Avelumab Maintenance Therapy*, below).

***Pembrolizumab Plus Enfortumab Vedotin-ejfv***

A combination of the immune checkpoint inhibitor, pembrolizumab, with the antibody-drug conjugate, enfortumab vedotin, was initially studied in certain cohorts of the phase Ib/II EV103 study, which included cisplatin-ineligible patients with previously untreated, locally advanced or metastatic urothelial cancer.[248,249] Forty-five patients within cohort A received the combination of enfortumab vedotin and pembrolizumab.[248] After a median of nine treatment cycles, the confirmed ORR was 73.3%, with a complete response rate of 15.6%. The most common treatment-related AEs were peripheral sensory neuropathy (55.6%), fatigue (51.1%), and alopecia (48.9%); 64.4% of patients had grade ≥3 treatment-related AEs and one death was classified as treatment-related. Cohort K randomized patients who were ineligible to receive cisplatin to first-line enfortumab vedotin, alone or in combination with pembrolizumab.[249] The primary endpoint of confirmed ORR was 64.5% (95% CI, 52.7%–75.1%) for the combination compared to 45.2% (95% CI, 33.5%–57.3%) for enfortumab vedotin monotherapy. The median DOR was not reached for the combination and was 13.2 months for the monotherapy.

Subsequently, enfortumab vedotin and pembrolizumab was investigated in the phase III EV-302 trial, which randomized 886 patients with previously untreated locally advanced or metastatic urothelial carcinoma to either enfortumab vedotin plus pembrolizumab or gemcitabine in combination with either cisplatin or carboplatin.[250] After a median follow-up of 17.2 months, median PFS was significantly longer with enfortumab vedotin plus pembrolizumab compared to chemotherapy (12.5 months vs. 6.3 months; HR, 0.45; 95% CI, 0.38–0.54; $P < .001$). Median OS was also significantly longer with enfortumab vedotin plus pembrolizumab (31.5 months vs. 16.1 months; HR, 0.47; 95% CI, 0.38–0.58; < .001). Confirmed ORR was 67.7% and 44.4% for enfortumab vedotin plus pembrolizumab and chemotherapy, respectively ($P < .001$), with complete responses observed in 29.1% of patients in the enfortumab vedotin plus pembrolizumab group and 12.5% of those in the chemotherapy group. Treatment-related AEs grade ≥3 occurred in 55.9% of patients receiving enfortumab vedotin plus pembrolizumab and 69.5% of those receiving chemotherapy.

Based on these results, the combination of pembrolizumab plus enfortumab vedotin is the preferred first-line systemic therapy option for patients with advanced or metastatic urothelial carcinoma, regardless of whether or not they are eligible for cisplatin. Based on high-level data from the EV-302 trial, this regimen has been given a category 1 designation by the panel.

***Gemcitabine, Cisplatin, and Nivolumab***

The multinational, phase III CheckMate901 study compared nivolumab plus gemcitabine-cisplatin to gemcitabine-cisplatin alone in 608 patients with previously untreated unresectable or metastatic urothelial carcinoma.[251] Patients who received the nivolumab combination also received maintenance nivolumab for up to 2 years. After a median follow-up of 33.6 months, nivolumab plus gemcitabine-cisplatin showed longer median OS compared to gemcitabine-cisplatin alone (21.7 vs. 18.9 months; HR, 0.78; 95% CI, 0.63–0.96; *P* = .02). The median PFS was similar for the two arms (7.9 vs. 7.6 months; *P* = .001), but the PFS curves separated over time. At 12 months, the PFS was 34.2% with the nivolumab combination compared to 21.8% with chemotherapy alone. The ORR was 57.6% with the nivolumab combination compared to 43.1% with chemotherapy alone. For those in the nivolumab plus gemcitabine-cisplatin group, 21.7% had complete responses. Grade ≥3 AEs occurred in 61.8% of those in the nivolumab combination group and 51.7% of those who received chemotherapy alone. Based on the results from this phase III trial, the NCCN Panel designated the regimen a category 1 recommendation as first-line therapy.

***Checkpoint Inhibitor Monotherapy as First-Line Treatment***

In addition to the combination of pembrolizumab and enfortumab vedotin, two checkpoint inhibitors have been tested as monotherapy first-line options for cisplatin-ineligible patients.

The single-arm, phase II KEYNOTE-052 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 ORR of 24%, with 5% of patients achieving a complete response. Grade 3 or higher treatment-related AEs occurred in 16% of patients treated with pembrolizumab at the time of data cutoff.[252] Long-term outcomes of KEYNOTE-052 were similar to the initial analysis with an ORR of 28.6% and a median OS of 11.3 months.[253] 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 two clinical trials (KEYNOTE-361 and IMvigor130) showed decreased survival for patients receiving pembrolizumab or atezolizumab as first-line monotherapy compared to those receiving cisplatin- or carboplatin-based therapy.[254] Based on these data, the pembrolizumab prescribing information was initially 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 (CPS) of at least 10; or 2) are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.[255] Subsequently, the first-line indication was further restricted to only patients who were not eligible for any platinum-containing chemotherapy, removing eligibility for first-line pembrolizumab from the PD-L1–high, platinum-eligible population.[256] This amended indication was granted a full (regular) approval by the FDA.

The final approval for pembrolizumab as a first-line therapy for patients who were not eligible for any platinum-containing chemotherapy was based on results of the phase III KEYNOTE-361 trial, which randomized 1010 patients with previously untreated advanced, unresectable, or metastatic urothelial carcinoma to treatment with pembrolizumab plus platinum-based chemotherapy, pembrolizumab alone, or platinum-based chemotherapy alone.[257] After a median follow-up of 31.7 months, the addition of pembrolizumab to chemotherapy did not significantly prolong median PFS or OS compared to chemotherapy alone (8.3 vs. 7.1 months for PFS; *P* = .0033 and 17.0 vs. 14.3 months for OS; *P* = .0407). Additionally, analyses for first-line pembrolizumab versus chemotherapy alone found that OS was similar both for the total population (14.3 vs. 15.6 months) as well as those with high PD-L1 expression as measured by a CPS of at least 10 (16.1 vs. 15.2 months).

