National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Bladder Cancer

NCCN Evidence Blocks™

Version 1.2020 — November 27, 2019

NCCN.org

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Continue

For important information regarding the BCG shortage see MS-11. Also see the AUA BCG Shortage Notice.

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[NCCN Guidelines Panel Disclosures]

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Þ Internal medicine
† Medical oncology
≠ Pathology
§ Radiotherapy/Radiation oncology
¶ Surgery/Surgical Oncology
ϖ Urology
* Discussion writing committee member

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NCCN Bladder Cancer Panel Members
NCCN Evidence Blocks Definitions (EB-1)

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- Clinical Presentation and Initial Evaluation (BL-1)
- Non-Muscle Invasive or Tis, Primary Evaluation/Surgical Treatment (BL-1)
  - Secondary Surgical Treatment, Adjuvant Intravesical Treatment, Follow-up (BL-2)
  - Posttreatment cTa, cT1, Tis Recurrent or Persistent Cancer (BL-3)
- Muscle Invasive or Metastatic, Primary Evaluation/Surgical Treatment, Additional Workup (BL-1)
  - Stage II (cT2, N0) Primary and Adjuvant Treatment (BL-5)
  - Stage IIIA (cT3, N0; cT4a, N0; cT1-cT4a, N1) Primary and Adjuvant Treatment (BL-7)
  - Stage IIIB (cT1-cT4a, N2,3) Primary and Subsequent Treatment (BL-8)
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  - Metastatic Disease, Additional Workup, Primary Treatment (BL-10)
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- Principles of Surgical Management (BL-B)
- Principles of Pathology Management (BL-C)
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- Renal Pelvis (UTT-1)
- Urothelial Carcinoma of the Ureter (UTT-2)
- Urothelial Carcinoma of the Prostate (UCP-1)
- Primary Carcinoma of the Urethra (PCU-1)

Staging (ST-1)

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

To find clinical trials online at NCCN Member Institutions, click here: nccn.org/clinical_trials/member_institutions.aspx.

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.

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

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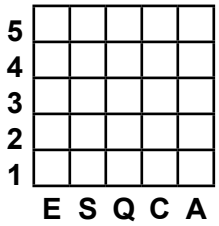
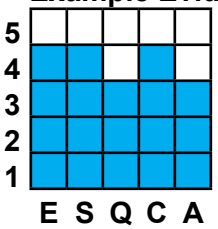
NCCN EVIDENCE BLOCKS CATEGORIES AND DEFINITIONS



E = Efficacy of Regimen/Agent
S = Safety of Regimen/Agent
Q = Quality of Evidence
C = Consistency of Evidence
A = Affordability of Regimen/Agent

Example Evidence Block



E = 4
S = 4
Q = 3
C = 4
A = 3

Efficacy of Regimen/Agent

5	**Highly effective:** Cure likely and often provides long-term survival advantage
4	**Very effective:** Cure unlikely but sometimes provides long-term survival advantage
3	**Moderately effective:** Modest impact on survival, but often provides control of disease
2	**Minimally effective:** No, or unknown impact on survival, but sometimes provides control of disease
1	**Palliative:** Provides symptomatic benefit only

Safety of Regimen/Agent

5	**Usually no meaningful toxicity:** Uncommon or minimal toxicities; no interference with activities of daily living (ADLs)
4	**Occasionally toxic:** Rare significant toxicities or low-grade toxicities only; little interference with ADLs
3	**Mildly toxic:** Mild toxicity that interferes with ADLs
2	**Moderately toxic:** Significant toxicities often occur but life threatening/fatal toxicity is uncommon; interference with ADLs is frequent
1	**Highly toxic:** Significant toxicities or life threatening/fatal toxicity occurs often; interference with ADLs is usual and severe

Note: For significant chronic or long-term toxicities, score decreased by 1

Quality of Evidence

5	**High quality:** Multiple well-designed randomized trials and/or meta-analyses
4	**Good quality:** One or more well-designed randomized trials
3	**Average quality:** Low quality randomized trial(s) or well-designed non-randomized trial(s)
2	**Low quality:** Case reports or extensive clinical experience
1	**Poor quality:** Little or no evidence

Consistency of Evidence

5	**Highly consistent:** Multiple trials with similar outcomes
4	**Mainly consistent:** Multiple trials with some variability in outcome
3	**May be consistent:** Few trials or only trials with few patients, whether randomized or not, with some variability in outcome
2	**Inconsistent:** Meaningful differences in direction of outcome between quality trials
1	**Anecdotal evidence only:** Evidence in humans based upon anecdotal experience

Affordability of Regimen/Agent (includes drug cost, supportive care, infusions, toxicity monitoring, management of toxicity)

5	**Very inexpensive**
4	**Inexpensive**
3	**Moderately expensive**
2	**Expensive**
1	**Very expensive**

INTRODUCTION

NCCN and the NCCN Bladder Cancer Panel believes that the best management for any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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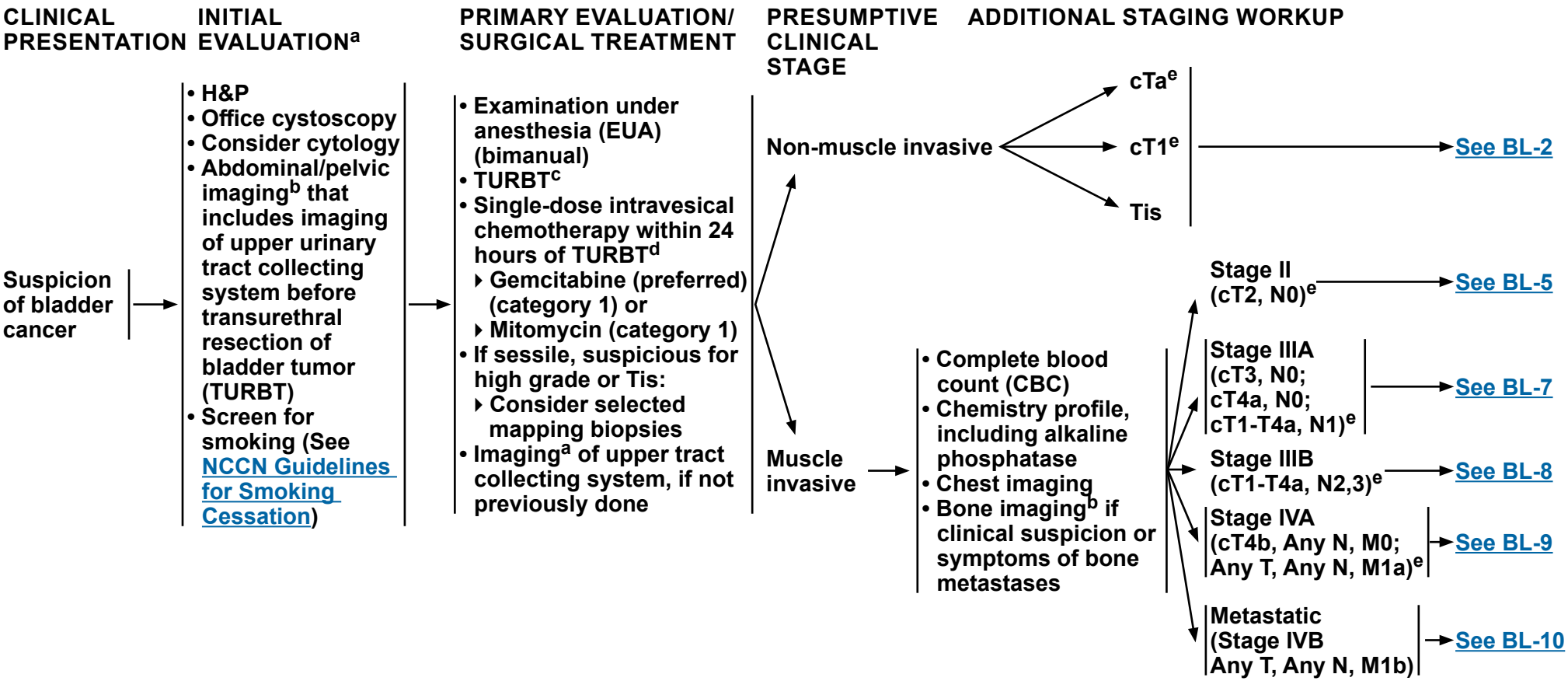

[a] For tools to aid optimal assessment and management of older adults with cancer, see NCCN Guidelines for Older Adult Oncology.
[b] See Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
[c] See Principles of Surgical Management (BL-B).
[d] Immediate intravesical chemotherapy reduces the recurrence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

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

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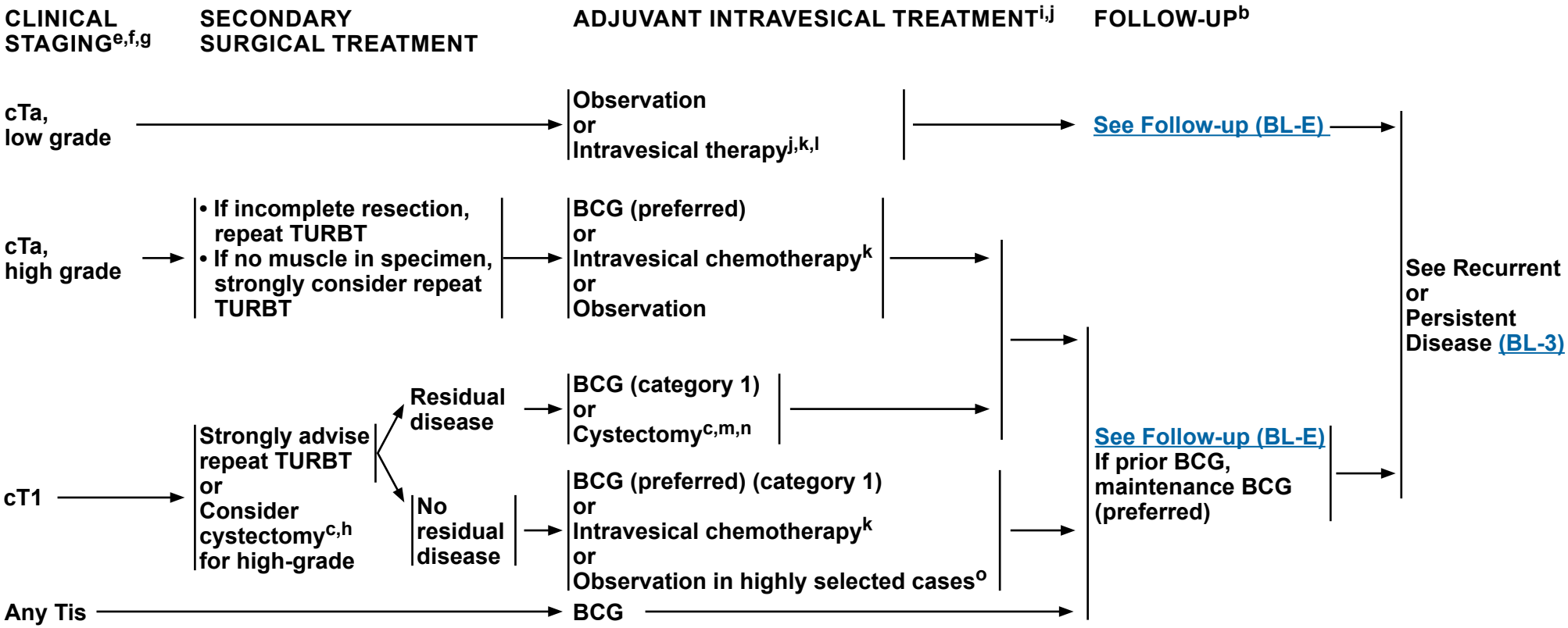

[b] See Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
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[e] The modifier "c" refers to clinical staging based on bimanual examination under anesthesia, endoscopic surgery (biopsy or transurethral resection), and imaging studies. The modifier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

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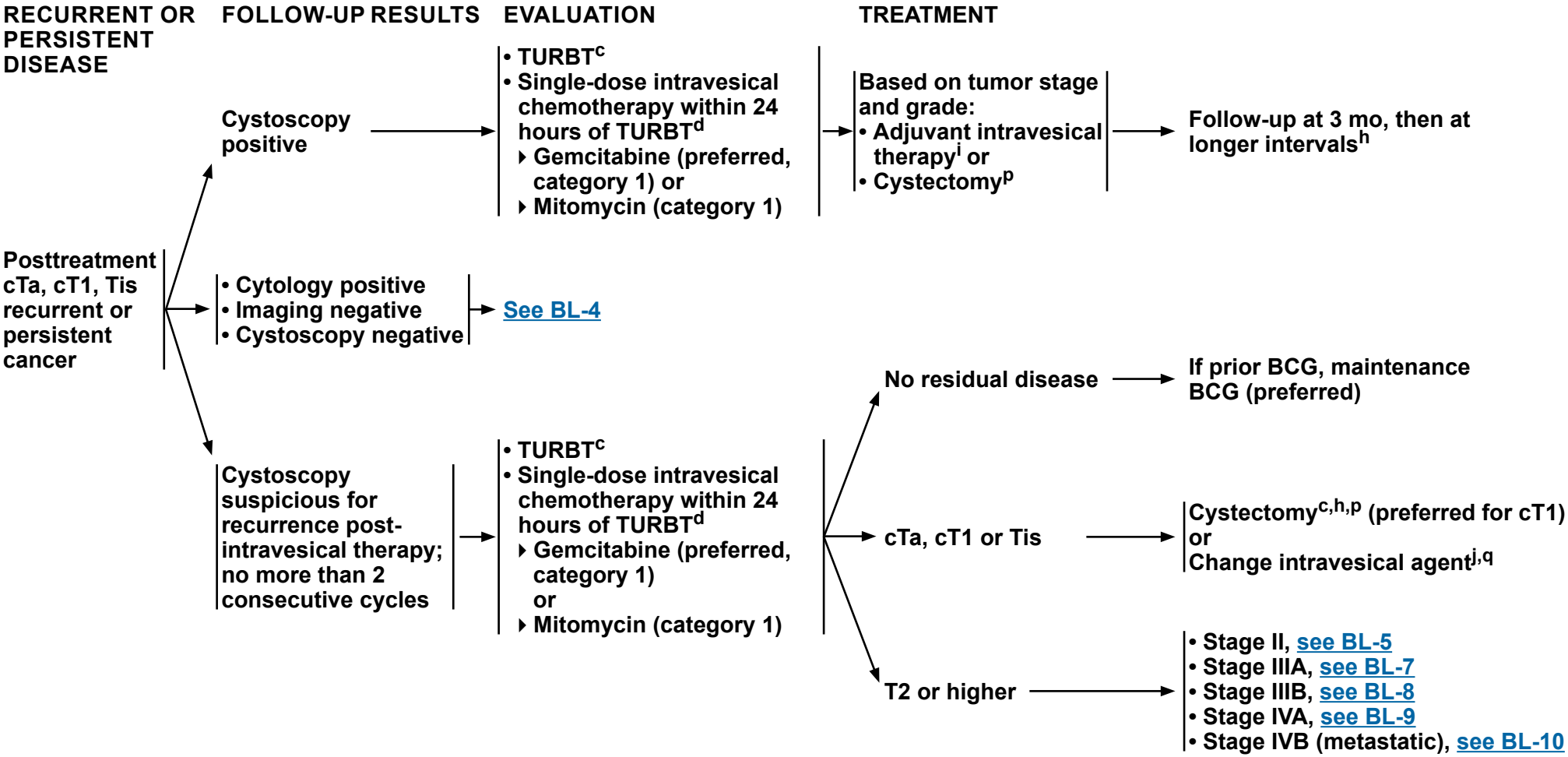
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



[c] See Principles of Surgical Management (BL-B).
[d] Most efficacious in patients with low grade, low-volume Ta urothelial cancer. See Principles of Intravesical Treatment (BL-F).
[h] See Follow-Up (BL-E).
[i] Indications for adjuvant induction therapy: Based on probability of recurrence and progression to muscle-invasive disease, such as size, number, and grade.
[j] See Principles of Intravesical Treatment (BL-F).
[p] If not a cystectomy candidate, and recurrence is cTa or cT1, consider concurrent chemoradiotherapy (category 2B for cTa, category 2A for cT1) or a clinical trial. See Principles of Systemic Therapy (BL-G 5 of 7).
[q] Valrubicin is approved for BCG-refractory carcinoma in situ.

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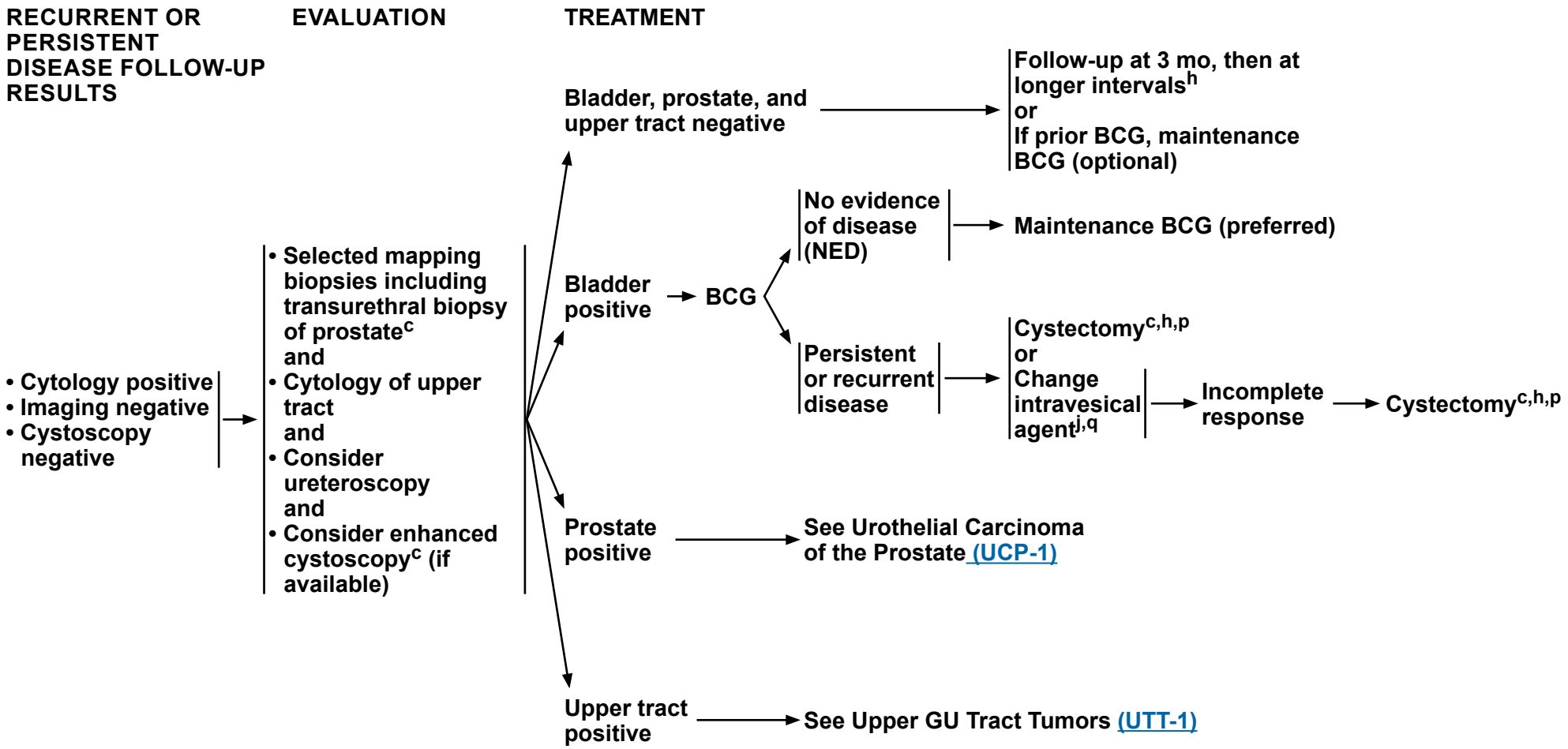

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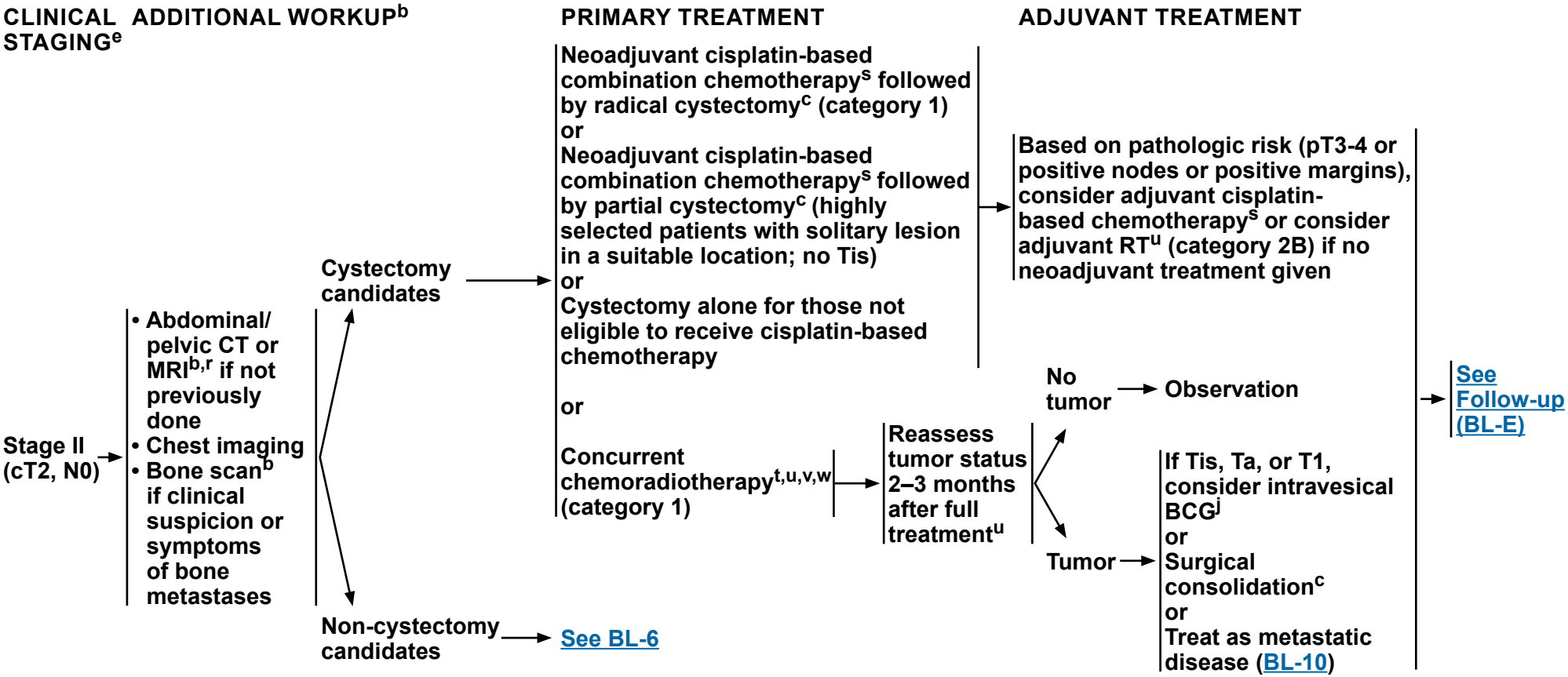

[b] See Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
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[e] The modifier “c” refers to clinical staging based on bimanual examination under anesthesia, endoscopic surgery (biopsy or transurethral resection), and imaging studies. The modifier “p” refers to pathologic staging based on cystectomy and lymph node dissection.
[j] See Principles of Intravesical Treatment (BL-F).
[r] Consider FDG-PET/CT scan (skull base to mid-thigh) (category 2B).
[s] See Principles of Systemic Therapy (BL-G 1 of 7).
[t] See Principles of Systemic Therapy (BL-G 5 of 7).
[u] See Principles of Radiation Management of Invasive Disease (BL-H).
[v] There are data to support equivalent survival rates. Not all institutions have experience with these multidisciplinary treatment approaches, which require a dedicated team.
[w] Optimal candidates for bladder preservation with chemoradiotherapy include patients with tumors that present without hydronephrosis, are without concurrent extensive or multifocal Tis, and are <6 cm. Ideally, tumors should allow a visually complete or maximally debulking TURBT. See Principles of Radiation Management of Invasive Disease (BL-H).

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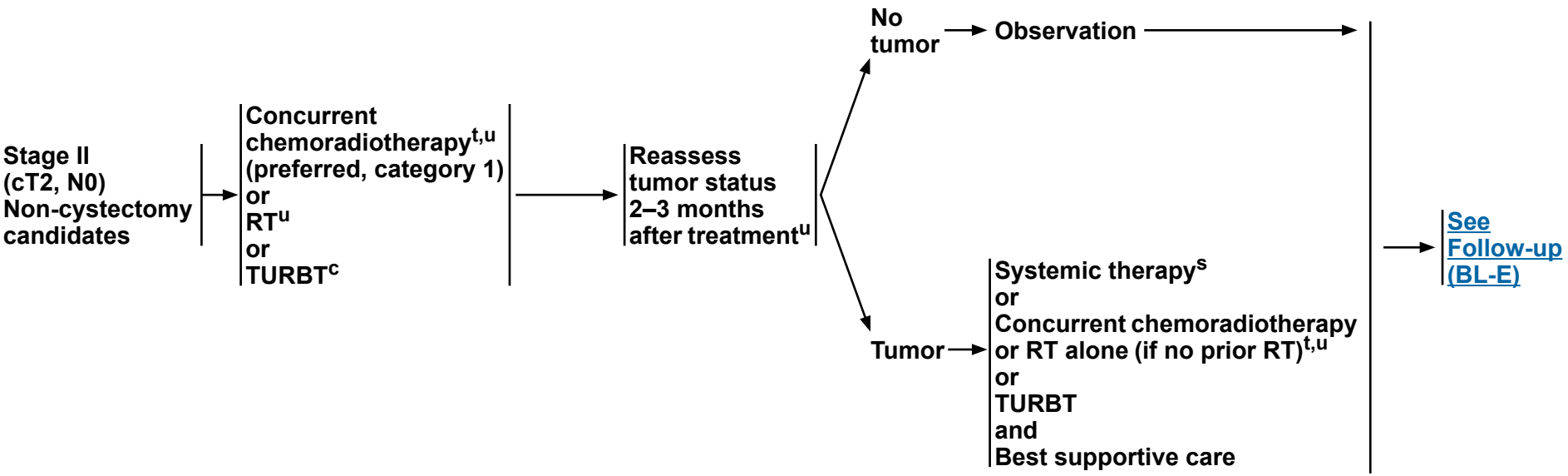
See Recurrent or Persistent Disease (BL-11)



[c] See Principles of Surgical Management (BL-B).
[s] See Principles of Systemic Therapy (BL-G 2 of 7).
[t] See Principles of Systemic Therapy (BL-G 5 of 7).
[u] See Principles of Radiation Management of Invasive Disease (BL-H).

See Recurrent or Persistent Disease (BL-11)

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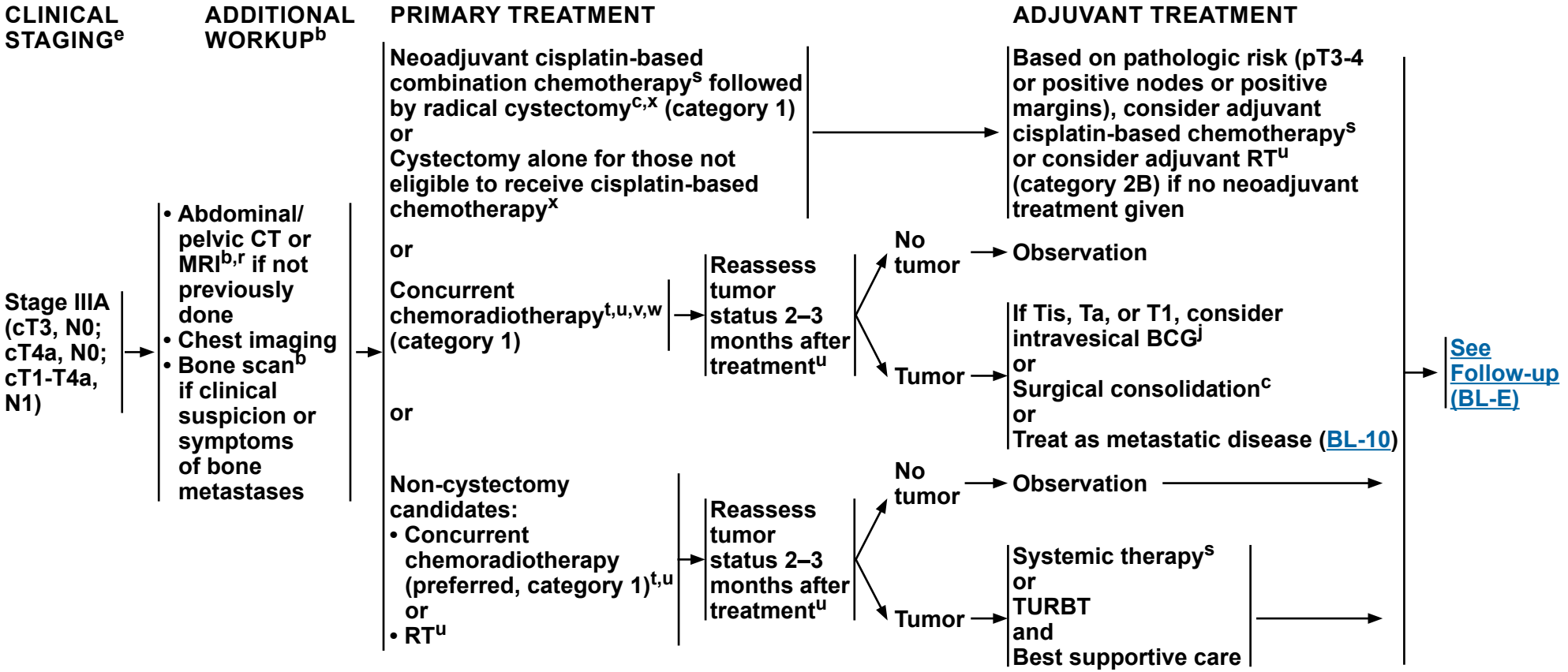

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[j] See Principles of Intravesical Treatment (BL-F).
[r] Consider FDG-PET/CT scan (skull base to mid-thigh) (category 2B).
[s] See Principles of Systemic Therapy (BL-G).
[t] See Principles of Systemic Therapy (BL-G 5 of 7).
[u] See Principles of Radiation Management of Invasive Disease (BL-H).
[v] There are data to support equivalent survival rates. Not all institutions have experience with these multidisciplinary treatment approaches, which require a dedicated team.
[w] Optimal candidates for bladder preservation with chemoradiotherapy include patients with tumors that present without hydronephrosis, are without concurrent extensive or multifocal Tis, and are <6 cm. Ideally, tumors should allow a visually complete or maximally debulking TURBT. See Principles of Radiation Management of Invasive Disease (BL-H).
[x] Patients with cN1 disease have better outcomes they are given neoadjuvant chemotherapy and have a response.

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See Recurrent or Persistent Disease (BL-11)

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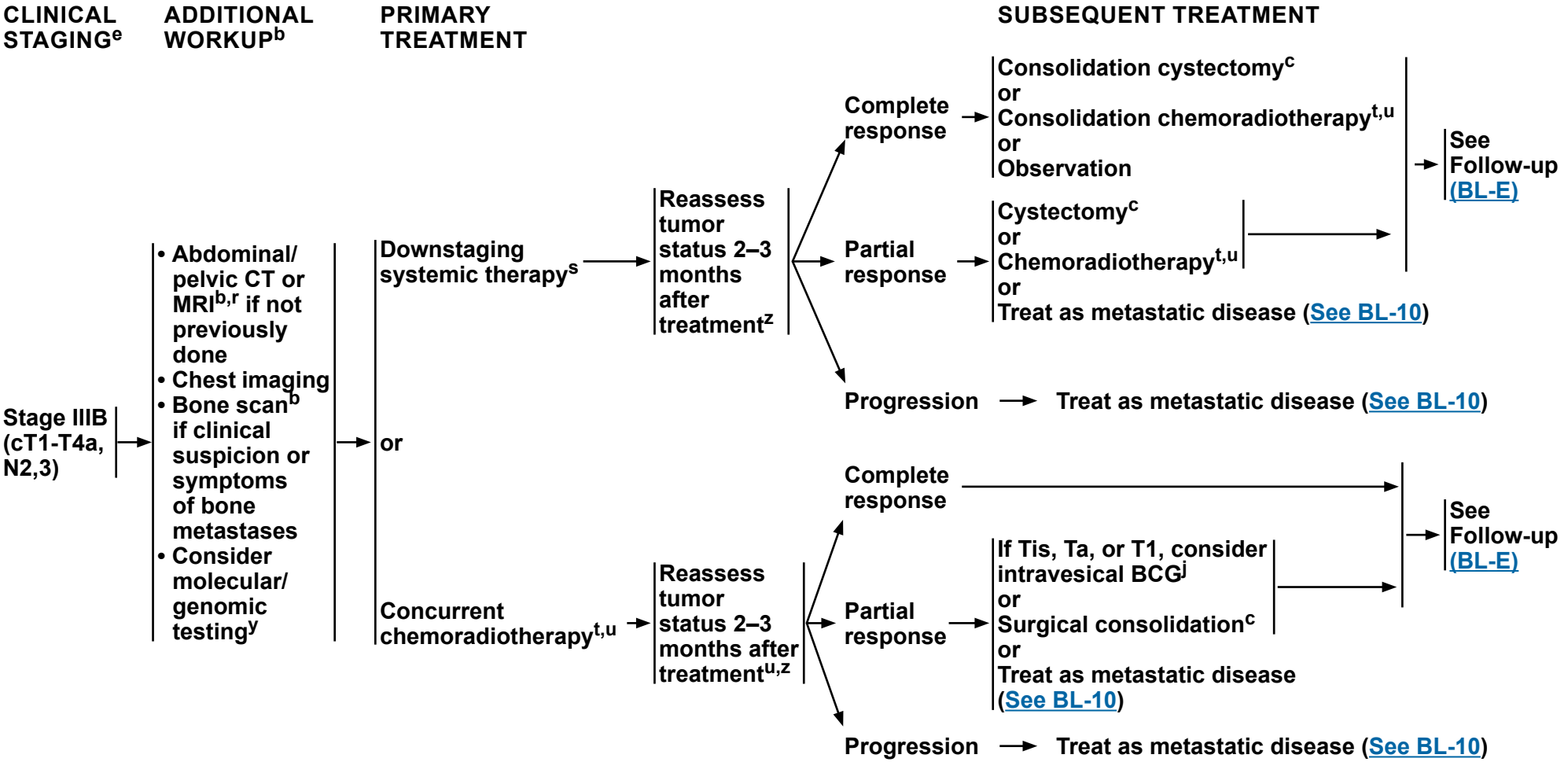

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[j] See Principles of Intravesical Treatment (BL-F).
[r] Consider FDG-PET/CT scan (skull base to mid-thigh) (category 2B).
[s] See Principles of Systemic Therapy (BL-G 2 of 7).
[t] See Principles of Systemic Therapy (BL-G 5 of 7).
[u] See Principles of Radiation Management of Invasive Disease (BL-H).
[y] Including FGFR RGQ RT-PCR for *FGFR3* or *FGFR2* genetic alterations.
[z] 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 is recommended.