Data from the two-cohort, multicenter, phase II IMvigor210 trial evaluated atezolizumab in patients with metastatic disease. In cohort 1, 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.[258] 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 two ongoing clinical trials (KEYNOTE-361 and IMvigor130) showed decreased survival for patients receiving pembrolizumab or atezolizumab as first-line monotherapy compared to those receiving cisplatin- or carboplatin-based therapy.[254] Based on these data, the atezolizumab prescribing information was initially 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.[259]

The IMvigor130 trial was a multicenter phase III trial where 1213 patients with previously untreated, locally advanced or metastatic urothelial carcinoma were randomized to one of three treatment groups: atezolizumab plus platinum-based chemotherapy (group A), atezolizumab monotherapy (group B), or placebo plus platinum-based chemotherapy (group C).[260] Chemotherapy regimens included gemcitabine in combination with either cisplatin or carboplatin. At the time of the analysis, median PFS in the ITT population was 8.2 months in group A and 6.3 months in group C. Median OS was 16.0 months for group A compared to 13.4 months for group C (HR, 0.83; 0.69–1.00; one-sided $P = .027$). For the comparison of group B to group C, the median OS was 15.7 and 13.1 months, respectively.

In November 2022 the manufacturer announced that they were voluntarily withdrawing the first-line bladder cancer indications for atezolizumab since atezolizumab plus chemotherapy did not meet the co-primary endpoint of OS compared with chemotherapy alone in the IMvigor130 trial.[261] Despite this withdrawal, the NCCN Panel has maintained the inclusion of atezolizumab as a first-line option in patients who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 or who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression (both recommendations are category 2B).

***Other Non-Platinum Based Chemotherapy Regimens***

Taxanes have been shown to be active as treatment options for urothelial bladder cancer.[262-265] Based on these results, several groups are exploring two- and three-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.[266] The addition of paclitaxel to GC resulted in higher response rates and a borderline OS advantage, which was not statistically significant in the ITT analysis. Analysis of eligible patients only (92%) resulted in a small (3.2 months) but statistically significant survival advantage in favor of the three-drug regimen ($P = .03$). There was no difference in PFS. The incidence of neutropenic fever was substantially higher with the three-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,[267] gemcitabine/paclitaxel,[268] cisplatin/gemcitabine/paclitaxel,[269] carboplatin/gemcitabine/paclitaxel,[270] and

cisplatin/gemcitabine/docetaxel,[271] have shown modest activity in patients with bladder cancer in phase I–II trials.

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 comorbidities (see *Principles of Systemic Therapy* in the algorithm).

***Avelumab Maintenance Therapy***

For patients who show either response or stable disease through their full course of platinum-based first-line chemotherapy, maintenance therapy with the PD-L1 inhibitor, avelumab, is recommended. The randomized, phase III JAVELIN Bladder 100 trial showed that avelumab significantly prolonged OS in all 700 randomized patients compared to best supportive care alone (median OS, 21.4 vs. 14.3 months; HR, 0.69; 95% CI, 0.56–0.86; $P$ = .001).[272] The OS benefit was observed in all prespecified subgroups, including patients with PD-L1–positive tumors. Grade ≥3 AEs were reported in 47.4% of patients treated with avelumab compared to 25.2% of those with best supportive care alone. Based on these positive OS data in a phase III trial, the NCCN Panel has assigned avelumab maintenance therapy a category 1 recommendation.

For patients treated with gemcitabine, cisplatin, and nivolumab as first-line therapy, nivolumab may be used as maintenance therapy.

**Second-Line and Subsequent Therapy for Metastatic Disease**

With the recent changes to first-line treatment options for metastatic disease, many providers are moving towards immune checkpoint inhibitor combinations such as enfortumab vedotin plus pembrolizumab as a first-line treatment option. In this evolving paradigm, there is limited evidence to guide optimal selection of second- and subsequent-line therapies following these new first-line regimens.

The FDA has approved the PD-L1 inhibitor avelumab as well as the PD-1 inhibitors nivolumab and pembrolizumab 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. Pembrolizumab has also been approved in combination with enfortumab vedotin for treatment of adult patients with locally advanced or metastatic urothelial carcinoma and as first-line monotherapy for patients who are ineligible to receive a platinum-containing regimen. Avelumab has also been approved as maintenance treatment for patients with locally advanced or metastatic urothelial carcinoma that has not progressed with first-line platinum-containing chemotherapy. See *First-Line Systemic Therapy for Metastatic Disease*, above, for more discussion of these regimens.

***Pembrolizumab Monotherapy***

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.[273] 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 to 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 to those treated with chemotherapy (15.0% vs. 49.4%).[274] Long-term results (>2 year 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 to chemotherapy.[275] The median DOR was not reached for pembrolizumab compared to 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 to chemotherapy. Results from this phase 3 trial have led the NCCN Panel to assign pembrolizumab a category 1 recommendation as a second-line therapy.

Pembrolizumab has also been studied as a combination therapy with enfortumab vedotin (see *Pembrolizumab Plus Enfortumab Vedotin-ejfv*, above).

***Nivolumab Monotherapy***

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) following treatment with nivolumab that was unaffected by PD-1 tumor status.[276] Out 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.[276] The median OS was 8.74 months (95% CI, 6.05–not yet reached). Based on PD-L1 expression of less than 1% and 1% or greater, 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, two experienced grade 5 treatment-related AEs, and grade 3 or 4 treatment-related AEs were reported in 22% of patients.[277] 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.[278]

Nivolumab has also been studied for adjuvant therapy of muscle invasive bladder cancer or UTUC after surgery (see section on *Adjuvant Systemic Therapy* under *Muscle Invasive Urothelial Bladder Cancer*).

***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 1b trial for 44 patients with platinum-refractory disease demonstrated an ORR of 18.2% that consisted of five complete responses and three 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.[279] A pooled analysis of two 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 post-platinum 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.[280]

Avelumab is also recommended as a maintenance therapy following first-line platinum-containing treatment. For this setting, see *Avelumab Maintenance Therapy*, above.

***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 two 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.[281] Upon long-term follow-up (median 24.0 months) of the aforementioned study, the investigator-assessed ORR was 40% (95% CI, 30–49) and the safety profile remained similar to the primary analysis.[282]

The phase III THOR trial compared erdafitinib to chemotherapy (docetaxel or vinflunine) or pembrolizumab in patients with metastatic urothelial carcinoma with susceptible *FGFR3* or *FGFR2* alterations who had progressed on or after prior treatment. THOR had two cohorts: cohort 1 required one or two prior treatments, at least one of which included a checkpoint inhibitor; cohort 2 required one prior treatment that did not include a checkpoint inhibitor. For the 266 patients in cohort 1, after a median follow-up of 15.9 months, the median OS was longer with erdafitinib compared to chemotherapy (12.1 vs. 7.8 months; HR, 0.64; 95% CI, 0.47–0.88; $P = .005$).[283] Median PFS was also longer with erdafitinib than with chemotherapy (5.6 vs. 2.7 months; $P < .001$). The incidence of grade ≥3 treatment-related AEs was similar between the two groups, with 45.9% reporting in the erdafitinib group compared to 46.4% in the chemotherapy group. Treatment-related AEs that lead to death occurred in 0.7% of those treated with erdafitinib and 5.4% of those treated with chemotherapy. In the intention-to-treat population of 351 patients in cohort 2, there was no significant difference between the treatment arms for median OS (10.9 months for erdafitinib vs. 11.1 months for pembrolizumab; HR, 1.18; 95% CI, 0.92–1.51; $P = .18$).[284] ORR was 40% for erdafitinib compared to 21.6% for pembrolizumab, although pembrolizumab had a longer DOR at 14.4 months, compared to 4.3 months for erdafitinib. Grade 3–4 AEs were reported in 64.7% of patients treated with erdafitinib versus 50.9% treated with pembrolizumab. AEs led to death in 2.9% of patients treated with erdafitinib and 6.9% of those treated with pembrolizumab.

Based on the phase III THOR trial results, where all patients had previously received an immune checkpoint inhibitor, and 89.1% had also received at least one line of chemotherapy (cisplatin in 50.8% and carboplatin in 29.3%),[283] erdafitinib was given a category 1 designation in the subsequent-line, post-platinum, post-checkpoint inhibitor setting. Also, since around 11% of patients on the THOR trial had not previously received platinum-based chemotherapy, erdafitinib is recommended as a preferred regimen in the second-line, post-checkpoint inhibitor setting.

In January 2024, the FDA amended the indication for erdafitinib that was previously granted under accelerated approval to provide full approval for adult patients with locally advanced or metastatic urothelial carcinoma with susceptible *FGFR3* genetic alterations, whose disease has progressed on or after at least one prior line of systemic therapy.[285] Furthermore, the FDA indication notes that erdafitinib is not recommended for the treatment of patients who are eligible for and have not received prior PD-1 or PD-L1 inhibitor therapy. In response to the amended FDA indication, the NCCN Panel made the decision to match the biomarker requirements and specify susceptible *FGFR3* genetic alterations; however, NCCN retains the erdafitinib recommendation for second-line therapy, post-platinum or other chemotherapy without a checkpoint inhibitor.

***Enfortumab Vedotin-ejfv Monotherapy***

Enfortumab vedotin is a Nectin-4-directed antibody–drug conjugate that was evaluated in a global, phase II, single-arm EV-201 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 DOR was 7.6 months. Grade ≥3 treatment-related AEs were reported in 54% of patients and treatment-related AEs led to dose reductions or discontinuation of therapy in 32% and 12% of patients, respectively.[286] Subsequently, an open-label, phase III trial of enfortumab vedotin (EV-301) evaluated the therapy in 608 patients with advanced urothelial carcinoma who had previously received both a platinum-containing regimen as well as a checkpoint inhibitor.[287] Patients were randomized 1:1 to either enfortumab vedotin or the investigator's choice of chemotherapy (docetaxel, paclitaxel, or vinflunine). After a median follow-up of 11.1 months, OS was longer with enfortumab vedotin than with chemotherapy (12.88 vs. 8.97 months; HR, 0.70; 95% CI, 0.56–0.89; $P$ = .001). Median PFS was also longer for enfortumab vedotin (5.55 vs. 3.71 months; HR, 0.62; 95% CI, 0.51–0.75; $P$ < .001). The incidence of grade 3 or greater AEs was similar in both groups, 51.4% with enfortumab vedotin compared to 49.8% with chemotherapy.

Enfortumab vedotin has also been evaluated as a second-line treatment option. Cohort 2 of the phase II EV-201 study enrolled 91 patients who had previously been treated with a PD-1 or PD-L1 checkpoint inhibitor therapy and were ineligible for a cisplatin-containing regimen.[288] Of the 89 patients who received treatment with enfortumab vedotin, the confirmed ORR was 52% (95% CI, 41%–62%) with 20% of patients having a complete response. Fifty-five percent of patients had grade 3 or higher AEs, with neutropenia, maculopapular rash, and fatigue being the most common. Four deaths were considered to be related to treatment, caused by acute kidney injury, metabolic acidosis, multiple organ dysfunction, and pneumonitis. Data supporting second-line use of enfortumab vedotin post-platinum or other non-platinum chemotherapy are more limited than post-checkpoint inhibitor, although the phase I EV-101 dose escalation/expansion study included patients with pretreated metastatic urothelial carcinoma who had not previously received a checkpoint inhibitor.[289] Of the 23 patients in this category, 43.5% showed a clinical response to enfortumab vedotin treatment. Furthermore, the FDA indication for second-line enfortumab vedotin specifies that the therapy is "indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer who are ineligible for cisplatin-containing chemotherapy and have previously received one or more prior lines of therapy."[290]

***Sacituzumab Govitecan-hziy***

Sacituzumab govitecan is another antibody–drug conjugate composed of an anti-Trop-2 humanized monoclonal antibody coupled to SN-38, the active metabolite of the topoisomerase 1 inhibitor, irinotecan. Sacituzumab govitecan has been evaluated in cohort 1 of TROPHY-U-01, a phase II open-label study with 113 patients in cohort 1.[291] Patients within this cohort had locally advanced, unresectable, or metastatic urothelial carcinoma that had progressed following prior platinum-based and PD-1/PD-L1 checkpoint inhibitor therapy and were treated with sacituzumab govitecan. At a median follow-up of 9.1 months, ORR was 27% (95% CI, 19.5%–36.6%) and 77% of participants showed a decrease in measurable disease. The median DOR was 7.2 months (95% CI, 4.7–8.6 months), median PFS was 5.4 months (95% CI, 3.5–7.2 months), and median OS was 10.9 months (95% CI, 9.0–13.8 months). Key grade greater than or equal to three treatment-related AEs were neutropenia (35%), leukopenia (18%), anemia (14%), diarrhea (10%), and febrile neutropenia (10%). Six percent of patients in the study discontinued treatment as a result of treatment-related AEs.