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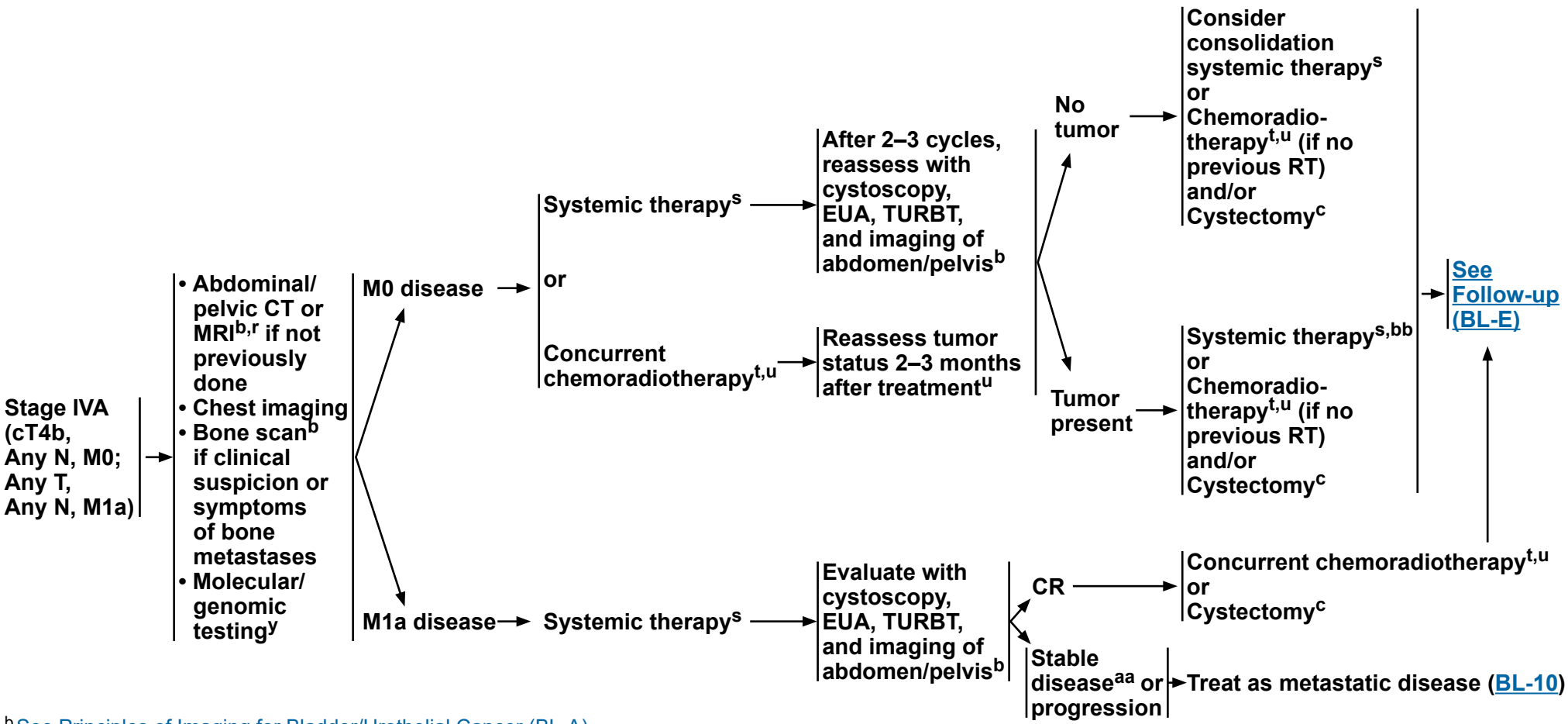
See Recurrent or Persistent Disease (BL-11)



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[r] Consider FDG-PET/CT scan (skull base to mid-thigh) (category 2B).
[s] See Principles of Systemic Therapy (BL-G 2 of 7).
[t] See Principles of Systemic Therapy (BL-G 5 of 7).
[u] See Principles of Radiation Management of Invasive Disease (BL-H).
[y] Including FGFR RGQ RT-PCR for *FGFR3* or *FGFR2* genetic alterations.
[aa] Non-bulky disease and no significant clinical progression.
[bb] See Principles of Systemic Therapy (BL-G 3 of 7 and 4 of 7).

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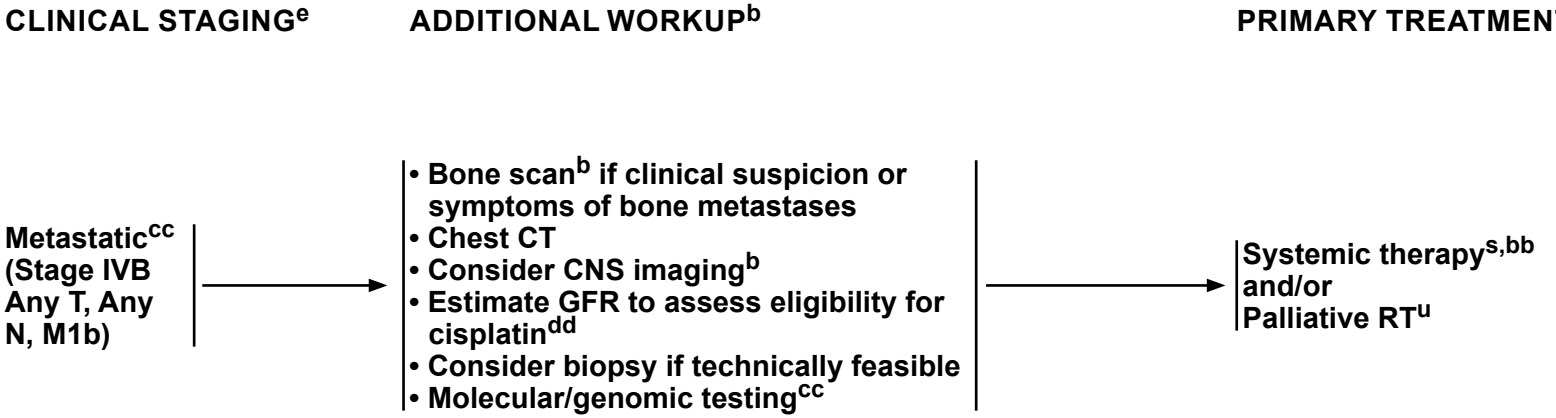
See Recurrent or Persistent Disease (BL-11)



[b] See Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
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[u] See Principles of Radiation Management of Invasive Disease (BL-H).
[y] Including FGFR RGQ RT-PCR for *FGFR3* or *FGFR2* genetic alterations.
[s] See Principles of Systemic Therapy (BL-G 2 of 7).
[bb] See Principles of Systemic Therapy (BL-G 3 of 7 and 4 of 7).
[cc] Molecular/genomic testing in a CLIA-approved laboratory, including FGFR RGQ RT-PCR for *FGFR3* or *FGFR2* genetic alterations. See Discussion.
[dd] For patients with borderline GFR, consider timed urine collection which may more accurately determine eligibility for cisplatin.

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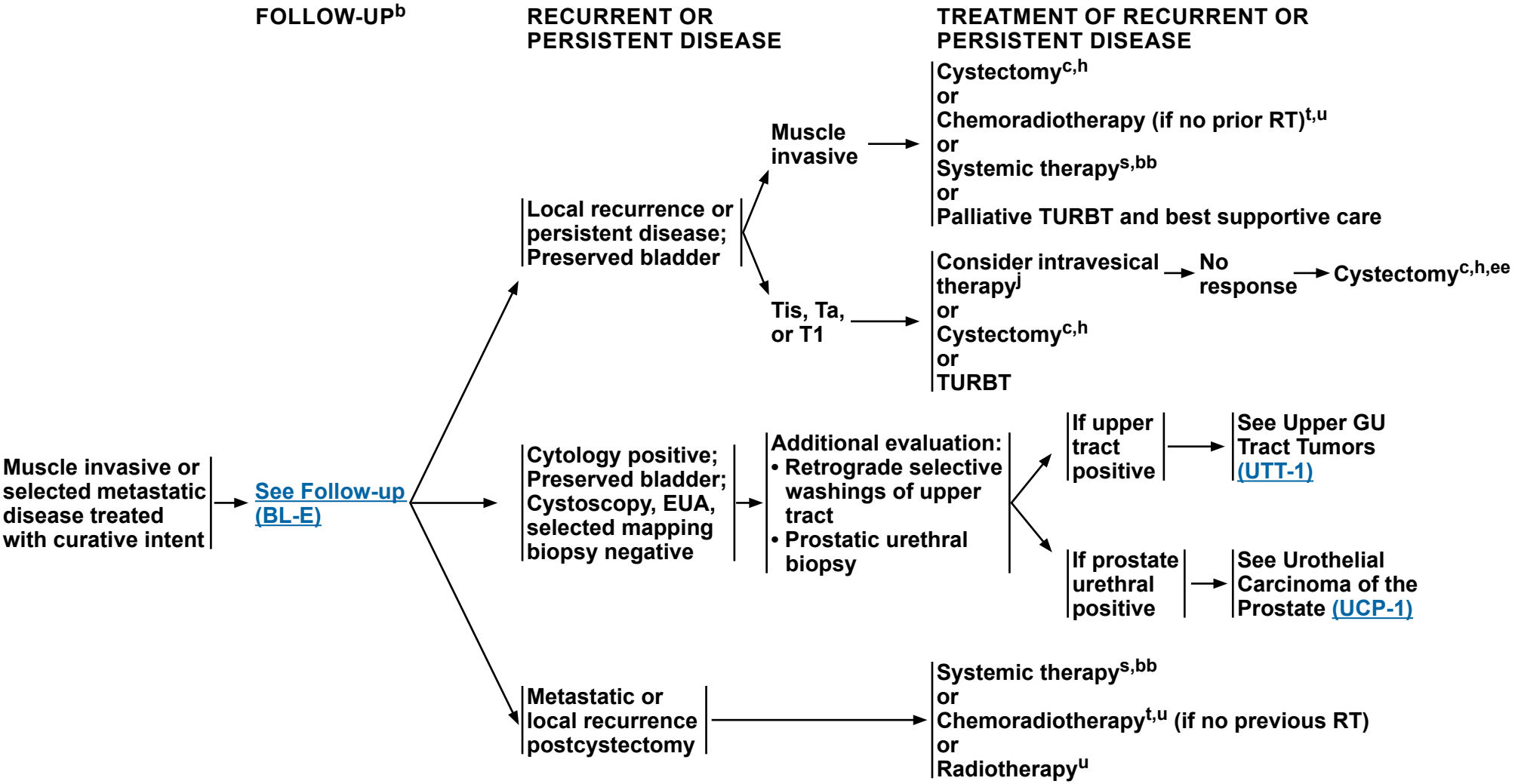

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[t] See Principles of Systemic Therapy (BL-G 5 of 7).
[u] See Principles of Radiation Management of Invasive Disease (BL-H).
[s] See Principles of Systemic Therapy (BL-G 2 of 7).
[bb] See Principles of Systemic Therapy (BL-G 3 of 7 and 4 of 7).
[ee] If not a cystectomy candidate, consider concurrent chemoradiotherapy (See BL-G 5 of 7) (if no prior RT), change in intravesical agent, or a clinical trial.

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PRINCIPLES OF IMAGING FOR BLADDER/UROTHELIAL CANCER

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

Non-Muscle-Invasive Bladder Cancer (NMIBC)

Chest Imaging

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

Abdominal and Pelvic Imaging

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

Evaluation for Suspected Bone Metastasis

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

Neurologic/Brain Imaging[4,5]

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

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Continued
References

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

Chest Imaging

- **Staging:[4]**
  - **PA and lateral chest x-ray**
  - **CT of the chest with or without contrast (preferred)[6]**
  - **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: (See BL-E)**
  - **PA and lateral chest x-ray**
  - **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.**
  - **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 abdomen and pelvis. FDG-PET/CT should not be used to delineate the anatomy of the upper urinary tract.**

- **Follow-up of cT4b (See BL-E) and metastatic disease:**
  - **PA and lateral chest x-ray**
  - **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.**
  - **FDG-PET/CT (category 2B) may be performed if not previously done or in high-risk patients 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.**

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References

PRINCIPLES OF IMAGING FOR BLADDER/UROTHELIAL CANCER

Muscle-Invasive Bladder Cancer (continued)

Abdominal and Pelvic 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 management 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 (See BL-E):**
  - **Upper-tract and abdominal/pelvic imaging as defined previously at 3- to 6-month intervals for 2 years, then abdominal/pelvic imaging annually for up to 5 y and as indicated thereafter.**
  - **FDG-PET/CT (category 2B) may be performed if not previously done or in high-risk patients 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 high-risk patients, 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.**

Neurologic/Brain Imaging[4,5]

- **Staging**
  - **Brain MRI without and with IV contrast is recommended only in symptomatic or selected "high-risk" (eg, small cell histology) patients.**
  - **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).**

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References

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:
  - PA and lateral chest x-ray or chest CT.
  - Consider abdominal 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 non-prostatic male urethra or female 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.

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PRINCIPLES OF IMAGING FOR BLADDER/UROTHELIAL CANCER
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PRINCIPLES OF SURGICAL MANAGEMENT

Transurethral Resection of the Bladder Tumor (TURBT) for Staging

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

TURBT/Maximal TURBT for Treatment

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

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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 [see Principles of Intravesical Treatment (BL-F)].

Transurethral Resection (TUR) of the Urethral Tumor
- Primary treatment of Tis, 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 [see Principles of Intravesical Treatment (BL-F)].

Partial Cystectomy
- May be used for cT2 muscle-invasive disease with solitary lesion in location amenable to segmental resection with adequate margins. May also be appropriate in other select situations including cancer in a bladder diverticulum.
- No carcinoma in situ as determined by random biopsies.
- Should be given with neoadjuvant cisplatin-based combination chemotherapy.
- Bilateral pelvic lymphadenectomy should be performed and include common, internal iliac, external iliac, and obturator nodes.

Radical Cystectomy/Cystoprostatectomy
- In non-muscle-invasive disease, radical cystectomy is generally reserved for residual high-grade cT1.
- 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.
- Should be given with neoadjuvant cisplatin-based combination chemotherapy for patients with cT2-cT4a disease. For patients who cannot receive neoadjuvant chemotherapy, radical cystectomy alone is an option.
- Bilateral pelvic lymphadenectomy should be performed and include common, internal iliac, external iliac, and obturator nodes.

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

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PRINCIPLES OF SURGICAL MANAGEMENT

Urethrectomy
- Neoadjuvant chemotherapy (category 2B) or chemoradiation should be considered.
- Distal urethrectomy may include inguinal lymph node dissection in selected cases.
- Total urethrectomy may include inguinal lymphadenectomy in selected cases.
- 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.

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

Pelvic Exenteration (category 2B)
- Therapy for recurrence in female patients with ≥T2 primary carcinoma of the urethra.
- Ilioinguinal lymphadenectomy and/or chemoradiotherapy can be considered in patients with ≥T3 disease.

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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 in fundibulum 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
  - Hereditary predisposition (eg, hereditary nonpolyposis colon cancer [HNPCC])
- 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 (Nd:YAG – penetration 4–6 mm; Ho:YAG – shallow penetration <0.5 mm)
- 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
  - 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
- 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.

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PRINCIPLES OF PATHOLOGY MANAGEMENT
2016 WHO Classification of Tumors of the Urothelial Tract[1,2]

Urothelial tumors
- Infiltrating urothelial carcinoma
  - Infiltrating urothelial carcinoma
  - Infiltrating urothelial carcinoma with divergent differentiation
    - ◊ Squamous differentiation
    - ◊ Glandular differentiation
    - ◊ Trophoblastic differentiation
    - ◊ Müllerian differentiation
  - Infiltrating urothelial carcinoma, variants:
    - ◊ Nested, including large nested
    - ◊ Microcystic
    - ◊ Micropapillary
    - ◊ Lymphoepithelioma-like
    - ◊ Plasmacytoid/ signet ring cell/diffuse
    - ◊ Sarcomatoid
    - ◊ Giant cell
    - ◊ Poorly-differentiated
    - ◊ Lipid-rich
    - ◊ Clear cell
- Non-Invasive urothelial neoplasms
  - Urothelial carcinoma in situ
  - Non-invasive papillary urothelial carcinoma, low grade
  - Non-Invasive 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

Melanocytic tumors
- Malignant melanoma
- Naevus
- Melanosis

Mesenchymal Tumors
- Rhabdomyosarcoma
- Leiomyosarcoma
- Angiosarcoma
- Inflammatory myofibroblastic tumor
- Perivascular epithelioid cell tumor
  - Benign
  - Malignant
- Solitary fibrous tumour
- Leiomyoma
- Haemangioma
- Granular cell tumour
- Neurofibroma

Urothelial Tract Haematopoietic and Lymphoid tumors

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

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

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PRINCIPLES OF PATHOLOGY MANAGEMENT

- **The pathology report on biopsy/TURBT specimens should specify:**
  - **If muscularis propria (detrusor muscle) is present and if present whether it is invaded by tumor**
  - **Presence or absence of lamina propria invasion**
  - **Presence or absence of lymphovascular space invasion**
  - **Presence or absence of adjacent urothelial carcinoma in-situ**
- **Urothelial tumors with an inverted growth pattern should be graded similar to the system for papillary tumors as described above**

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BLADDER CANCER: NON-UROTHELIAL AND UROTHELIAL WITH VARIANT HISTOLOGY

Mixed Histology:
- Urothelial carcinoma plus squamous, adenocarcinoma, micropapillary, nested, plasmacytoid, and sarcomatoid 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.
- Micropapillary,[1,2] plasmacytoid,[3] and sarcomatoid histologies are generally at higher risk for progression to muscle-invasive disease and a more aggressive approach should be considered.

Pure Squamous:
- No proven role for neoadjuvant/adjuvant chemotherapy for pure squamous cell carcinoma of the bladder.
- Local control with surgery or RT and best supportive care recommended.
- For advanced disease, clinical trial preferred. For selected patients, combination chemotherapy with paclitaxel, ifosfamide, and cisplatin may be considered.[4]
- Consider postoperative RT in selected cases (positive margins).[5]

Pure Adenocarcinoma Including Urachal:
- 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 recommended.
- 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.
- For node-positive disease, consider chemotherapy with colorectal regimen (FOLFOX [oxaliplatin, leucovorin, and 5-FU] or GemFLP [5-FU, leucovorin, gemcitabine, and cisplatin]). Consider post-chemotherapy surgical consolidation in responding disease.
- For advanced disease, clinical trial preferred. For selected patients, combination chemotherapy with a 5-FU–based regimen (FOLFOX or GemFLP) or ITP (paclitaxel, ifosfamide, and cisplatin). Alternatively, combination paclitaxel and platinum may be considered.[4,6]
- For non-urachal pure adenocarcinoma, consider additional metastatic workup. See NCCN Guidelines for Occult Primary.

Any Small-Cell Component (or neuroendocrine features):
- Concurrent chemoradiotherapy or neoadjuvant chemotherapy followed by local treatment (cystectomy or radiotherapy) is recommended for any patient with small-cell component histology with localized disease regardless of stage.
- Neoadjuvant chemotherapy
  - Standard cisplatin eligible
    - ◊ Etoposide + cisplatin[7]
    - ◊ Alternating ifosfamide + doxorubicin with etoposide + cisplatin[8-10]
  - Standard cisplatin ineligible
    - ◊ Etoposide + carboplatin[11]
- Metastatic chemotherapy
  - Standard cisplatin eligible
    - ◊ Etoposide + cisplatin[7]
  - Standard cisplatin ineligible
    - ◊ Etoposide + carboplatin[11]
  - Alternate regimen for select patients
    - ◊ Alternating ifosfamide + doxorubicin with etoposide + cisplatin[8-10]

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

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BLADDER CANCER: NON-UROTHELIAL AND UROTHELIAL WITH VARIANT HISTOLOGY
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FOLLOW-UP

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

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

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

*Reproduced 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.