***Fam-trastuzumab deruxtecan-nxki (T-DXd)***

Fam-trastuzumab deruxtecan is a HER2-directed antibody-conjugate composed of a HER2 antibody coupled to a topoisomerase inhibitor that has been FDA approved for adult patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options.[292] Fam-trastuzumab deruxtecan was studied in the open-label phase II DESTINY-PanTumor02 trial, which included 267 patients across 7 tumor cohorts: endometrial, cervical, ovarian, bladder, biliary tract, pancreatic, and other.[293] Eligibility for this trial included a HER2-expressing tumor (IHC 3+/2+ by local or central testing) with locally advanced or metastatic disease after at least 1 systemic treatment or without alternative treatments. In all patients on the study, the ORR was 37.1%, median PFS was 6.9 months, and median OS was 13.4 months. For the 41 patients with bladder cancer, ORR was 39.0%, median PFS was 7.0 months, and median OS was 12.8 months. For the 75 patients with HER2 IHC 3+ expression, the ORR was 61.3%, median PFS was 11.9 months, and median OS was 21.1 months. For the patients with bladder cancer on this study, 65.9% had IHC 3+ HER2 overexpression. Grade ≥3 drug-related AEs were observed in 40.8% of all patients on the study, including 10.5% with adjudicated drug-related interstitial lung disease, of which 3 patients (1.1%) died.

### NCCN Recommendations for Systemic Therapy of Metastatic Disease

Based on the available data, the NCCN Panel recommends that patients with metastatic urothelial carcinoma who are eligible for a cisplatin-containing regimen receive either a cisplatin-based regimen or pembrolizumab in combination with enfortumab vedotin as first-line therapy, with pembrolizumab plus enfortumab vedotin being the preferred option. First-line cisplatin-based regimens include GC, ddMVAC with growth factor support, or gemcitabine-cisplatin plus nivolumab. All four of these regimens are supported by category 1 data. A patient who is ineligible for cisplatin, but eligible for carboplatin, may receive gemcitabine in combination with carboplatin first-line, although pembrolizumab plus enfortumab vedotin is the preferred option regardless of cisplatin-eligibility. If there is no progression on a first-line platinum-containing chemotherapy, avelumab maintenance therapy is preferred (category 1), unless nivolumab was included in the first-line regimen, in which case nivolumab maintenance therapy should be used.

First-line treatment options that may be useful under certain circumstances for patients who are not eligible for cisplatin-containing chemotherapy include pembrolizumab for patients who are not eligible for any platinum-containing chemotherapy and atezolizumab for patients whose tumors express PD-L1 or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression (both atezolizumab recommendations are category 2B). However, for these patients, enfortumab vedotin plus pembrolizumab should be prioritized if it can be given. Several chemotherapy regimens, including gemcitabine, alone or in combination with paclitaxel, or the combination of ifosfamide, doxorubicin, and gemcitabine may also be appropriate first-line treatment options for some patients.

Clinical trial enrollment is recommended by the NCCN Panel for all patients when appropriate, but is strongly recommended for second-line and subsequent therapies since data for locally advanced or metastatic disease treated with subsequent-line therapy are highly variable. The available second-line options depend on what was given as first-line. If a chemotherapy regimen, without a checkpoint inhibitor, was given first-line, pembrolizumab, nivolumab, avelumab, erdafitinib (if eligible on the basis of *FGFR3* genetic alteration), or enfortumab vedotin are preferred second-line treatment options. Pembrolizumab is supported by category

1 level data in the post-platinum setting. If PFS was more than 1 year following treatment with a platinum-containing regimen, retreatment with platinum may be considered.[294] Platinum rechallenge has been studied in the post-platinum and post-checkpoint inhibitor, subsequent-line setting.[295] If a checkpoint inhibitor was given first-line, preferred second-line options include enfortumab vedotin, erdafitinib (if eligible on the basis of *FGFR3* genetic alteration), or gemcitabine in combination with carboplatin for those who are cisplatin-ineligible or GC or ddMVAC with growth factor support for those who are cisplatin-eligible. Other regimens may also be appropriate in the second-line setting (see *Principles of Systemic Therapy* within the algorithm).

For subsequent therapy, after treatment with a platinum-based therapy and a checkpoint inhibitor, if the patient is eligible for these, the preferred regimens are enfortumab vedotin or erdafitinib, if eligible based on *FGFR3* testing results. Both regimens are supported by category 1 level data in this setting. A number of chemotherapy regimens and the antibody-drug conjugates, sacituzumab govitecan or fam-trastuzumab deruxtecan (if eligible on the basis of HER2 overexpression), are also recommended options in this setting.

***Targeted Therapies Not Recommended***

Early results from a phase I/II multicenter study of durvalumab for 61 patients with PD-L1–positive inoperable or metastatic urothelial bladder cancer that progressed following a 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.[296] A 2017 update on this study (N = 191) showed an ORR of 17.8% and a median OS of 18.2 months, with 55% of patients surviving at 1 year.[297] In May 2017, the FDA granted accelerated approval to durvalumab based on these initial results. Subsequently, in February 2021, the makers of durvalumab voluntarily withdrew this indication based on negative results from the phase III DANUBE trial.[298] DANUBE evaluated the use of durvalumab, with or without tremelimumab, compared to chemotherapy for first-line treatment of advanced urothelial carcinoma.[299] The trial did not meet its primary endpoints as both durvalumab alone and in combination with tremelimumab failed to improve OS compared to chemotherapy.

Likewise, atezolizumab had initially received accelerated approval for patients with metastatic urothelial carcinoma post-platinum treatment based on early results from the IMvigor210 and IMvigor211 trials.[300-302] The phase IIIb SAUL study and another expanded access study of atezolizumab also reported similar efficacy and safety results in a real-world population, including those ineligible for IMvigor211.[303-305] However, in March 2021, the makers of atezolizumab voluntarily withdrew their indication for patients with locally advanced or metastatic urothelial carcinoma that was previously treated with a platinum-based chemotherapy.[306] This withdrawal was based on the IMvigor211 trial failing to meet its primary endpoint of improved OS. In November 2022, the remaining bladder cancer indications for atezolizumab were withdrawn by the manufacturer based on results from the IMvigor130 trial.[261]

In response to these voluntary withdrawals, the NCCN Panel voted to remove atezolizumab and durvalumab as treatment options for patients with metastatic urothelial carcinoma in the post-platinum setting, although atezolizumab is maintained in the Guidelines as a non-preferred first-line option for certain patients (see *NCCN Recommendations for Systemic Therapy of Metastatic Disease*, above).

While several ongoing studies are investigating the addition of a targeted therapy agent to chemotherapy for treatment of bladder cancer, there are no sufficient data to support this approach. The phase III KEYNOTE-361 trial of pembrolizumab alone or in combination with

chemotherapy for first-line treatment of advanced urothelial carcinoma showed no improved efficacy compared to chemotherapy and, therefore, this combination is not recommended for treatment of metastatic bladder cancer.[257]

## Non-Urothelial Carcinomas of the Bladder

Approximately 10% of bladder tumors are non-urothelial (non-transitional cell) carcinoma. These pathologic entities include mixed histology, pure squamous, adenocarcinoma, small cell tumors, urachal carcinoma, or primary bladder sarcoma. Depending on the pathologic findings, perioperative chemotherapy may or may not be recommended. The regimens effective for urothelial carcinoma histologies have limited efficacy for patients with non-urothelial carcinomas.

These individuals are often treated based on the identified histology. In general, patients with non-urothelial invasive disease are treated with cystectomy, although those with certain urachal tumors require complete urachal resection (en bloc resection of the urachal ligament with the umbilicus) or may be appropriately treated with partial cystectomy. For example, adenocarcinomas are managed surgically with radical or partial cystectomy and with individualized adjuvant chemotherapy and radiotherapy for maximum benefit. Pure squamous cell tumors are treated by cystectomy, chemoradiotherapy, or agents commonly used for squamous cell carcinoma of other sites such as 5-FU or taxanes. However, overall experience with chemotherapy in non-urothelial carcinomas is limited.

Data are limited to support perioperative chemotherapy for non-urothelial carcinomas; however, neoadjuvant chemotherapy may benefit patients with small cell carcinoma of the bladder and is recommended by the panel for any patient with small-cell component histology with localized disease regardless of stage.[307-311] In addition, a retrospective analysis has shown that neoadjuvant chemotherapy may have a modest benefit for other variant histologies.[312] In patients with non-urothelial carcinomas of any stage, no data support the use of adjuvant chemotherapy, although the risk for relapse may be high. Some of the general principles of management applicable to urothelial carcinomas are appropriate with minor variations.

Patients with small cell carcinoma of the bladder are best treated with initial systemic therapy (see NCCN Guidelines for Small Cell Lung Cancer) followed by either RT or cystectomy as consolidation, if there is no metastatic disease.[313] In addition to the regimens recommended for small cell lung cancer, a regimen alternating ifosfamide plus doxorubicin with etoposide plus cisplatin has also been tested specifically for small cell bladder cancer and found to be effective both as neoadjuvant and metastatic therapy.[309] The combination of nivolumab plus ipilimumab has also been tested in a phase II trial for advanced rare genitourinary malignancies, including the BUTCVH cohort of 19 patients with bladder or upper tract tumors of variant histology (3 patients with small cell bladder cancer).[314] ORR for the BUTCVH cohort was 37%, with two complete responses. Concurrent chemoradiotherapy is also an option for these patients.[315] Primary bladder sarcomas are treated as per the NCCN Guidelines for Soft Tissue Sarcoma.

## Upper Tract Urothelial Carcinoma

Upper tract tumors, including those that originate in the renal pelvis or in the ureter, are relatively uncommon.[316] The treatment recommendations discussed in this section are based on the most common histology of upper tract tumors, urothelial carcinoma.

## Renal Pelvis Tumors

Tumors that develop in the renal pelvis may be identified during evaluation of hematuria or a renal mass. In the latter case, renal pelvic tumors must be distinguished from the more typical adenocarcinomas that originate in the renal parenchyma. These tumors may also be detected during an assessment to pinpoint the source of a positive cytology in a negative cystoscopy with a retrograde ureteropyelography.

### *Workup*

The evaluation of a patient with a suspected renal pelvic tumor should include cystoscopy and imaging of the upper tract collecting system with CT or MR urography; renal ultrasound or CT without contrast with retrograde ureteropyelography; or ureteroscopy with biopsy; or percutaneous biopsy; and/or selective washings. A chest radiograph or CT can help evaluate for possible metastasis and assess for any comorbid diseases. Urine cytology obtained from a urine sample or during a cystoscopy may help identify carcinoma cells. Hematologic, renal, and hepatic function should also be evaluated. Additional imaging studies, such as a renal scan or bone scan, may be needed if indicated by the test results or by the presence of specific symptoms. Recent evidence has suggested a high prevalence of Lynch syndrome in patients with UTUC.[8,317] Therefore, it is recommended to take a thorough family history for all patients with UTUC and consider evaluation for Lynch syndrome for those who are at high risk (see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal for information on the criteria and strategies for evaluation of Lynch syndrome).