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

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

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

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

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See NCCN Guidelines for Survivorship

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

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

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

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

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

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FOLLOW-UP

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Table 5: Post-Cystectomy Non-Muscle-Invasive Bladder Cancer

Test	Year						
	1	2	3	4	5	5–10	>10
Cystoscopy	N/A						
Imaging[4]	CTU or MRU (image upper tracts + axial imaging of abdomen/pelvis) at 3 and 12 mo	CTU or MRU (image upper tracts + axial imaging of abdomen/pelvis) annually				Renal US annually[6]	As clinically indicated
Blood tests	• Renal function testing (electrolytes and creatinine) every 3–6 mo • LFT[7] every 3–6 mo • CBC, CMP every 3–6 mo if received chemotherapy	• Renal function testing (electrolytes and creatinine) annually • LFT[7] annually • B_{12} annually				B_{12} annually	
Urine tests	• Urine cytology[5] every 6–12 mo • Consider urethral wash cytology every 6–12 mo[8]	Urine cytology as clinically indicated Urethral wash cytology as clinically indicated					

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

[4] See Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
[5] Urine cytology should be done at time of cystoscopy if bladder in situ.
[6] Renal US to look for hydronephrosis.
[7] Liver function testing includes AST, ALT, bilirubin, and alkaline phosphatase.
[8] Urethral wash cytology is reserved for patients with high-risk disease. High-risk disease includes: positive urethral margin, multifocal CIS, and prostatic urethral invasion.

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Table 6: Post-Cystectomy Muscle-Invasive Bladder Cancer

Test	Year						
	1	2	3	4	5	5–10	>10
Cystoscopy	N/A						
Imaging[4]	• CTU or MRU (image upper tracts + axial imaging of abdomen/pelvis) every 3–6 mo • Chest x-ray or CT chest every 3–6 mo or • FDG PET/CT (category 2B) only if metastatic disease suspected		• Abdominal/pelvic CT or MRI annually • Chest x-ray or CT chest annually or • FDG PET/CT (category 2B) only if metastatic disease suspected			Renal US annually[6]	As clinically indicated
Blood tests	• Renal function testing (electrolytes and creatinine) every 3–6 mo • LFT[7] every 3–6 mo • CBC, CMP every 3–6 mo if received chemotherapy	• Renal function testing (electrolytes and creatinine) annually • LFT[7] annually • B_{12} annually				B_{12} annually	
Urine tests	• Urine cytology[5] every 6–12 mo • Consider urethral wash cytology every 6–12 mo[8]		Urine cytology as clinically indicated Urethral wash cytology as clinically indicated				

Post-Bladder Sparing (BL-E 5 of 5)
See Recurrent or Persistent Disease (BL-11)

[4] See Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
[5] Urine cytology should be done at time of cystoscopy if bladder in situ.
[6] Renal US to look for hydronephrosis.
[7] Liver function testing includes AST, ALT, bilirubin, and alkaline phosphatase.
[8] Urethral wash cytology is reserved for patients with high-risk disease. High-risk disease includes: positive urethral margin, multifocal CIS, and prostatic urethral invasion.

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FOLLOW-UP

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Table 7: Post-Bladder Sparing (ie, Partial Cystectomy or Chemoradiation)

Test	Year						
	1	2	3	4	5	5–10	>10
Cystoscopy	Every 3 mo		Every 6 mo		Annually		As clinically indicated
Imaging[4]	• CTU or MRU (image upper tracts + axial imaging of abdomen/pelvis) every 3–6 mo for MIBC • Chest x-ray or CT chest every 3–6 mo for MIBC or • FDG PET/CT (category 2B) only if metastatic disease suspected		• Abdominal/pelvic CT or MRI annually • Chest x-ray or CT chest annually or • FDG PET/CT (category 2B) only if metastatic disease suspected[9]			As clinically indicated	
Blood tests	• Renal function testing (electrolytes and creatinine) every 3–6 mo • LFT[6] every 3–6 mo • CBC, CMP every 3–6 mo if received chemotherapy		• Renal function testing (electrolytes and creatinine) as clinically indicated • LFT[6] as clinically indicated				
Urine tests	Urine cytology[4] every 6–12 mo		Urine cytology as clinically indicated				

[4] See Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
[9] PET/CT not recommended for NMIBC.

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PRINCIPLES OF INTRAVESICAL TREATMENT

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

Intravesical Therapy for Bladder Cancer

Immediate Postoperative Intravesical Chemotherapy

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

Induction (Adjuvant) Intravesical Chemotherapy or BCG

- Treatment option for NMIBC (See BL-2, BL-3, and BL-10).
- The most commonly used agents are BCG, mitomycin, and gemcitabine.
- In the event of a BCG shortage, BCG should be prioritized for induction of high-risk patients (eg, high-grade T1 and CIS). Preferable alternatives to BCG include mitomycin or gemcitabine.
  - Other options include: epirubicin, valrubicin, docetaxel, or sequential gemcitabine/docetaxel or gemcitabine/mitomycin.
  - If feasible, the dose of BCG may be split (⅓ or ½ dose) so that multiple patients may be treated with a single vial in the event of a shortage.
- Initiated 3–4 weeks after TURBT with or without maintenance.
- Weekly instillations during induction are given for approximately 6 weeks.
- Maximum of 2 consecutive cycle inductions without complete response.
- Withhold if traumatic catheterization, bacteriuria, persistent gross hematuria, persistent severe local symptoms, or systemic symptoms.

Maintenance Intravesical BCG

- Although there is no standard regimen for maintenance BCG, many NCCN Member Institutions follow the SWOG regimen consisting of a 6-week induction course of BCG followed by maintenance with 3 weekly instillations at months 3, 6, 12, 18, 24, 30, and 36.[4]
- In the event of a BCG shortage, BCG should be prioritized for high-risk patients (eg, high-grade T1 and CIS), especially in the early maintenance period (ie, 3 and 6 months post-induction).
  - If feasible, the dose of BCG may be split (⅓ or ½ dose) so that multiple patients may be treated with a single vial in the event of a shortage.
- Ideally maintenance should be given for 1 year for intermediate-risk and 3 years for high-risk NMIBC.
- BCG would be withheld if traumatic catheterization, bacteriuria, persistent gross hematuria, persistent severe local symptoms, or systemic symptoms.
- Dose reduction is encouraged if there are substantial local symptoms during maintenance therapy.
- Data suggest the benefit of maintenance BCG therapy through a decreased rate of recurrence for NMIBC.[4]

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Continued
References

PRINCIPLES OF INTRAVESICAL TREATMENT

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.**

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 Tis, 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.**

Postsurgical Therapy for Upper Tract Tumors

- **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 with mitomycin or gemcitabine may be given following nephroureterectomy with cuff of bladder resection.**

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References

PRINCIPLES OF INTRAVESICAL TREATMENT
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PRINCIPLES OF SYSTEMIC THERAPY

Perioperative chemotherapy (neoadjuvant or adjuvant)
Preferred regimens • DDMVAC (dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin) with growth factor support for 3 or 4 cycles[1,2] • Gemcitabine and cisplatin for 4 cycles[3,4]
Other recommended regimens • CMV (cisplatin, methotrexate, and vinblastine) for 3 cycles[5]

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

See Evidence Blocks on BL-G (EB-1)

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Continued
References

EVIDENCE BLOCKS FOR NEOADJUVANT AND ADJUVANT PERIOPERATIVE CHEMOTHERAPY

Regimen	Neoadjuvant	Adjuvant
Preferred Regimens		
DDMVAC (dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin) with growth factor support		
Gemcitabine and cisplatin		
Other Recommended Regimens		
CMV (cisplatin, methotrexate, and vinblastine)		

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PRINCIPLES OF SYSTEMIC THERAPY

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

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

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

See Evidence Blocks on BL-G (EB-2)

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Continued
References

EVIDENCE BLOCKS FOR FIRST-LINE SYSTEMIC THERAPY FOR LOCALLY ADVANCED OR METASTATIC DISEASE

Cisplatin-Eligible Patients	
Preferred Regimens	
Gemcitabine and cisplatin	
DDMVAC (dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin) with growth factor support	

Cisplatin-Ineligible Patients	
Preferred Regimens	
Gemcitabine and carboplatin	
Atezolizumab	
Pembrolizumab	
Other Recommended Regimens	
Gemcitabine	
Gemcitabine and paclitaxel	
Useful in Certain Circumstances	
Ifosfamide, doxorubicin, and gemcitabine	

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PRINCIPLES OF SYSTEMIC THERAPY

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

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

See Evidence Blocks on BL-G (EB-3)

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

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Continued
References

EVIDENCE BLOCKS FOR SECOND-LINE SYSTEMATIC THERAPY FOR LOCALLY ADVANCED OR METASTATIC DISEASE (STAGE IV)

	Post-Platinum
Preferred Regimens	
Pembrolizumab	
Atezolizumab	
Nivolumab	
Durvalumab	
Avelumab	
Erdafitinib	
Other Recommended Regimens	
Paclitaxel	
Docetaxel	
Gemcitabine	
Useful in Certain Circumstances	
Ifosfamide, doxorubicin, and gemcitabine	
Gemcitabine and paclitaxel	
Gemcitabine and cisplatin	
DDMVAC with growth factor support	

	Post-Checkpoint Inhibitor	
	Cisplatin-Ineligible	Cisplatin-Eligible
Preferred Regimens		
Gemcitabine and carboplatin		—
Gemcitabine and cisplatin	—	
DDMVAC with growth factor support	—	
Other Recommended Regimens		
Erdafitinib	*	*
Paclitaxel		
Docetaxel		
Gemcitabine		
Useful in Certain Circumstances		
Ifosfamide, doxorubicin, and gemcitabine		
Gemcitabine and paclitaxel		

*Evidence Block development in progress

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PRINCIPLES OF SYSTEMIC THERAPY

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

See Evidence Blocks on BL-G (EB-4)

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

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Continued
References

EVIDENCE BLOCKS FOR SUBSEQUENT-LINE SYSTEMIC THERAPY FOR LOCALLY ADVANCED OR METASTATIC DISEASE (STAGE IV)

Preferred Regimen	
Erdafitinib	*
Other Recommended Regimens	
Gemcitabine	*
Paclitaxel	*
Docetaxel	*
Ifosfamide, doxorubicin, and gemcitabine	*
Gemcitabine and paclitaxel	*
Gemcitabine and cisplatin	*
DDMVAC with growth factor support	*

*Evidence Block development in progress

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PRINCIPLES OF SYSTEMIC THERAPY

Radiosensitizing chemotherapy regimens for organ-preserving chemoradiation
Preferred regimens (doublet chemotherapy is preferred when feasible) • Cisplatin[f] and 5-FU[28,29] • Cisplatin[f] and paclitaxel[28,30] • 5-FU and mitomycin[31] • Cisplatin[f] alone[32]
Other recommended regimen • Low-dose gemcitabine[29,33,34] (category 2B)

Radiosensitizing chemotherapy given concurrently with conventionally fractionated radiation with palliative intent for regional disease
Preferred regimen • Cisplatin[f]
Other recommended regimens • Taxane (docetaxel or paclitaxel) (category 2B) • 5-FU (category 2B) • 5-FU and mitomycin (category 2B) • Low-dose gemcitabine[29] (category 2B) • Capecitabine (category 3)

See Evidence Blocks on BL-G (EB-5)

[f] 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.)

References

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EVIDENCE BLOCKS FOR RADIOSENSITIZING CHEMOTHERAPY

Radiosensitizing Chemotherapy Regimens for Organ-Preserving Chemoradiation	
Preferred Regimens	
Cisplatin and fluorouracil + RT	
Cisplatin and paclitaxel + RT	
Fluorouracil and mitomycin + RT	
Cisplatin + RT	
Other Recommended Regimens	
Low-dose gemcitabine + RT	

Radiosensitizing Chemotherapy Given Concurrently with Conventionally Fractionated Radiation with Palliative Intent for Regional Disease	
Preferred Regimens	
Cisplatin + RT	
Other Recommended Regimens	
Docetaxel + RT	
Paclitaxel + RT	
Fluorouracil + RT	
Fluorouracil and mitomycin + RT	
Low-dose gemcitabine + RT	
Capecitabine + RT	

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PRINCIPLES OF RADIATION MANAGEMENT OF INVASIVE DISEASE

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

- **Precede radiation therapy (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 hydronephrosis and without extensive carcinoma in situ associated with their muscle-invading tumor.**
- **For patients with stage Ta, T1, or Tis, external beam RT (EBRT) alone is rarely appropriate. For patients with recurrent Ta-T1 disease usually following BCG therapy but without extensive Tis who are not candidates for cystectomy, concurrent chemoradiotherapy may be considered as a potentially curative alternative to radical cystectomy, which is the standard treatment by NCCN Guidelines.**
- **Treat the whole bladder with or without pelvic nodal radiotherapy 39.6–50.4 Gy using conventional or accelerated hyperfractionation. Elective treatment to the lymph nodes is optional and should take into account patient comorbidities and the risks of toxicity to adjacent critical structures. Then boost either the whole or partial bladder between 60–66 Gy. For node-positive disease, consider boosting grossly involved nodes to the highest achievable dose that does not violate DVH parameters based on the clinical scenario. Reasonable alternatives to conventional fractionation include taking the whole bladder to 55 Gy in 20 fractions, or using simultaneous integrated boosts to sites of gross disease.**
- **When irradiating the bladder only or bladder tumor boost, consider daily image guidance.**
- **Concurrent chemoradiotherapy is 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 or RT alone should be considered as potentially curative therapy for medically inoperable patients or for local palliation in patients with metastatic disease.**
- **When giving palliative radiation for metastatic bladder cancer or for recurrent pelvic tumor, combining radiation with radiosensitizing chemotherapy should be considered. See BL-G 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.**
- **Tumor status assessment after completion of full-dose primary chemoradiotherapy: After 2–3 months, imaging with CT of chest/abdomen/pelvis with contrast ± bone scan. Cystoscopic surveillance and biopsy are also recommended as follow-up after completion of full-dose chemoradiotherapy.**
- **In highly selected T4b tumor cases, may consider intraoperative RT.**

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Continued
References

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 radiation therapy**
    - ◊ **Treatment field should encompass areas at risk for harboring residual microscopic disease based on pathologic findings at resection and may include resection bed, inguinal lymph nodes, and pelvic lymph nodes. Areas at risk for harboring residual microscopic disease should receive 45–50.4 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.**

References

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PRINCIPLES OF RADIATION MANAGEMENT OF INVASIVE DISEASE
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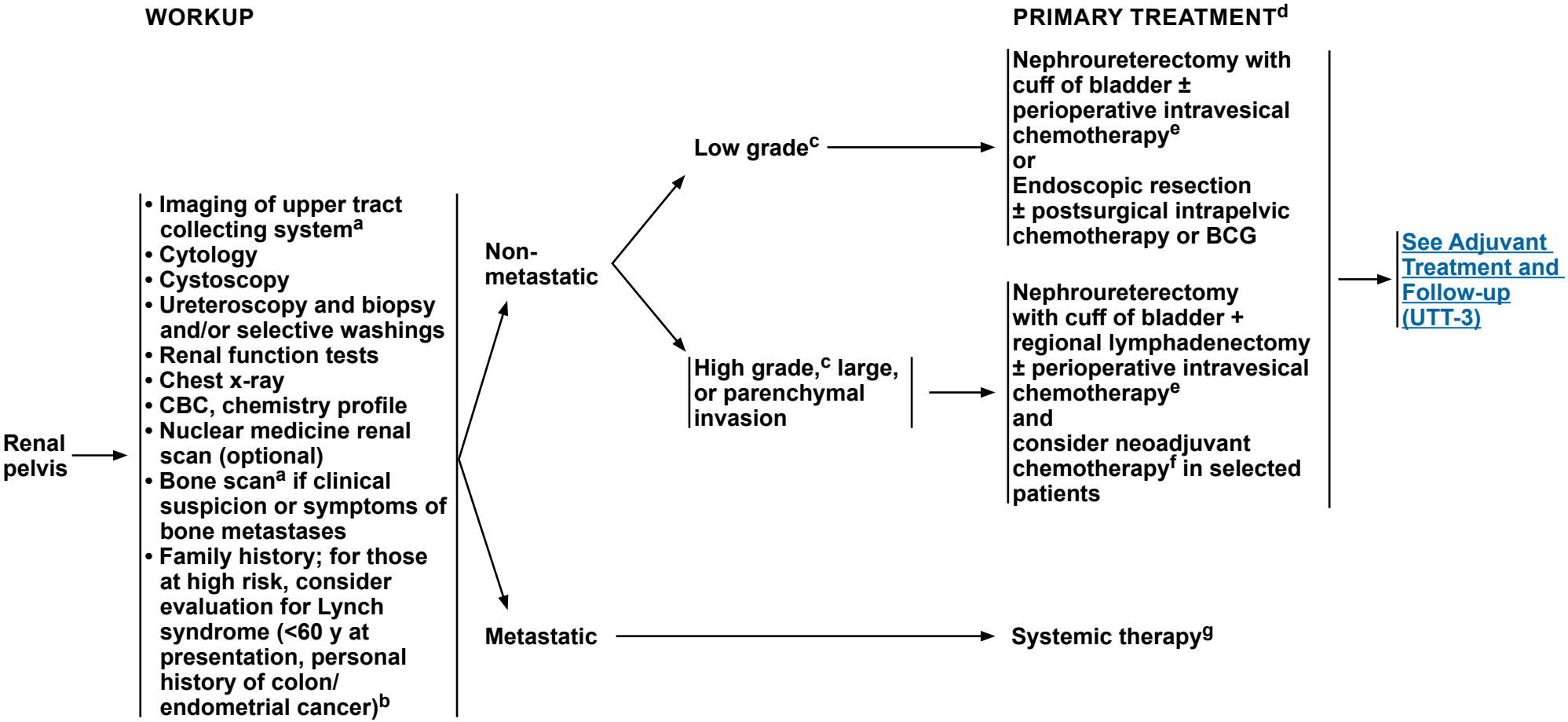

[a] See Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
[b] See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.
[c] Montironi R, Lopez-Beltran A. The 2004 WHO classification of bladder tumors: A summary and commentary. Int J Surg Pathol 2005;13:143-153. See Principles of Pathology Management (BL-C).
[d] See Principles of Surgical Management (BL-B).
[e] See Principles of Intravesical Treatment (BL-F).
[f] See Principles of Systemic Therapy (BL-G 1 of 7).
[g] See Principles of Systemic Therapy (BL-G 2 of 7, 3 of 7 and 4 of 7).