### *Primary Treatment*

In general, the primary form of treatment for renal pelvic tumors is surgery.

Well-differentiated tumors of low grade may be managed with a nephroureterectomy with a bladder cuff with or without perioperative intravesical chemotherapy. Several prospective, randomized, clinical trials have shown a reduction of risk of bladder recurrence following nephroureterectomy when a single postoperative intravesical instillation of chemotherapy was administered.[318-320] While the studies have generally looked at early instillation (within 24–48 hours of surgery),[319,320] some centers are delaying intravesical instillation of chemotherapy by up to 1 week to administer a cystogram confirming there is no perforation. While mitomycin is most commonly used, gemcitabine is an option for select patients. As an alternate to nephroureterectomy, a nephron-sparing procedure through a transureteroscopic approach or a percutaneous approach may be used, with or without postsurgical intrapelvic chemotherapy or BCG (see *Endoscopic Management of UTUC*).

High-grade tumors or those that are large and/or invade the renal parenchyma are managed through nephroureterectomy with a bladder cuff and regional lymphadenectomy with or without perioperative intravesical chemotherapy. Decline in renal function following surgery may preclude adjuvant therapy. Hence, in selected patients, cisplatin-based neoadjuvant chemotherapy is recommended. The data supporting the use of neoadjuvant chemotherapy for UTUC are more limited than for urothelial bladder cancer, although a growing body of evidence suggests that this approach may be beneficial to certain patients. A phase II trial demonstrated the safety and activity of accelerated MVAC as neoadjuvant therapy for high-grade UTUC with a pathologic complete response rate of 14% and a final pathologic stage of ypT1 or less in more than 60% of patients.[321] Systematic reviews and meta-analyses have also reported that neoadjuvant chemotherapy may also improve outcomes compared to no perioperative treatment, although more prospective data are needed.[322-325]

If metastatic disease is documented, or comorbid conditions that do not allow for surgical resection are present, treatment should include systemic therapy with regimens similar to those used for metastatic urothelial bladder tumors.

In positive upper tract cytology but negative imaging and biopsy studies, treatment remains controversial and appropriate management is currently poorly defined. Frequent monitoring for disease is necessary for these patients.

***Endoscopic Management of UTUC***

Nephron-sparing endoscopic treatment is a treatment option for certain patients with UTUC, depending on clinical and pathologic criteria and/or comorbid conditions that may contraindicate nephroureterectomy. Favorable clinical and pathologic criteria for nephron preservation include a papillary, unifocal, low-grade tumor, and size less than 1.5 cm, where cross-sectional imaging shows no concern for invasive disease.[316,326] Although there are no randomized controlled trials, systematic reviews of retrospective studies have shown that nephron-sparing approaches show similar outcomes compared to nephroureterectomy for these patients.[327,328] In addition, patients with bilateral disease, solitary functional or anatomic kidney, chronic kidney disease, or renal insufficiency are contraindicated from nephroureterectomy and should receive nephron-sparing treatment.[316,329] Long-term surveillance (>5 years), including urine cytology and cross-sectional urography or endoscopic visualization, is required following nephron-sparing treatment due to a high risk of disease recurrence.[316]

Mitomycin for pyelocalyceal solution (also called UGN-101 or mitomycin gel) has been FDA-approved for treatment of adult patients with low-grade UTUC.[330] This approval was based on OLYMPUS, a single-arm, multicenter, phase 3 trial of patients with treatment-naïve or recurrent low-grade noninvasive UTUC with at least one measurable papillary tumor above the ureteropelvic junction who were scheduled to receive 6 weekly instillations of mitomycin ureteral gel via retrograde catheter to the renal pelvis and calyces.[331] Of the 71 patients who received at least one dose of mitomycin gel, 59% showed a complete response at the primary disease evaluation visit (95% CI, 47%–71%; $P < .0001$). Durability of response was estimated at 84.2% 12 months after the primary disease evaluation, with a median time to recurrence of 13 months. The most common all-cause AEs in this study were ureteric stenosis, urinary tract infections, hematuria, flank pain, and nausea. Based on these data, the NCCN Panel recommends mitomycin gel be considered for use in this setting, with the caveat that complete or near complete endoscopic resection or ablation is recommended prior to gel application. Treatment with mitomycin gel is most appropriate for patients with a solitary residual, low-grade, UTUC tumor that is low volume (eg, 5–15 mm) and who are not candidates for or are not seeking nephroureterectomy as a definitive treatment. Long-term follow-up of OLYMPUS showed a durable response to mitomycin ureteral gel in those who had a complete response to induction therapy (56% remained in complete response after 12 months).[332] Fifty percent of those who did not receive any maintenance instillations of mitomycin gel and 59% of those who received at least one maintenance instillation remained in complete response at 12 months.

***Adjuvant Treatment and Follow-up***

Subsequent management is dictated by the extent of disease at surgery. Tumors that are pT0 or pT1 should be followed up with serial cystoscopies at 3-month intervals for the first year and, if negative, at longer intervals. Cytology may also be considered at similar intervals for high-grade tumors. Tumors that are pT0 or pT1 and were treated with nephron-sparing surgery should also be followed up with ureteroscopy and upper tract imaging at 3- to 12-month intervals.

While a previous retrospective study of 1544 patients with pT2–4 or node-positive UTUC showed no difference in OS between adjuvant chemotherapy and observation following radical nephroureterectomy,[333] the more recent phase III POUT trial has demonstrated benefit of adjuvant therapy for these patients.[334] POUT randomized 261 patients with pT2–4 or pN1–3, M0 UTUC after nephroureterectomy to either surveillance or adjuvant chemotherapy. Chemotherapy consisted of gemcitabine, in combination with either cisplatin or carboplatin. Adjuvant therapy significantly improved DFS (HR, 0.45; 95% CI, 0.30–0.68; *P* = .0001) after a median follow-up of 30.3 months. Three-year event-free estimates were 71% for those who received adjuvant chemotherapy and 46% for surveillance. Forty-four percent of those who started chemotherapy had grade 3 or higher treatment-emergent AEs compared to 4% with surveillance. Nivolumab has also been investigated for adjuvant treatment of UTUC as the above-mentioned CheckMate 274 trial included 21% of patients with UTUC (96 renal pelvis and 53 ureter).[185] Results from the full trial population are detailed in the section on *Adjuvant Systemic Therapy* under *Muscle Invasive Urothelial Bladder Cancer*, above. While the authors note that the analysis shows the possibility of a larger effect size for bladder compared to UTUC, they caution that the trial was designed to measure the entire trial population and that further analyses are planned to test the effects on these subgroups.