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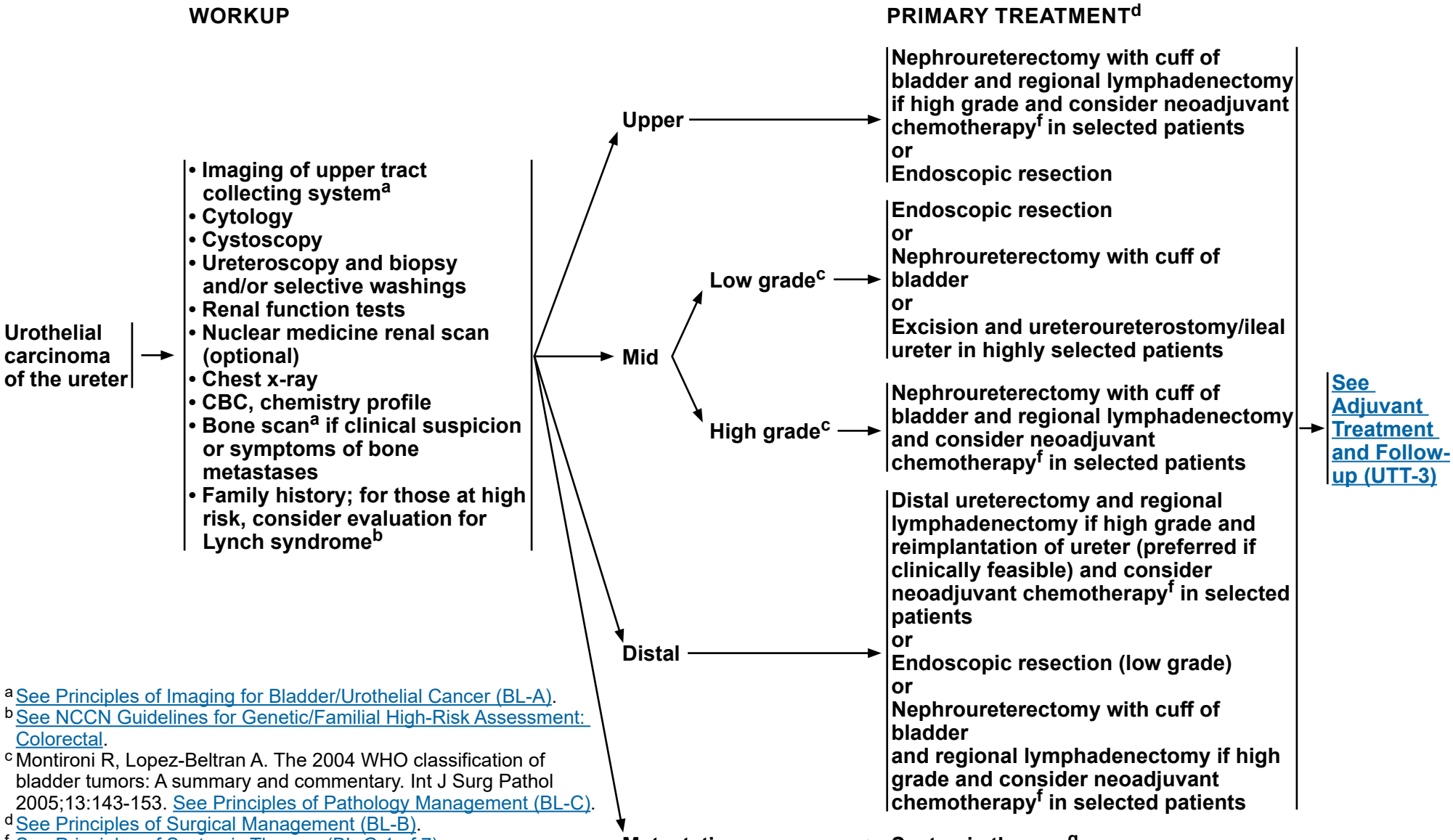

[a] See Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
[b] See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.
[c] Montironi R, Lopez-Beltran A. The 2004 WHO classification of bladder tumors: A summary and commentary. Int J Surg Pathol 2005;13:143-153. See Principles of Pathology Management (BL-C).
[d] See Principles of Surgical Management (BL-B).
[f] See Principles of Systemic Therapy (BL-G 1 of 7).
[g] See Principles of Systemic Therapy (BL-G 2 of 7, 3 of 7 and 4 of 7).

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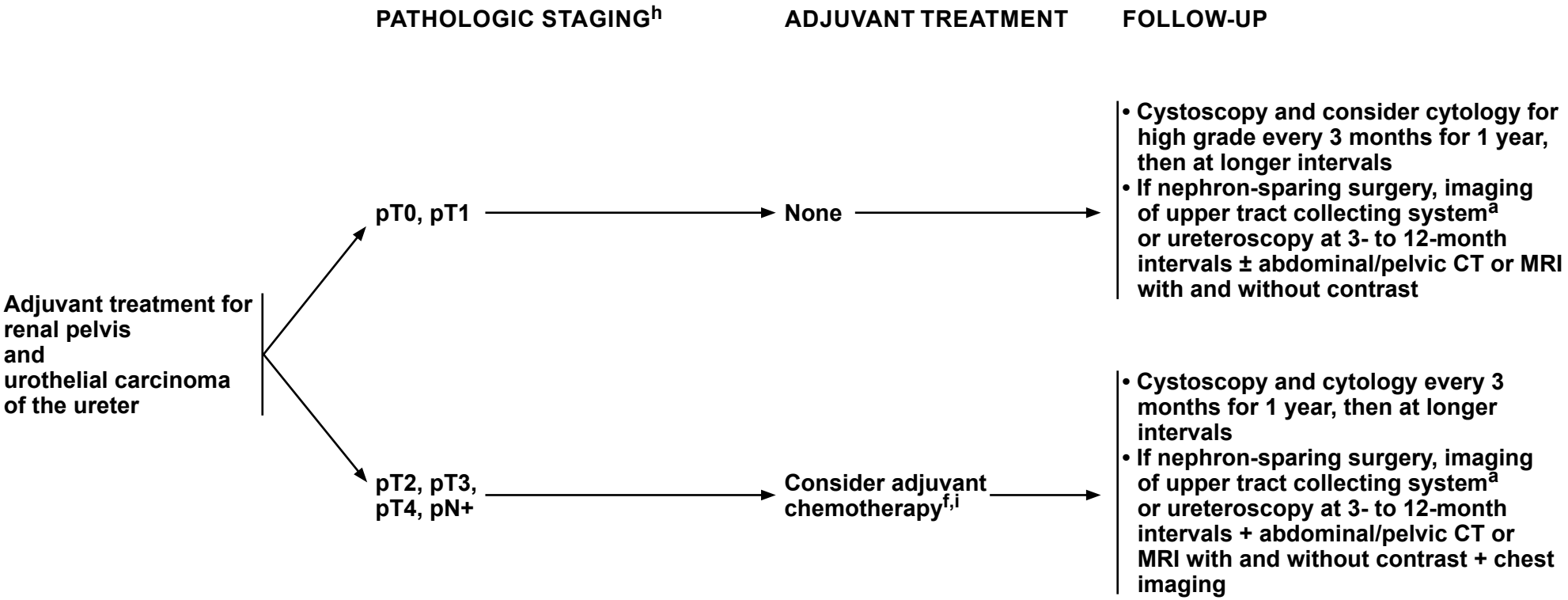

[a] See Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
[f] See Principles of Systemic Therapy (BL-G 1 of 7).
[h] The modifier “p” refers to pathologic staging based on surgical resection and lymph node dissection.
[i] Follow recommendations for adjuvant chemotherapy after ensuring that patient is fully staged to rule out metastatic disease.

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NCCN Guidelines Version 1.2020
Urothelial Carcinoma of the Prostate
NCCN Evidence Blocks™

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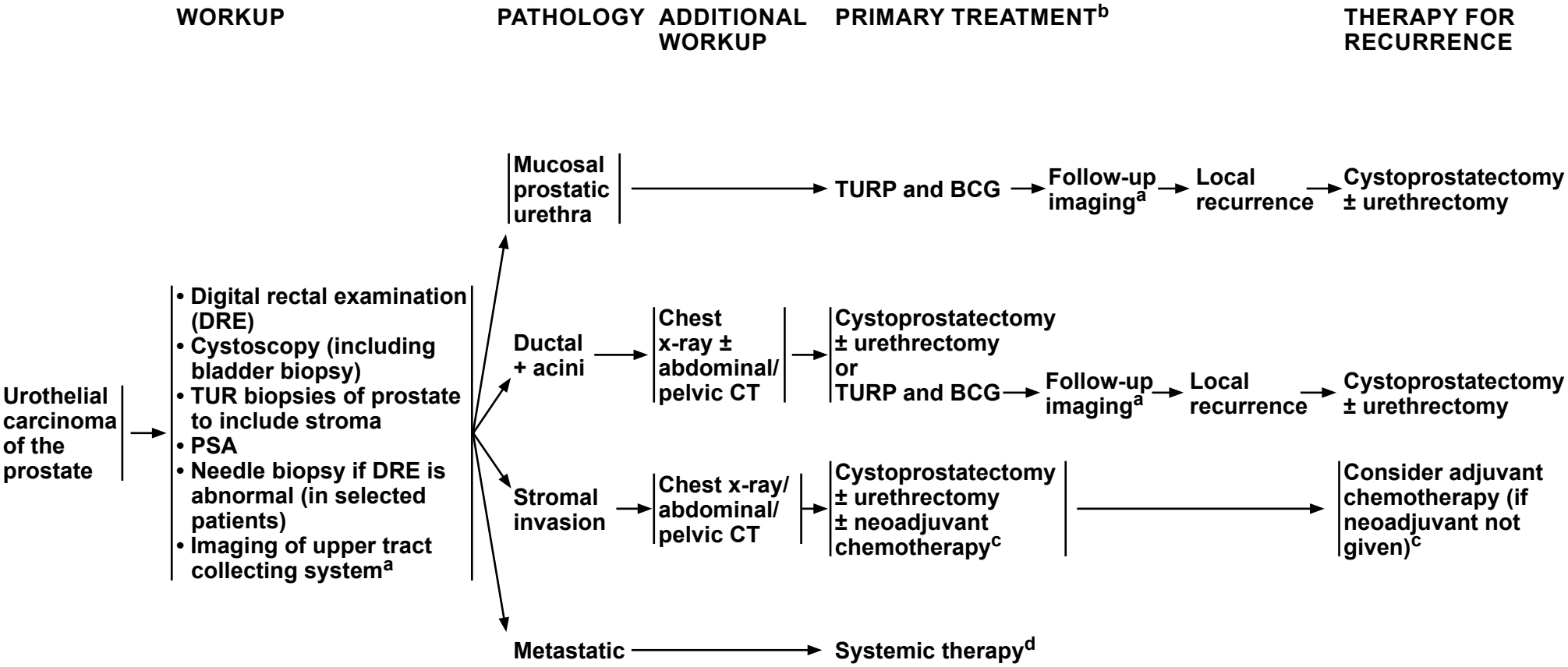

[a] See Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
[b] See Principles of Surgical Management (BL-B).
[c] See Principles of Systemic Therapy (BL-G 1 of 7).
[d] See Principles of Systemic Therapy (BL-G 2 of 7, 3 of 7 and 4 of 7).

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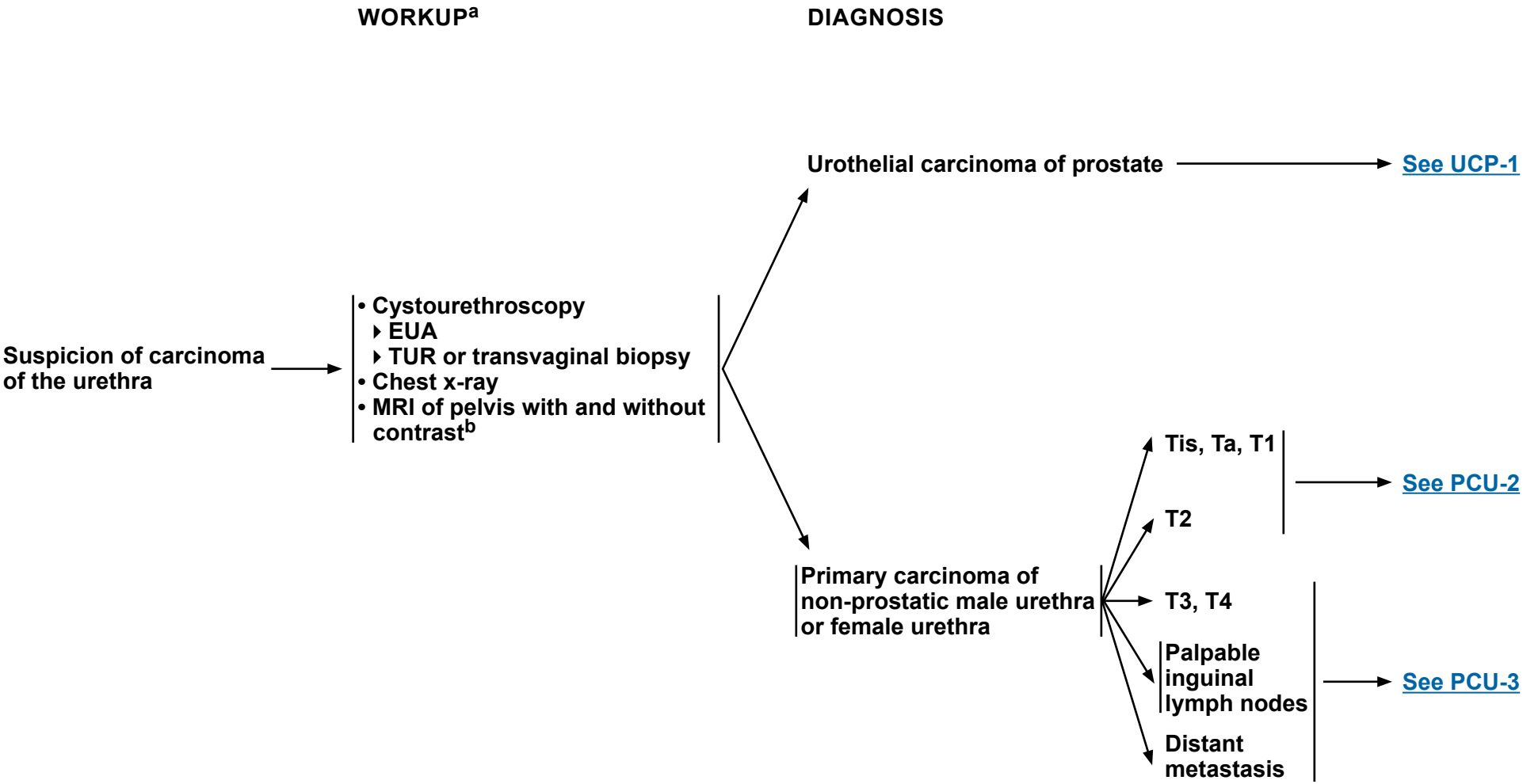

[a] Referral to a specialized center is recommended.
[b] See Principles of Imaging for Bladder/Urothelial Cancer (BL-A).

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
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National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2020
Primary Carcinoma of the Urethra
NCCN Evidence Blocks™

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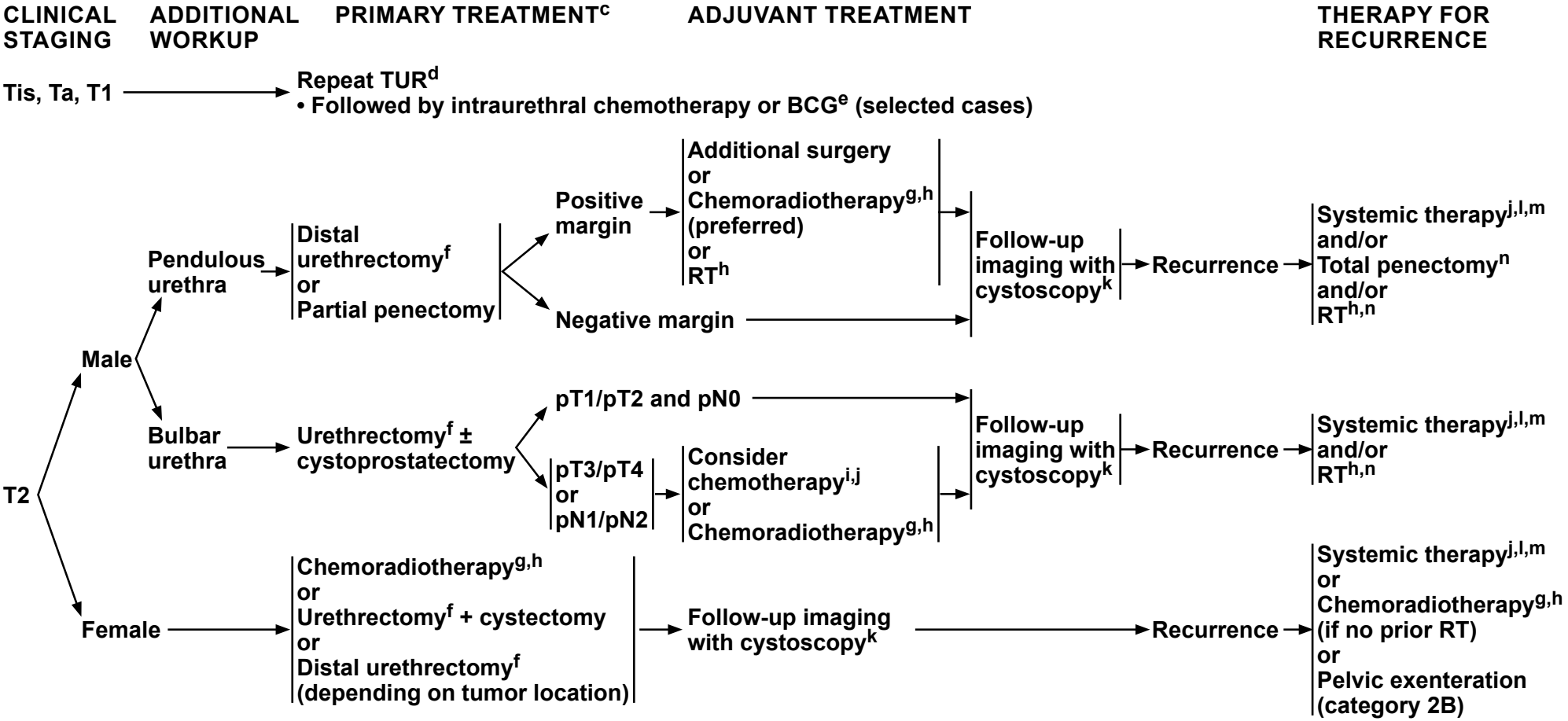
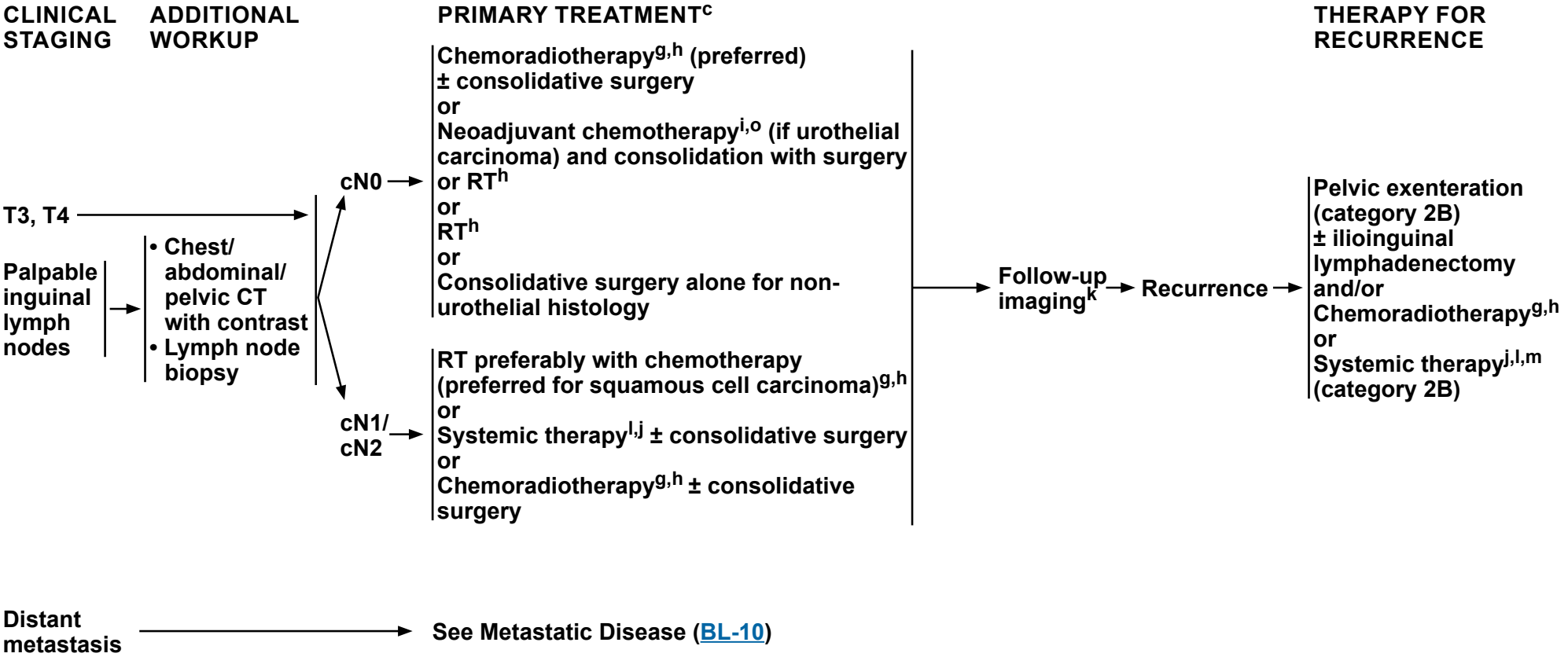


[c] See Principles of Surgical Management (BL-B).
[d] In patients with a prior radical cystectomy and a cutaneous diversion, consider a total urethrectomy.
[e] See Principles of Intravesical Treatment (BL-F).
[f] Consider neoadjuvant chemotherapy (category 2B) or chemoradiation.
[g] See Principles of Systemic Therapy (BL-G 5 of 7).
[h] See Principles of Radiation Management of Invasive Disease-Carcinoma of the Urethra (BL-H 2 of 3).
[i] See Principles of Systemic Therapy (BL-G 1 of 7).
[j] Chemotherapy regimen based on histology. (Dayyani F, Pettaway C, Kamat A, et al. Retrospective analysis of survival outcomes and the role of cisplatin-based chemotherapy in patients with urethral carcinomas referred to medical oncologists. Urol Oncol 2013;31:1171-1177.) Also see Non-Urothelial Cell and Urothelial with Variant Histology (BL-D).
[k] See Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
[l] See 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).

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



[c] See Principles of Surgical Management (BL-B).
[g] See Principles of Systemic Therapy (BL-G 5 of 7).
[h] See Principles of Radiation Management of Invasive Disease-Carcinoma of the Urethra (BL-H 2 of 3).
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[k] See Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
[l] See 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: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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

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
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. 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	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

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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
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
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	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.

NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise 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

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Overview

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

Risk factors for developing bladder cancer include male sex, white race, smoking, personal or family history of bladder cancer, pelvic radiation, environmental/occupational exposures, exposure to certain drugs, chronic infection or irritation of the urinary tract, and certain medical conditions including obesity and diabetes.[3-5] 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.[6]

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

Literature Search Criteria and Guidelines Update Methodology

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 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 only peer-reviewed biomedical literature.[7]

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 and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available at www.NCCN.org.

Clinical Presentation and Workup

The most common presenting symptom in patients with bladder cancer is microscopic or gross hematuria, although urinary frequency due to

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

If the cystoscopic appearance of the tumor is solid (sessile), high-grade, or suggests invasion into muscle, a CT scan or MRI of the abdomen and pelvis is recommended before the TURBT. In tumors with a purely papillary appearance or in cases where only the mucosa appears to be abnormal, suggesting carcinoma in situ (CIS), a CT scan or other upper tract imaging can be deferred until after surgery because the results of a CT scan rarely alter management. 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. 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) must be in the resection specimen. 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 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) within 24 hours of TURBT is recommended if non–muscle-invasive disease is suspected (see *Intravesical Therapy)*.

The involvement of the prostatic urethra and ducts in male patients with non–muscle-invasive bladder tumors has been reported. The risk is higher in the case of tumors in the bladder neck. Therefore, if the lesion is sessile or if Tis or high-grade disease is suspected, especially in the setting of bladder preservation, selected mapping biopsies and transurethral biopsy of prostate may be considered. While selected mapping biopsies may be indicated in specific situations (eg, planned partial cystectomy, definitive chemoradiotherapy, evaluation of an unexplained positive urine cytology, certain clinical trials), random biopsies rarely yield positive results, especially for low-risk tumors.[8] Therefore, mapping biopsies of normal-appearing urothelium is not necessary for most patients.

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

Clinical investigation of the specimen obtained by TURBT or biopsies is an important step in the diagnosis and subsequent management of bladder cancer. The modifier “c” before the stage refers to clinical staging based on bimanual EUA followed by 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[9] (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 Tis) and muscle-invasive disease (≥T2 disease). Management of bladder cancer is based on the findings of the biopsy specimen, 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.

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%).[10,11] 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 same portion or another part of the bladder, and these recurrences can be either at the same stage as the initial tumor or at a more advanced stage.

Papillary tumors confined to the mucosa or submucosa are generally managed endoscopically with 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.[12] 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 is defined by malignant extension past the basement membrane. Muscularis propria invasion is the criterion for T2 disease and perivesical tissue involvement defines T3 disease. Extravesical invasion into the surrounding organs (ie, the prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall) delineates T4 disease. The depth of invasion is the most important determinant of prognosis and treatment.

The 8th edition of the AJCC Staging Manual included changes to the staging of urinary bladder carcinoma, including the subdivision of stages III and IV disease (stage III into stage IIIA and stage IIIB; stage IV into stage IVA and stage IVB).[9] 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.[9,13] 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 with 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 heme-biosynthesis metabolism. In normal cells, the photosensitizer is excreted; however, enzymatic abnormalities in malignant cells result in the formation of photoactive porphyrins that remain in the cell and fluorescence with a red emission in the presence of blue light. Earlier studies used the photosensitizer 5-aminolevulinic acid (5-ALA), although more recent studies use the only 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.[14-19] Particularly CIS, which is often missed by WLC, was detected at a higher rate. A meta-analysis of fluorescence cystoscopy TURBT in non–muscle-invasive bladder cancer included 12 randomized controlled trials with a total of 2258 patients.[20] A lower recurrence rate was observed (OR, 0.5; $P < .00001$) with a delayed time to first recurrence by 7.39 weeks ($P < .0001$). Recurrence-free survival was improved at 1 year (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,[21] 1345 patients with Ta, T1 or CIS disease showed improved detection of bladder tumors and a reduction in recurrence.[21] 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 2 studies that used both methodologies. The results from this review also support greater detection and reduced recurrence but no reduction in disease progression.[22]

Although most studies have not found a 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 ($P = .05$).[23] 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 employ 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.[22] 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 (nm) and 540 nm that are absorbed by hemoglobin. The shorter wavelength provides analysis of the mucosa and the longer wavelength allows for evaluation of the deeper submucosal blood vessels. Studies suggest that there is an increase in bladder tumor detection compared with WLC, although the rate of false positives is higher.[24-28]

A systematic review and meta-analysis including 7 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 5 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, .62).[29] However, the small number of patients in this study is limiting. A larger international, multicenter, randomized controlled trial compared 1-year recurrence rates in 965 patients who received either NBI- or WLC-guided TUR for treatment of non–muscle-invasive bladder cancer. 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 low-risk patients (5.6% for NBI vs. 27.3% for WLC; $P = .002$).[30] 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.[31,32]

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.[30-33] However, the current implementation of NBI remains limited at this time due in large part to limited access to this technology and unfamiliarity with the benefit it may impart in detecting occult disease versus conventional WLC.

Histology

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

Non–muscle-invasive urothelial tumors may have flat and papillary histologies. Flat lesions may be classified as Tis, or as dysplasia if the criteria for CIS are not met but atypical dysplasia is present. Papillary lesions may be benign (ie, urothelial papilloma, inverted papilloma) or of malignant potential. The latter group includes papillary urothelial neoplasms of low malignant potential and noninvasive papillary urothelial carcinomas (low and high grade). In some cases, a papillary or T1 lesion will be documented as having an associated Tis component.

Urothelial (transitional cell) carcinomas are the most common histologic subtype in the United States and Europe and may develop anywhere transitional epithelium is present, from the renal pelvis to the ureter, bladder, and proximal two thirds of the urethra. Variant histology is common with higher grades. The fourth edition of the WHO Classification of Tumors has reclassified these histologic subtypes into the following: infiltrating urothelial carcinoma with divergent differentiation; nested, including large nested; microcystic; micropapillary; lymphoepithelioma-like; plasmacytoid/signet ring cell/diffuse; sarcomatoid; giant cell; poorly differentiated; lipid-rich; and

clear cell.[34] Two review articles highlight the changes between the third and fourth additions of this classification.[35,36] The presence of histologic variants in urothelial carcinoma should be documented as data suggest that the subtype may reflect the risk of disease 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 Variant Histology* in the algorithm). 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 are a second histologic subtype, which constitute 3% of the urinary tumors diagnosed in the United States. In regions where Schistosoma is endemic, this subtype is more prevalent and may account for up to 75% of bladder cancer cases. The distal third of the urethra is dominated by squamous epithelium. The diagnosis of squamous cell tumors requires the presence of keratinization in the pathologic specimen.[37] 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.[38] 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. The NCCN Guidelines for Bladder Cancer generally manage non–muscle-invasive disease with intravesical therapy or, for those at particularly high risk, cystectomy.

Intravesical Therapy

Intravesical chemotherapy 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.[39] This study also found that the instillation did not reduce recurrences in patients who had a prior recurrence rate of >1 recurrence per year or with an EORTC recurrence store ≥5. Therefore, immediate intravesical chemotherapy should not be given to patients who meet these criteria.

Phase III trials have reported a reduced risk of recurrence for patients with suspected non–muscle-invasive disease who are treated with

immediate postoperative gemcitabine or mitomycin. A randomized, double-blind, phase III trial of 406 patients with suspected low-grade non–muscle-invasive bladder cancer based on cystoscopic appearance showed that immediate post-TURBT instillation of gemcitabine reduced the rate of recurrence compared to saline instillation (placebo).[40] In the intention to treat analysis, 35% of patients treated with gemcitabine and 47% of those who received placebo had disease recurrence within 4 years (HR, 0.66; 95% CI, 0.48–0.90; $P < .001$).[40] Intravesical therapy for a previous non–muscle-invasive bladder cancer 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 non–muscle-invasive bladder cancer showed that an immediate instillation of mitomycin C after TURBT reduces recurrence regardless of the number of adjuvant instillations. Recurrence risk was 27% for immediate instillation versus 36% for delayed instillation ($P < .001$) for all patients in the study, with the benefit of immediate instillation present across risk groups.[41] 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 adverse events (AEs) did not significantly differ between the treatment and control groups, indicating that immediate intravesical instillation of gemcitabine or mitomycin was well tolerated.[40,41] Gemcitabine is preferred over mitomycin based on toxicity profiles.[42] For tumors with an intermediate or high risk of progression, subsequent treatment with intravesical induction (adjuvant) therapy may be given. Treatment should not be given to any patient if there is extensive TURBT or if there is suspected bladder perforation.

Induction (Adjuvant) Intravesical Chemotherapy or BCG

Although only intravesical chemotherapy is recommended in the immediate postoperative setting, both intravesical chemotherapy and BCG have been given as induction therapy in patients with non–muscle-invasive bladder cancer.[43] The most commonly used chemotherapy agents are mitomycin C and gemcitabine, although gemcitabine is preferred over mitomycin due to better tolerability.

Induction BCG has been shown to prevent bladder cancer recurrences 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.[44] There are 4 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.[45-48] A meta-analysis including 9 trials of 2820 patients with non–muscle-invasive bladder cancer reported that mitomycin C was superior to BCG without maintenance in preventing recurrence, but inferior to BCG in trials with maintenance.[49] Using the SEER database, a reduction in mortality of 23% was reported in patients receiving BCG therapy. Another study reported long-term data that BCG was better at reducing recurrence in intermediate- and high-risk non–muscle-invasive bladder cancer when compared to mitomycin C.[50]

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.[51] 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 and disease-specific survivals; progression was similar.[52] Long-term data comparing BCG to epirubicin in combination with interferon[52,53] in patients with T1 disease showed a better reduction in recurrence with BCG; however, no

differences in progression or AEs were seen.[53] 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 non–muscle-invasive bladder cancer is more established, though 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-week and 6-week schedules have been evaluated. To date, the strongest data support the 3-week BCG regimen used in the SWOG trial that demonstrated reduced disease progression and metastasis.[54] The 3-week timing of BCG has shown improved outcomes compared with epirubicin[53] or isoniazid.[52] 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.[55] 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 intermediate-risk patients.[56] Conversely, 3-year maintenance BCG reduced recurrence compared to 1-year maintenance but did not impact progression or survival in high-risk patients. These data suggest that 1 year may be suitable for patients at intermediate risk 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.[43,45,46,54,57,58]

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.[59] Installation of BCG into the bladder also mimics a urinary tract infection and may produce intense local discomfort. The side effects of treatment have translated to patient refusal of BCG therapy. Local dysuria has been reported in 60% of patients in clinical trials.[59] However, the side effects are treatable in almost all cases[60] 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.[61,62]

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.[63] Among all 4 groups, the percentage of patients with greater than or equal to 1 side effect was similar (P = .41). Though 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.[64-66] Full-dose BCG is recommended by the panel until more data are available to evaluate the low-dose BCG regimen. However, dose reduction may be used if there are substantial local symptoms during maintenance.

BCG Shortage

An ongoing shortage of BCG has existed in the United States, necessitating development of strategies to prioritize use of intravesical BCG and identify alternative treatment approaches for some patients with non-muscle invasive bladder cancer.[67] Several organizations, including the American Urological Association (AUA), American Association of Clinical Urologists (AACU), Bladder Cancer Advocacy Network (BCAN), Society of Urologic Oncology (SUO), the Large Urology Group Practice Association (LUGPA), and the Urology Care Foundation (UCF), issued a notice outlining strategies to maximize care for patients with non–muscle-invasive bladder cancer in the context of this shortage.[68] NCCN Panel Members recommend several strategies to help alleviate problems associated with this shortage.

In the event of a BCG shortage, priority for BCG treatment should be given to patients with high-risk non–muscle-invasive bladder cancer (cT1 high grade or CIS). 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[42,69] and mitomycin.[70] Two separate meta-analyses of randomized trials reported that there were no differences in risk of recurrence between BCG and mitomycin,[43,71] although BCG may show more favorable outcomes from maintenance regimens.[43] Other options include epirubicin,[52,72] valrubicin,[73] docetaxel,[74] sequential gemcitabine/docetaxel,[75] or gemcitabine/mitomycin.[76] Another alternative to intravesical BCG for patients with non–muscle-invasive bladder cancer at high risk of recurrence is initial radical cystectomy.[77]

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,[65,78,79] a phase 3 trial of 1355 patients with intermediate- or high-risk non–muscle-invasive bladder cancer reported that patients receiving the full dose of BCG show a longer disease-free interval, compared with those receiving the one-third dose.[56] 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.[56] Based on these data, the panel recommends that one-half or one-third dose may be considered for BCG induction during times of shortage and should be used for BCG maintenance, if supply allows. Maintenance BCG should be prioritized for patients with high-risk non–muscle-invasive bladder cancer (cT1 high grade or CIS) in the early maintenance period (eg, 3- and 6-months post-induction).

Treatment of cTa, Low-Grade Tumors

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

The need for adjuvant therapy depends on the patient prognosis. If the patient has a low risk for recurrence, a single immediate intravesical treatment may be sufficient. Factors to consider include the size, number, T category, and grade of the tumor(s), as well as concomitant CIS and prior recurrence.[12] Meta-analyses have confirmed the efficacy

of adjuvant intravesical chemotherapy in reducing the risk of recurrence.[80,81] 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 cTa, High-Grade Tumors

Tumors staged as cTa, high-grade lesions are papillary tumors with a relatively high risk for recurrence and progression towards more invasiveness. Restaging TURBT detected residual disease in 27% of Ta patients when muscle was present in the original TURBT.[82] In the absence of muscularis propria in the initial TURBT specimen, 49% of patients with superficial disease will be understaged versus 14% if muscle is present.[83] Repeat resection is recommended if there is incomplete resection, or should be strongly considered if there is no muscle in the specimen. Repeat resection may also be considered for high-risk (large or multifocal) lesions, as recommended in the AUA/SUO Guideline.[10]

After TURBT, patients with Ta, high-grade tumors may be treated with intravesical BCG (preferred), intravesical chemotherapy, or observation. In the literature, there are 4 meta-analyses confirming that BCG after TURBT is superior to TURBT alone, or TURBT and chemotherapy in preventing recurrences of high-grade Ta and T1 tumors.[45-48] The NCCN Bladder Cancer Panel Members recommend BCG as the preferred option over intravesical chemotherapy for adjuvant treatment of high-grade lesions.