Based on these data, adjuvant therapy should be discussed for patients with pT3–4 or nodal disease. If no platinum-based neoadjuvant treatment was given, adjuvant treatment with a platinum-based regimen should be discussed. Alternatively, adjuvant nivolumab may be considered (category 2B). If platinum-based neoadjuvant therapy was given and the disease was determined to be ypT2–4 or ypN+ after surgery, adjuvant nivolumab may be considered, although adjuvant therapy would be most appropriate for patients who value the opportunity to delay recurrence, and who accept the risk of side effects, even if the chance for cure was not improved in this situation. Follow-up should be the same as pT0/pT1 disease with the addition of chest imaging and a stronger recommendation for cytology.

There have been some data on the use of adjuvant RT or chemoradiotherapy following nephroureterectomy for UTUC. One study reported on local recurrence patterns and risk factors in 389 patients with UTUC who were treated with radical nephroureterectomy.[335] This study found that adjuvant RT reduced local recurrence rates (HR, 0.177; 95% CI, 0.064–0.493; *P* = .001). However, another retrospective study of 198 patients with pT3, N0, M0 UTUC found no significant differences in 2-year OS, DSS, or RFS for those who received adjuvant RT compared to those who did not.[336] In addition, a retrospective review of 31 patients with UTUC who were treated with RT, with or without concurrent chemotherapy, following attempted curative resection found that 5-year actuarial OS and DSS were longer in the patients who received adjuvant cisplatin-based chemoradiotherapy compared to those who received RT alone.[337] In this study, 5-year actuarial OS was 27% for RT alone compared to 67% for chemoradiotherapy (*P* = .01) and DSS was 41% for RT compared to 76% for chemotherapy (*P* = .06). Based on the lack of data supporting this approach for UTT, adjuvant RT is not recommended.

### Urothelial Carcinoma of the Ureter

Ureteral tumors may develop de novo or in patients who have undergone successful treatment for superficial tumors that originate in the bladder. The presentation varies as a function of disease extent. Ureteral tumors may be identified in patients who have a positive cytology with a negative cystoscopy in whom selective catheterization of the ureters is performed. More extensive lesions may result in pain or obstruction.

***Workup***

The evaluation is similar to that outlined for tumors that originate in the renal pelvis.

***Primary Treatment***

For resectable ureteral tumors, the primary management is surgery (see *Endoscopic Management of UTUC* within the *Renal Pelvis Tumors* section of this Discussion for more discussion of nephron-sparing approaches), with or without perioperative intravesical chemotherapy. The specific procedure required varies depending on the location of the tumor (upper, mid, or distal location) and disease extent. Neoadjuvant chemotherapy may be considered in selected patients, such as when the degree of invasiveness is established before definitive surgery.[322,338]

Tumors that originate in the upper ureter occasionally can be managed endoscopically, if low-grade, but more commonly are treated with nephroureterectomy with a bladder cuff, with or without perioperative intravesical chemotherapy, plus regional lymphadenectomy for high-grade tumors. Neoadjuvant chemotherapy should be considered in select patients, including patients with retroperitoneal lymphadenopathy; bulky (>3 cm) high-grade tumor; sessile histology; or suspected parenchymal invasion. A portion of the bladder is removed to ensure complete removal of the entire intramural ureter.

Tumors that originate in the mid portion may also be managed differently depending on grade. Low-grade tumors may be managed by endoscopic resection or excision, with or without perioperative intravesical chemotherapy, followed by ureteroureterostomy, or segmental or complete ureterectomy, or ileal ureter interposition may also be an option in highly selected patients. High-grade lesions are generally managed with nephroureterectomy with a bladder cuff, with or without perioperative intravesical chemotherapy, and regional lymphadenectomy. Neoadjuvant chemotherapy can be considered in select patients.

Distal ureteral tumors may be managed with a distal ureterectomy and regional lymphadenectomy if high grade followed by reimplantation of the ureter (preferred if clinically feasible), with or without perioperative intravesical chemotherapy. Other primary treatment options include endoscopic resection for low-grade tumors, or, in some cases, a nephroureterectomy with a bladder cuff, and regional lymphadenectomy if high grade. Neoadjuvant chemotherapy can be considered for select patients with distal ureteral tumors following distal ureterectomy or the nephroureterectomy with bladder cuff.

***Follow-up***

The final pathologic stage is used to guide subsequent management, as is the case for tumors that originate in other sites. No adjuvant therapy is advised for lesions that are pT1 or less, but serial follow-up of the urothelial tracts or remaining unit (as previously described under *Renal Pelvis Tumors*) is recommended.

Patients with more extensive disease are advised to consider adjuvant treatment, depending on the disease stage, whether neoadjuvant treatment was given, and patient preference. Please see *Adjuvant Treatment and Follow-up* for *Renal Pelvis Tumors*, above, for more discussion of the recommendations and data on adjuvant therapy for UTUC.

## Urothelial Carcinomas of the Prostate

Urothelial (transitional cell) carcinomas of the prostate represent a distinct entity with a unique staging system. In this respect, they must be distinguished from urothelial carcinomas of bladder origin that invade into the prostate through the bladder wall. Urothelial carcinomas of the prostate may occur de novo or, more typically, concurrently or after

treatment of bladder cancer. Similar to tumors originating in other sites of the urothelium, management of prostate urothelial carcinomas is based on the extent of disease with particular reference to the urethra, duct, acini, and stroma.

### Workup

The evaluation of a suspected urothelial carcinoma of the prostate includes a digital rectal examination (DRE), cystoscopy with bladder biopsy, and TURP that includes the prostatic stroma. Prostate-specific antigen testing should be performed. Multiple stromal biopsies are advised and, if the DRE is abnormal, additional needle biopsies may be required in selected patients to exclude primary adenocarcinoma of the prostate. Upper tract collecting system imaging is also recommended.