Treatment of cT1 Tumors

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

These tumors are treated with a complete endoscopic resection. In patients with high-risk disease, especially if the complete resection is uncertain due to tumor size and location, lack of muscle in the specimen, presence of lymphovascular invasion, or inadequate staging, repeat TURBT is strongly advised.[84] 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.[85] All patients received adjuvant intravesical therapy. Although overall survival (OS) was similar, the 3-year recurrence-free survival was significantly higher in the repeat TURBT arm versus the control arm (69% vs. 37%, respectively), especially among patients with high-grade tumors.

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

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

Treatment of Tis

Primary Tis is a high-grade lesion that is believed to be a precursor of invasive bladder cancer. Standard therapy for this lesion is resection

followed by intravesical therapy with BCG. BCG is preferred over intravesical chemotherapy based on a meta-analysis of randomized trials showing that patients with CIS treated with BCG had higher complete response rates (68.1% vs. 51.5%) and a longer duration of response compared to intravesical chemotherapy.[43] If the patient is unable to tolerate BCG, intravesical chemotherapy may be considered, but data supporting this approach are limited.

Surveillance

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

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

Posttreatment of Recurrent or Persistent Disease

Treatment of Patients With Positive Cystoscopy

Patients under observation after initial TURBT, who show a documented recurrence by positive cystoscopy, should undergo another TURBT followed by single-dose intravesical chemotherapy within 24 hours and then adjuvant intravesical therapy or cystectomy based on the stage and grade of the recurrent lesion. Patients should be followed at 3 months and then at longer intervals (see *Follow-up* in the algorithm).

Recurrence Following Intravesical Treatment

In a phase II multicenter study of non–muscle-invasive bladder cancer that recurred following 2 courses of BCG, intravesical gemcitabine demonstrated activity that was relegated to high-risk non–muscle-invasive bladder cancer.[90] In the 47 patients with evaluable response, 47% had disease-free survival (DFS) at 3 months. The 1-year relapse-free survival (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 main option.[91]

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

If residual disease is seen following TURBT, patients with persistent high-grade cT1 tumors are recommended to proceed to cystectomy. Non-surgical candidates can consider concurrent chemoradiation, change of the intravesical agent (if Tis or cTa), or a clinical trial. Patients with persistent Tis, cTa, or cT1 low-grade disease after TURBT may be treated with a different intravesical agent or cystectomy. Valrubicin is approved for CIS that is refractory to BCG, although panelists disagree on its value.[73] For patients with disease that does not respond or shows an incomplete response to treatment, subsequent management is cystectomy. Concurrent chemoradiotherapy (category 2B) can be considered for non-cystectomy candidates.

Treatment of Patients With Positive Cytology

In patients without a documented recurrence but with positive cytology and negative cystoscopy and imaging, selected mapping biopsies including transurethral resection of the prostate (TURP) is indicated. In addition, cytology of the upper tract must be evaluated and ureteroscopy may be considered for detecting tumors of the upper tract.

If the selected mapping biopsy of the bladder is positive, then the recommendation is to administer intravesical BCG followed by maintenance BCG (preferred) if a complete response is seen. For tumors that fail BCG or show an incomplete response, the subsequent management options include cystectomy, changing the intravesical agent, or participation in a clinical trial. Further investigation and validation of results is warranted for establishing the efficacy of alternative agents in second-line treatments.

If transurethral biopsy of the prostate is positive, treatment of the prostate should be initiated as described below (see *Urothelial Carcinomas of the Prostate*). If cytology of the upper tract and/or ureteroscopy results is positive, then the treatment described below should be followed [see *Upper Tract Urothelial Carcinoma (UTUC)*].

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

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 cell count and chemistry profile, including alkaline phosphatase, must be performed, and the patient should be assessed for the presence of regional or distant metastases. This evaluation should include chest imaging (x-ray, CT, or 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). Bone imaging may include a bone scan, MRI, or PET/CT (category 2B). Imaging studies help assess the extent of tumor spread to lymph nodes or distant organs.[92,93] An abdominal/pelvic CT or MRI is used to assess the local and regional extent of disease.[94,95] 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.[96,97] 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.

Radical Cystectomy

Radical surgical treatment of bladder cancer involves a cystoprostatectomy in men and a cystectomy and commonly a hysterectomy in women, followed by the formation of a urinary diversion. This surgery can be performed in an open or robotic manner.[98] Prostatectomy includes removal of the prostate, seminal vesicles, proximal vas deferens, and proximal urethra. Hysterectomy should include removal of the uterus, ovaries, fallopian tubes, urethra, and part of the vagina. Forms of urinary diversion include an ileal conduit or directing urine to an internal urinary reservoir (such as a continent pouch), with drainage to the abdominal wall or the urethra (orthotopic neobladder). Relative contraindications to urethral drainage include Tis in the prostatic ducts or positive urethral margin. Orthotopic diversion or a neobladder provides the closest bladder function to that of a native bladder albeit with an increased risk for nighttime incontinence as well as urinary retention requiring intermittent self-catheterization.

Unfortunately, the accuracy of the staging cystoscopy, 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.[99] 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.[100-104] 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 Tis in other areas of the urothelium. Relative contraindications to this procedure are lesions that occur in the trigone or bladder neck. The requirement for a ureteral reimplantation, however, is not an absolute contraindication. Outcome data on partial cystectomy are varied and, in general, partial cystectomy is not considered the gold-standard surgical treatment of 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 chemotherapy is based on the pathologic stage (ie, positive nodes or perivesical tissue involvement) or presence of a positive margin, similar to that for patients who undergo a radical cystectomy.

Neoadjuvant Chemotherapy

One of the most noteworthy issues in 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.[105-110] 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 months 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.[105] 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).[111]

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 CR rate compared to standard (28-day) dosing of MVAC (11% vs. 25%; 2-sided *P* = .006).[112] 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.[113] 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.[113] A separate single-arm phase II study also reported pathologic downstaging in 49% of patients receiving neoadjuvant ddMVAC with a similar safety profile.[114] An additional neoadjuvant clinical trial of ddMVAC with bevacizumab reported 5-year survival outcomes of 63% and 64% (OS and disease-specific survival, respectively; median follow-up, 49 months), with pT0N0 and less than or equal to pT1N0 downstaging rates of 38% and 53%, respectively.[115] Bevacizumab had no definitive impact on overall outcomes. 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.[110]

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. Patients with hearing loss or neuropathy, poor performance status, or renal insufficiency may not be eligible for cisplatin-based chemotherapy. If neoadjuvant cisplatin-based chemotherapy cannot be given, neoadjuvant chemotherapy is not recommended. Cystectomy alone is an appropriate option for these patients. For patients with borderline renal function or minimal dysfunction, a split-dose administration of cisplatin may be considered (category 2B). Although split-dose is a safer alternative, the relative efficacy remains undefined.

Adjuvant Chemotherapy

Data are less clear regarding the role of adjuvant systemic chemotherapy in invasive bladder cancer. Studies have shown that adjuvant chemotherapy may delay recurrences and improve OS;[116-118] however, no randomized comparisons of adequate sample size have definitively shown a survival benefit, in large part due to poor accrual.[119] 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.[120-122] However, methodologic issues call into question the applicability of these studies to all patients with urothelial

tumors. In the MVEC trial, patients who experienced relapse in the control arm did not receive chemotherapy, which is not typical of more contemporary treatment approaches. Many of these trials were not randomized, raising the question of selection bias in the analysis of outcomes.

A meta-analysis of 6 trials found a 25% mortality reduction with adjuvant chemotherapy, but the authors pointed out several limitations of the data and concluded that evidence is insufficient for treatment decisions.[123] Interestingly, the follow-up analysis included 3 more studies for a total of 9 trials (N = 945 patients).[118] 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.[118] An observational study evaluated 5653 patients of which 23% received adjuvant chemotherapy post-cystectomy.[117] Patients who received adjuvant chemotherapy had an improved OS (HR, 0.70; 95% CI, 0.06–0.76).[117] Although evidence for adjuvant therapy is not as strong as for neoadjuvant therapy, the growing body of data support the administration of adjuvant chemotherapy for patients with a high risk for relapse who did not receive neoadjuvant therapy.

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

A minimum of 3 cycles of a cisplatin-based combination, such as ddMVAC; gemcitabine plus cisplatin (GC); or CMV, may be used in patients undergoing perioperative chemotherapy. Regimen and dosing recommendations are mainly based on studies in advanced disease.[105,110,124-126] 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 chemotherapy.

Adjuvant Radiation

Patients with locally advanced disease (pT3-4) have high rates of pelvic failure 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).[127-129] 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.[130] 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 1 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).[131]

While there are no conclusive data demonstrating improvements in OS, it is reasonable to consider adjuvant radiation in patients with pT3/pT4 pN0-2 urothelial bladder cancer following radical cystectomy. Patients meeting these characteristics with positive surgical margins and/or

lymph nodes identified in the pelvic dissection have especially high pelvic failure rates (40%–45% by 5 years), and adjuvant radiation is reasonably well tolerated and improves pelvic failure rates. Radiation with a dose range of 45 to 50.4 Gy without concurrent chemotherapy may be used. In patients who have not had prior neoadjuvant chemotherapy, it may be reasonable to sandwich adjuvant radiation between cycles of adjuvant chemotherapy.[131] The safety and efficacy of concurrent sensitizing chemotherapy and radiation in the adjuvant setting needs to be further studied.

Bladder Preservation

All bladder-sparing approaches are based on the principle that not all cases require an immediate cystectomy, and the decision to remove the bladder can be deferred until the response to organ-sparing therapy is assessed. Bladder-preserving approaches are reasonable alternatives to cystectomy for patients who are medically unfit for surgery and those seeking an alternative to radical cystectomy. Combined modality chemoradiation therapy as an alternative to immediate cystectomy for 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.[132-134] There is an apparent underutilization of aggressive bladder-preserving therapies for non-cystectomy candidates, especially the elderly and racial minorities.[135,136] Between 23% and 50% of patients with muscle-invasive bladder cancer who are 65 years of age and older 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 of age, with a 2-year OS of 94.4% and 2-year DFS of 72.6%.[137]

With any of the alternatives to cystectomy, there is a concern that bladders that appear to be endoscopically free of tumor based on a clinical assessment (cT0) that includes a repeat TURBT may not be pathologically free of tumor (pT0). Reports have suggested that up to 45% of bladders may be clinically understaged after TURBT.[136,138,139] Conversely, one series reported that all patients who achieved a complete response after radiotherapy with concurrent cisplatin and 5-FU were pT0 on immediate cystectomy.[140] 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 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.[141,142] 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.[143-145]

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.[142] 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 RT.[144,146]

Conversely, results from several prospective trials have demonstrated the effectiveness of this approach. 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.[142] 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%.[147] The RTOG 97-06 trial treated 47 patients with twice-daily irradiation and concurrent cisplatin; patients also received adjuvant chemotherapy with CMV.[148] 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%.[149] In RTOG 0233, 97 patients received twice-daily radiation with concurrent paclitaxel plus cisplatin or 5-FU plus cisplatin. Five-year OS was 73%.[150] Taken together, the complete response rates ranged from 59% to 81%.

Up to about 80% of long-term survivors maintain an intact bladder, while other patients ultimately require radical cystectomy.[141-149] A combined analysis of survivors from 4 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 toxicity (5.7% genitourinary and 1.9% gastrointestinal).[151] 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 fluorouracil and mitomycin concurrently with radiotherapy compared to radiotherapy alone, with no significant increase in AEs,[152] bladder preservation with concurrent chemoradiotherapy was given a category 1 designation for primary treatment of stage II or IIIA bladder cancer.

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 remains investigational. Studies showed that the proportions of complete pathologic response in the bladder using neoadjuvant chemotherapy alone were only up to 38%.[105] 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.[152,153] 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 toxicity.[152] 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.[154] For patients who receive TURBT as primary treatment, intravesical BCG may be considered.

If primary treatment consists of TURBT alone or TURBT with intravesical BCG, 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, the patient 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. If intravesical BCG was administered following initial TURBT, maintenance BCG should be given.

Treatment of Stage II and IIIA Tumors

The critical issues in the management and prognosis of these patients are whether a palpable mass is appreciated at EUA and if the tumor has extended through the bladder wall. Tumors that are organ-confined (T2, 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 Tis. Partial cystectomy is not an option for stage III patients. If no neoadjuvant cisplatin-based chemotherapy is given, postoperative adjuvant chemotherapy may be considered based on pathologic risk, such as positive nodes or pT3-T4 lesions. Adjuvant RT is another option for these patients.

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 hydronephrosis or with 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.[140-144,152,153,155] The following radiosensitizing regimens are recommended: cisplatin plus 5-FU; cisplatin plus paclitaxel; 5-FU plus mitomycin C; and cisplatin alone. Doublet chemotherapy is generally preferred. Low-dose gemcitabine (category 2B) may be considered as an alternative regimen.

After a complete TURBT, 60 to 66 Gy of external beam radiotherapy (EBRT) is administered. Two doses of concurrent radiosensitizing chemotherapy may be given on weeks 1 and 4 (though weekly schedules are possible as well). Alternatively, an induction dose of 40 to 45 Gy radiotherapy may be given following complete TURBT. The overall tumor status should be reassessed 2 to 3 months after treatment. If no residual tumor is detected, observation is appropriate. If residual disease is present, surgical consolidation of bladder-only residual disease or treatment as metastatic disease are appropriate. If residual disease is Tis, Ta, or T1, intravesical BCG may be considered.

In patients with extensive comorbid disease or poor performance status who are non-cystectomy candidates, treatment options include concurrent chemoradiation or radiotherapy alone. TURBT with consideration of intravesical BCG is another option for patients with stage II disease who are non-cystectomy candidates. Based on high-level evidence showing superiority to radiotherapy alone, the NCCN Panel recommends chemoradiotherapy.[152,153] The overall tumor status should be reassessed 2 to 3 months after treatment. If no tumor is evident, the patient should be observed. If tumor is observed, chemotherapy, concurrent chemoradiotherapy (if no prior radiotherapy), palliative TURBT, 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.[156,157] A population-based study of 659 patients with cT1-T4a, node-positive urothelial bladder cancer tested the effectiveness of induction chemotherapy for pathologic downstaging.[157] 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.[157] Another study used the National Cancer Database to analyze outcomes of 1783 patients with clinically node-positive bladder cancer who were treated with chemotherapy alone (n = 1388) or chemoradiotherapy (n = 395).[156] This study found that patients treated with chemoradiotherapy had a higher median OS than those treated with chemotherapy (19.0 months vs. 13.8 months, $P < .001$). The improvement in outcome with chemoradiotherapy persisted upon evaluation of propensity-matched populations ($P < .001$).[156] 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 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 is recommended.

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 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. Partial responses to concurrent chemoradiotherapy may be subsequently treated with surgical consolidation (for residual disease confined to the bladder), consideration of intravesical BCG (for Tis, Ta, or T1 residual disease), or treated as metastatic disease with systemic therapy (for remaining disease outside of 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.[9] 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, consolidation systemic therapy or completion of definitive RT may be considered. If a partial radiation dose of 40 to 45 Gy was given as primary treatment, completion of definitive RT is recommended. Alternatively, adjuvant treatment with 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 upon evaluation after primary therapy, systemic therapy or cystectomy is recommended. Systemic therapy may include a checkpoint inhibitor, chemoradiotherapy (if no prior radiotherapy), or chemotherapy. Cystectomy, if feasible, is an option.

Patients with M1a disease should receive systemic therapy or consideration of chemoradiotherapy in select patients. Those select patients with metastatic disease treated with curative intent should be evaluated with cystoscopy, EUA, TURBT, and abdominal/pelvic imaging. If a complete response is noted following primary treatment of metastatic disease, these patients may receive a radiation boost or a cystectomy. If the disease remains stable or progresses following primary therapy, these patients should follow treatment of recurrent or persistent disease.

Follow-up

Results from a meta-analysis of 13,185 patients who have undergone cystectomy reported a 0.75% to 6.4% prevalence of upper tract recurrence.[158] 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 Tis 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

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

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

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

Subsequent-line therapy for metastatic disease or local recurrence includes checkpoint inhibitors, chemotherapy, chemoradiotherapy (if no previous RT), or RT (see *Follow-up, Recurrent or Persistent Disease* in the algorithm).

Chemotherapy is sometimes combined with palliative radiation to treat metastases or pelvic recurrence after cystectomy. However, concurrent chemotherapy is inappropriate if high-dose radiation (>3 Gy fractions) is used. The radiosensitizing chemotherapy regimens remain controversial in this setting. Possible options include cisplatin (category 2A); docetaxel or paclitaxel (category 2B); 5-FU with or without mitomycin C (category 2B); capecitabine (category 3); and low-dose gemcitabine (category 2B). 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, about half of all patients relapse after cystectomy depending on the pathologic stage of the tumor and nodal status. Local recurrences account for about 10% 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 glomerular filtration rate (GFR) should be obtained to assess patient eligibility for cisplatin. If the evidence of spread is limited to nodes and biopsy is technically feasible, nodal biopsy should be considered and patients should be managed as previously outlined for positive nodal disease (stage IIIA, stage IIIB, or stage IVA). Patients who present with disseminated metastatic disease are generally treated with systemic therapy. Metastasectomy may also be useful for select patients.

Metastasectomy for Oligometastatic Disease

Highly select patients with oligometastatic disease who are without evidence of rapid progression may benefit from metastasectomy 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 urothelial carcinoma metastatic to the retroperitoneal lymph nodes who underwent complete bilateral retroperitoneal lymph node dissection reported 4-year disease-specific survival and RFS rates of 36% and 27%. Patients with viable tumor in no more than 2 lymph nodes showed the best survival rates indicating that a low burden of disease may be important in achieving benefit from metastastectomy.[159] 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.[160]

Beyond these prospective data, several retrospective studies have demonstrated a survival advantage following metastasectomy.[161-164] 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%.[165] Another population-based analysis of 497 patients aged ≥65 years who had at least one metastasectomy for treatment of urothelial carcinoma found that with careful patient selection, metastasectomy is safe and can be associated with long-term survival in this patient population.[166]

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

Molecular/Genomic Testing

The panel recommends that molecular/genomic testing be performed for stages IIIB, IVA, and IVB bladder cancer. 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.[167] The NCCN Bladder Cancer Panel recommends that molecular/genomic testing be carried out early, ideally at diagnosis of advanced bladder cancer, in order to facilitate treatment decision-making and to prevent delays in administering later lines of therapy. In addition to determining eligibility for FDA-approved therapies, molecular/genomic testing may be used to screen for clinical trial eligibility.

Based on the FDA approval of erdafitinib (see *Targeted Therapies*, below), molecular testing should include analysis for *FGFR3* or *FGFR2* genetic alterations. The *therascreen* FGFR RGQ RT-PCR Kit has been approved as a companion diagnostic for erdafitinib.[168,169] For certain patients who are ineligible to receive cisplatin, the checkpoint inhibitors atezolizumab or pembrolizumab may be considered for first-line therapy based on PD-L1 testing results (see *Targeted Therapies*, below). Companion diagnostics have been approved for each of these therapies when used in this setting.[169,170]

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.[171,172] Supporting this, a study that looked at

comprehensive genomic profiling of 295 cases of advanced urothelial carcinoma found that 93% of cases had at least 1 clinically relevant genetic alteration, with a mean of 2.6 clinically relevant genetic alterations per case. The most commonly identified clinically relevant genetic alterations were cyclin-dependent kinase inhibitor 2A (*CDKN2A*, 34%), *FGFR3* (21%), phosphatidylinositol 3-kinasecatalytic subunit alpha (*PIK3CA*, 20%), and *ERBB2* (17%).[173]

Chemotherapy for Metastatic Disease

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

GC[174,175] and ddMVAC[112,124] are commonly used in combinations that have shown clinical benefit. A large, international, phase III study randomized 405 patients with locally advanced or metastatic disease to GC or standard (28-day) MVAC.[126] 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%; progression-free survival [PFS], 9.8% vs. 11.3%, respectively).[175] Another large, randomized, phase III trial compared ddMVAC to standard (28-day) MVAC.[112,124] 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. Alternative first-line regimens also include carboplatin or taxane-based regimens (category 2B) or single-agent chemotherapy (category 2B).

The performance status of the patient is a major determinant in the selection of a regimen. Regimens with lower toxicity profiles are recommended in patients with compromised liver or renal status or serious comorbid conditions. In patients who are not cisplatin-eligible and whose tumors express PD-L1 or in patients who are not eligible for any platinum-containing chemotherapy, atezolizumab or pembrolizumab are appropriate first-line options (see *Targeted Therapies* in the discussion). Alternatively, carboplatin may be substituted for cisplatin in the metastatic setting for cisplatin-ineligible patients such as those with a GFR less than 60 mL/min. A phase II/III study assessed 2 carboplatin-containing regimens in medically unfit patients (performance status 2).[176] The overall response rate (ORR) was 42% for gemcitabine plus carboplatin and 30% for methotrexate, carboplatin, and vinblastine. However, the response rates dropped to 26% and 20%, respectively, with increased toxicity among patients who were both unfit and had renal impairment (GFR <60 mL/min).

Taxanes have been shown to be active as both front-line and palliative therapies. Based on these results, several groups are exploring 2- and 3-drug combinations using these agents, with and without cisplatin, as initial therapy. A randomized phase III trial was conducted to compare GC and GC plus paclitaxel in 626 patients with locally advanced or

metastatic urothelial cancer.[177] The addition of paclitaxel to GC resulted in higher response rates and a borderline OS advantage, which was not statistically significant in the intent-to-treat analysis. Analysis of eligible patients only (92%) resulted in a small (3.2 months) but statistically significant survival advantage in favor of the 3-drug regimen (*P* = .03). There was no difference in PFS. The incidence of neutropenic fever was substantially higher with the 3-drug combination (13.2% vs. 4.3%; *P* < .001). Panelists feel that the risk of adding paclitaxel outweighs the limited benefit reported from the trial. The alternative regimens, including cisplatin/paclitaxel,[178] gemcitabine/paclitaxel,[179] cisplatin/gemcitabine/paclitaxel,[180] carboplatin/gemcitabine/paclitaxel,[181] and cisplatin/gemcitabine/docetaxel,[182] have shown modest activity in patients with bladder cancer in phase I–II trials. Category 1 level evidence now supports the use of checkpoint inhibitors in patients with advanced disease previously treated with a platinum-containing regimen (see *Targeted Therapies* in the discussion).

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). Additionally, two checkpoint inhibitors, atezolizumab and pembrolizumab, have been FDA approved for use as a first-line therapy in certain patients. Consideration of checkpoint inhibitors must be integrated into the therapeutic planning for all patients with locally advanced and metastatic disease (see *Targeted Therapies* in the discussion). The NCCN Panel recommends enrollment in clinical trials of potentially less toxic therapies.

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

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

Clinical trial enrollment is recommended by the NCCN Panel for all patients when appropriate, but is strongly recommended for subsequent-line therapy since data for locally advanced or metastatic disease treated with subsequent-line therapy are highly variable. The available options depend on what was given as first line. Regimens used in this setting include checkpoint inhibitors and the following chemotherapies: docetaxel, paclitaxel, gemcitabine, or pemetrexed monotherapy.[183-186] Other options include albumin-bound paclitaxel; ifosfamide; methotrexate; ifosfamide, doxorubicin, and gemcitabine; gemcitabine and paclitaxel; GC; and ddMVAC.

Targeted Therapies

Platinum-based chemotherapy has been the standard of care in patients with metastatic disease with an OS of 9 to 15 months.[175,187] However, in patients with disease that relapses after this type of

chemotherapy, the median survival is reduced to 5 to 7 months.[188] Several new agents, notably checkpoint inhibitors and the FGFR inhibitor, erdafitinib, have data supporting improved outcomes compared to standard therapies for metastatic urothelial carcinoma. Cancers with higher rates of somatic mutations have been shown to respond better to checkpoint inhibitors.[189-194] Data from the Cancer Genome Atlas rank bladder cancer as the third highest mutated cancer,[171,172] suggesting that checkpoint inhibitors may have a substantial impact as a treatment option for this cancer.

The FDA has approved the PD-L1 inhibitors atezolizumab, durvalumab, and avelumab as well as the PD-1 inhibitors nivolumab and pembrolizumab for patients with urothelial carcinoma. Pembrolizumab, atezolizumab, nivolumab, durvalumab, and avelumab are approved for the treatment of locally advanced or metastatic urothelial cell carcinoma that has progressed during or after platinum-based chemotherapy or that has progressed within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy, regardless of PD-L1 expression levels. Additionally, atezolizumab and pembrolizumab are approved as a first-line treatment option for patients with locally advanced or metastatic urothelial cell carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression. Companion diagnostic tests have been approved by the FDA for measurement of PD-L1 expression.[169,170] All of these approvals have been based on category 2 level evidence with the exception of pembrolizumab as a subsequent treatment option, which has category 1 level evidence supporting the approval.[195]

Pembrolizumab

Pembrolizumab is a PD-1 inhibitor that has been evaluated as second-line therapy for patients with bladder cancer who previously received platinum-based therapy and subsequently progressed or metastasized.[196] 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 months 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%).[197] Results from this phase 3 trial have lead the NCCN Panel to assign pembrolizumab a category 1 recommendation as a second-line therapy.

A single-arm, phase II trial evaluated pembrolizumab as a first-line therapy in 370 patients with advanced urothelial carcinoma who were ineligible for cisplatin-based therapy. Data from this study showed an overall response rate of 24%, with 5% of patients 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.[198] In May 2018, the FDA issued a safety alert for the use of first-line pembrolizumab and atezolizumab, which warned that early reviews of data from 2 ongoing clinical trials (KEYNOTE-361 and IMvigor-130) showed decreased survival for patients receiving pembrolizumab or atezolizumab as first-line monotherapy compared to those receiving cisplatin- or carboplatin-based therapy.[170] Based on these data, the pembrolizumab prescribing information was subsequently amended to restrict first-line use to patients who either 1) are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 as measured by a combined positive score (CPS) of at least 10; or 2) are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.[199]

Atezolizumab

Data from the two-cohort, multicenter, phase II IMvigor-210 trial evaluated atezolizumab in patients with metastatic disease. Cohort 2 of the trial enrolled 310 patients with metastatic urothelial carcinoma post-platinum treatment and showed a significantly improved overall response rate compared to historical controls (15% vs. 10%; *P* = .0058).[200] Follow-up to date suggests these responses may be durable with ongoing responses recorded in 38 (84%) of 45 responders with a median follow-up of 11.7 months. Although a similar response rate was seen regardless of PD-L1 status of tumor cells, a greater response was associated with increased PD-L1 expression status on infiltrating immune cells in the tumor microenvironment. Grade 3 or 4 treatment-related or immune-mediated AEs occurred in 16% and 5% of patients, respectively. Furthermore, there were no treatment-related deaths in this trial, which suggests good tolerability. At the investigator's discretion, patients on this trial could continue atezolizumab beyond RECIST progression.[201] An analysis of post-progression outcomes showed that those who continued atezolizumab had longer post-progression OS (8.6 months) compared to those who received a different treatment (6.8 months) and those who received no further treatment (1.2 months).

The multicenter, randomized, controlled, phase III IMvigor-211 study compared atezolizumab to chemotherapy (vinflunine, paclitaxel, or docetaxel) in 931 patients with locally advanced or metastatic urothelial carcinoma following progression with platinum-based chemotherapy.[202] The primary endpoint of this study, median OS in patients with IC2/3 PD-L1 expression levels (n = 234), showed no significant difference between atezolizumab and chemotherapy (11.1 months vs. 10.6 months; *P* = .41). Likewise, confirmed ORR was similar between atezolizumab and chemotherapy treatments in this group of patients (23% vs. 22%). While atezolizumab was not associated with significantly longer OS compared to chemotherapy, the safety profile of atezolizumab was favorable, with 20% of patients experiencing grade 3 or 4 adverse effects compared to 43% with chemotherapy. Atezolizumab was also associated with a longer duration of response than chemotherapy, including durable responses, consistent with the observations in the previous phase II study.

In cohort 1 of the above-mentioned IMvigor-210 trial, atezolizumab was evaluated as a first-line therapy in 119 patients with locally advanced or metastatic urothelial carcinoma who were ineligible for cisplatin. Data from this study showed an ORR of 23% with 9% of patients showing a complete response. Median OS was 15.9 months. Grade 3 or 4 treatment-related AEs occurred in 16% of patients.[203] In May 2018, the FDA issued a safety alert for the use of first-line pembrolizumab and atezolizumab, which warned that early reviews of data from 2 ongoing clinical trials (KEYNOTE-361 and IMvigor-130) showed decreased survival for patients receiving pembrolizumab or atezolizumab as first-line monotherapy compared to those receiving cisplatin- or carboplatin-based therapy.[170] Based on these data, the atezolizumab prescribing information was subsequently amended to restrict first-line use to patients who either 1) are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 as measured by PD-L1–stained tumor-infiltrating immune cells covering at least 5% of the tumor area; or 2) are not eligible for any platinum-containing chemotherapy regardless of the level of tumor PD-L1 expression.[204]

Nivolumab

Data from a phase II trial in patients with locally advanced or metastatic urothelial carcinoma who progressed after at least one platinum-containing regimen reported an ORR in 52 of 265 patients (19.6%; 95% CI, 15.0–24.9) following treatment with nivolumab that was unaffected by PD-1 tumor status.[205] 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.[205] 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 months 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. Out of the 78 patients enrolled in this study, 2 experienced grade 5 treatment-related AEs, and grade 3 or 4 treatment-related AEs were reported in 22% of patients.[206]

Durvalumab

Early results from a phase I/II multicenter study of durvalumab for 61 patients with PD-L1–positive inoperable or metastatic urothelial bladder cancer who have tumor that has progressed during or after one standard platinum-based regimen showed that 46.4% of patients who were PD-L1 positive had disease that responded to treatment; no response was seen in patients who were PD-L1 negative.[207] A 2017 update on this study (N = 191) showed an ORR of 17.8% (27.6% ORR for PD-L1–high disease and a 5.1% ORR for PD-L1–low or –negative disease). Median OS was 18.2 months, with 55% of patients surviving at 1 year. Median duration of response was not yet reached at time of data cutoff. Grade 3 or 4 treatment-related AEs occurred in 6.8% of treated patients and 4 patients had a grade 3 or 4 immune-mediated AE.[208]

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 5 complete responses and 3 partial responses following treatment with avelumab. The median PFS was 11.6 weeks and the median OS was 13.7 months with a 54.3% OS rate at 12 months. Grade 3 or 4 treatment-related AEs occurred in 6.8% of patients treated with avelumab.[209] A pooled analysis of two expansion cohorts of the same trial reported results for 249 patients with platinum-refractory metastatic urothelial carcinoma or who are 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.[210]

Erdafitinib

Erdafitinib is a pan-FGFR inhibitor being evaluated in a global, open-label phase II trial. The first results from this trial reported on 96 patients with a prespecified *FGFR* alteration who had either previously received chemotherapy or who were cisplatin ineligible, chemotherapy naïve. Of these patients, 10% were chemotherapy naïve and 47% had received 2 or more prior lines of therapy. The confirmed ORR was 42%, consisting of 3% complete responses and 39% partial responses. Including stable disease, the disease control rate was 80%. The ORR was 70% among patients who had previously received a checkpoint inhibitor (n = 21). AEs were generally manageable with 7% serious treatment-related AEs and a 10% discontinuation rate due to AEs.[211]

NCCN Recommendations for Targeted Therapies

The value of the targeted therapies is reflected in the unanimous decision by the NCCN Panel to include pembrolizumab, atezolizumab, nivolumab, durvalumab, avelumab, and erdafitinib as second-line systemic therapy options after platinum-based therapy (and in the case of atezolizumab and pembrolizumab, as first-line therapy options for patients who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 or in patients who are not eligible for any

platinum-containing chemotherapy regardless of PD-L1 expression) for locally advanced or metastatic disease (see *Systemic Therapy* in the algorithm). With the exception of pembrolizumab as a subsequent treatment option (category 1), the use of targeted therapies are all category 2A recommendations.

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, adjuvant 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, RT, 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 have benefit in 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.[212-216] In addition, a retrospective analysis has shown that neoadjuvant chemotherapy may have a modest benefit for other variant histologies.[217] 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 chemotherapy (see NCCN Guidelines for Small Cell Lung Cancer) followed by either RT or cystectomy as consolidation, if there is no metastatic disease. Primary bladder sarcomas are treated as per the NCCN Guidelines for Soft Tissue Sarcoma.

Upper Tract Urothelial Carcinoma (UTUC)

Upper tract tumors, including those that originate in the renal pelvis or in the ureter, are relatively uncommon.[218] 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 the setting of 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 and/or selective washings. A chest radiograph can help evaluate for possible metastasis and assess any comorbid diseases that may be present. 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.[219,220] 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 more information).

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.[221-223] While the studies have generally looked at early instillation (within 24–48 hours of surgery),[222,223] some centers are delaying intravesical instillation of chemotherapy by up to a week to administer a cystogram confirming there is no perforation. The data supporting the use of neoadjuvant chemotherapy for UTUC are more limited and retrospective; however, a meta-analysis of 4 trials shows that neoadjuvant chemotherapy may also improve outcomes compared to no perioperative treatment.[224] While mitomycin is most commonly used, gemcitabine is an option for select patients.

Alternatively, a nephron-sparing procedure through a transureteroscopic approach or a percutaneous approach may be used, with or without postsurgical intrapelvic chemotherapy or BCG. 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, neoadjuvant chemotherapy may be considered based on extrapolation of data from bladder cancer series.[105-107] 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 the settings of 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 the presence of comorbid conditions that may contraindicate nephroureterectomy. Favorable clinical and pathologic criteria for nephron preservation include a papillary, unifocal, low-grade tumor, and size <1.5 cm, where cross-sectional imaging shows no concern for

invasive disease.[218,225] 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.[226,227] In addition, patients with bilateral disease, solitary functional or anatomic kidney, chronic kidney disease, renal insufficiency, or a hereditary predisposition to genitourinary cancers are contraindicated from nephroureterectomy and should receive nephron-sparing treatment.[218,228] 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.[218]

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. Such tumors should also be followed up with ureteroscopy and upper tract imaging at 3- to 12-month intervals if endoscopic resection is considered.

Data on role of adjuvant chemotherapy for patients with pT2, pT3, pT4, or nodal disease has been mixed. A retrospective study of 1544 patients meeting these criteria across 15 centers showed no difference in OS between adjuvant chemotherapy and observation following radical nephroureterectomy (HR, 1.14; 95% CI, 0.91–1.43).[229] On the other hand, initial findings from a phase 3 trial that randomized patients to 4 cycles of gemcitabine plus cisplatin/carboplatin or surveillance post nephroureterectomy reported that adjuvant chemotherapy improved PFS in this population (HR, 0.49; 95% CI, 0.30–.079; *P* = .003).[230] OS analysis is ongoing for this trial. Based on these data, adjuvant chemotherapy may be considered for patients with pT2-4 or nodal disease. Follow-up should be the same as pT0/pT1 disease with the addition of chest imaging.

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). 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.[224,231]

Tumors that originate in the upper ureter occasionally can be managed endoscopically but more commonly are treated with nephroureterectomy with a bladder cuff 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 can be divided by grade and size. Small, low-grade tumors can be managed with excision followed by ureteroureterostomy, segmental or complete ureterectomy, or ileal ureter interposition in highly selected patients. Alternatively, endoscopic resection or nephroureterectomy with a bladder cuff can be performed. Larger, high-grade lesions are managed with nephroureterectomy with a bladder cuff 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). Other primary treatment options include endoscopic resection, 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 systemic adjuvant treatment with chemotherapy, depending on the patient's anticipated tolerance to the regimen based on comorbidities. The reasons for considering adjuvant therapy are similar to those for tumors that originate in the bladder. Please see *Follow-up* for *Renal Pelvis Tumors*, above, for more discussion of the 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. 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, 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 may be considered in patients with stromal invasion.[105-107] 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.[232] The 5-year OS is 42%.[233,234] Stage and disease location are the most important prognostic factors for male patients, while tumor size and histology are prognostically significant for female patients.[232,234] 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 and MRI of the pelvis are recommended to evaluate the extent of the disease.

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

Treatment

Patients with Tis, 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 gender and tumor location. For male patients 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.

Male 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 female patients with T2 tumors include chemoradiation or urethrectomy with cystectomy. Partial urethrectomy has been associated with a high urethral recurrence rate.[235] At recurrence, the patient may receive systemic therapy or chemoradiotherapy (both category 2A) or pelvic exenteration (category 2B).

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.[236] Combined chemoradiation with 5-FU and mitomycin C has shown efficacy in a series of male patients with squamous cell carcinoma of the urethra.[237] Patients receiving 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 followed by consolidative surgery or radiation, or radiation preferably with chemotherapy with or without consolidative surgery. If positive nodes are present, radiation preferably with chemotherapy 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. Systemic therapy is a category 2B option.

Patients with distant metastases should receive similar treatment as metastatic bladder cancer. Systemic therapies include chemotherapy and checkpoint inhibitors 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. Continued monitoring for recurrence is an essential part of management, because most recurrences are superficial and can be treated endoscopically. Within each category of disease, more refined methods to determine prognosis and guide management, based on molecular staging, are under development with the goal of optimizing each patient's likelihood of cure and chance for organ preservation.

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

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

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