### Primary Treatment

Pending histologic confirmation, tumors that are limited to the mucosal prostatic urethra with no acinar or stromal invasion can be managed with TURP and intravesical BCG, with follow-up similar to that for superficial disease of the bladder. A systematic review and meta-analysis of intravesical BCG for treatment of noninvasive urothelial carcinoma of the prostate found that the complete response rate for prostatic disease was 88% (95% CI, 0.81–0.96).[339] If local recurrence is seen, cystoprostatectomy with or without urethrectomy is recommended. Patients with tumors that invade the ducts, acini, or stroma should undergo an additional workup with chest radiograph or CT, and abdominal/pelvic CT if necessary, to exclude metastatic disease, and then a cystoprostatectomy with or without urethrectomy should be performed. Based on data extrapolated from bladder cancer therapy, neoadjuvant chemotherapy is recommended in patients with stromal invasion.[153-155] Adjuvant chemotherapy may be advised for stromal invasion after primary treatment if neoadjuvant therapy was not given. Alternatively, TURP and intravesical BCG may be offered to patients with only ductal and acini invasion. Local recurrences in patients undergoing TURP and BCG therapy are treated with cystoprostatectomy with or without urethrectomy.

## Primary Carcinoma of the Urethra

Primary carcinoma that arises in the urethra is rare. Unlike for bladder cancer, squamous cell carcinoma is the most common histologic subtype for urethral cancer.[340] The 5-year OS is 42%.[341,342] Stage and disease location are the most important prognostic factors for male patients, while tumor size and histology are prognostically significant for female patients.[340,342] Unfortunately, there is a lack of robust, prospective data to support treatment decisions due to disease rarity. Treatment recommendations typically encompass all of the respective histologies (ie, squamous, transitional, adenocarcinomas) with the treatment approach based on location (ie, proximal vs. distal urethral tumors).

### Workup

A cystourethroscopy should be performed if carcinoma of the urethra is suspected. This includes EUA and transurethral or transvaginal biopsy. Chest x-ray or CT and MRI of the pelvis are recommended to evaluate the extent of the disease.

If palpable inguinal lymph nodes are present, a chest/abdomen/pelvis CT and lymph node biopsy should be performed.

### Treatment

Patients with CIS, Ta, or T1 disease should have a repeat transurethral or transvaginal resection. In select cases, TURBT is followed by intraurethral therapy with BCG, mitomycin, or gemcitabine. A total urethrectomy may be considered if the patient has undergone a radical cystectomy and cutaneous diversion.

Treatment for T2 disease is based on patient anatomy and tumor location. For patients assigned male at birth with pendulous urethra, a distal urethrectomy or partial penectomy are viable options. Patients may consider neoadjuvant chemotherapy (category 2B) or chemoradiation (category 2A) before a urethrectomy. Patients who have positive margins may undergo additional surgery or radiation, preferably with chemotherapy. At recurrence, options include systemic therapy, total penectomy, radiation, or a combination. Patients with T2 tumors in the bulbar urethra should undergo urethrectomy with or without cystoprostatectomy. Adjuvant chemotherapy or chemoradiation may be considered if pT3, pT4, or nodal disease is found. Recurrent cases may be treated with systemic therapy and/or radiation.

Initial treatment options for patients assigned female at birth with T2 tumors include chemoradiation or urethrectomy with cystectomy, with organ-sparing approaches used when feasible in appropriately selected cases.[139,140] Partial urethrectomy is possible in a minority of cases, depending on tumor location, and has been associated with a high local recurrence rate.[343] At recurrence, the patient may receive systemic therapy or chemoradiotherapy (both category 2A) or pelvic exenteration (category 2B). Pelvic exenteration for T2 urethral cancer consists of *en bloc* removal of the urethra, bladder, and anterior vagina.

A multimodal treatment approach (ie, surgery, systemic therapy, radiation) is common for advanced disease. A cohort study reported a 72% response rate with the following treatment scheme before surgery: cisplatin, gemcitabine, and ifosfamide for squamous cell carcinoma; 5-FU, gemcitabine, and cisplatin-based regimens for adenocarcinoma; and MVAC for urothelial tumors.[344] Combined chemoradiation with 5-FU and mitomycin C has shown efficacy in a series of male patients with squamous cell carcinoma of the urethra.[345] Patients undergoing surgery after chemoradiation had a higher 5-year DFS rate (72%) than those receiving chemoradiation alone (54%). If systemic therapy is used, the choice of regimen should be based on histology.

Patients with T3 or T4 disease but no clinical nodes should receive neoadjuvant chemotherapy (if urothelial carcinoma) followed by consolidative surgery or, if ineligible for standard systemic chemotherapy, radiation or chemoradiation with or without consolidative surgery. Surgery alone is an option for non-urothelial histologies. If node-positive, chemoradiation is the preferred treatment for squamous cell carcinoma. Systemic therapy or chemoradiotherapy with or without consolidative surgery are also treatment options. At recurrence, the patient may undergo pelvic exenteration (category 2B) with or without ilioinguinal lymphadenectomy and/or chemoradiotherapy. Pelvic exenteration for T3 urethral cancer consists of urethrectomy, cystectomy, and either a prostatectomy or anterior vaginectomy with hysterectomy, as applicable. For highly local advanced T4 tumors, the posterior vagina and rectum may also need to be removed en bloc with the specimen. Systemic therapy is a category 2B option.

Patients with distant metastases should receive similar treatment as metastatic bladder cancer. Systemic therapies include chemotherapy and targeted therapies as subsequent-line options. However, it should be noted that checkpoint inhibitors have only been evaluated in patients with urothelial histology.

## 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 three-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.

Within the category of metastatic disease, several new agents and combination regimens have been studied and seem to be superior to those that were previously considered standard therapies. In particular, immune checkpoint inhibitors, antibody-drug conjugates, and targeted therapies have emerged as new options for the treatment of metastatic bladder cancer. 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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