National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Bladder Cancer

Version 2.2017 — February 15, 2017

NCCN.org

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Bladder Cancer

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NCCN Guidelines Panel Disclosures

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‡ Hematology/Hematology oncology	≠ Pathology
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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/physician.html.

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

See NCCN Categories of Evidence and Consensus.

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Updates in Version 2.2017 of the NCCN Guidelines for Bladder Cancer from Version 1.2017 include:

BL-G 2 of 4

- **Principles of Systemic Therapy**
  - **Subsequent systemic therapy for locally advanced or metastatic disease,**
    - ◊ **Standard regimens, "Nivolumab" was added as an option with a category 2A designation.**

MS-1

- **The discussion section was updated to reflect the changes in the algorithm.**

Updates in Version 1.2017 of the NCCN Guidelines for Bladder Cancer from Version 2.2016 include:

General

- **Table titled, "Approximate Probability of Recurrence for Non-Muscle Invasive Bladder Cancer" was removed from the guidelines.**
- **Follow-up recommendations were removed from BL-2 and BL-8 and added to two new tables for**
  - **Table 1: Non-Muscle Invasive Bladder Cancer**
  - **Table 2: Post-cystectomy or Post-bladder Sparing (Partial cystectomy chemoradiation)**
  - **Hyperlinks were added throughout the guidelines to BL-E.**
  - **Statement added to all follow-up pages: "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."**

Bladder Cancer

BL-1

- **Primary Evaluation/Surgical Treatment,**
  - **4th bullet, 1st sub-bullet was revised, "*Consider* selected mapping biopsies."**
  - **5th bullet was added, "Imaging of upper tract collecting system, if not previously done."**
- **Additional workup heading was changed to "Additional *staging* workup."**
- **Footnote**
  - **Footnote c was revised, "Immediate intravesical chemotherapy, not immunotherapy, has been shown to decrease recurrence *in select subgroups of patients*."**
  - **Footnote was removed and content added to Principles of Imaging, "Imaging may include one or more of the following: CT urography, renal ultrasound or CT without contrast with bilateral retrograde ureteropyelogram, ureteroscopy, or MRI urogram." Also removed from BL-8.**

BL-2

- **cTa, high grade and cT1 low and high grade with no residual disease**
  - **For adjuvant intravesical treatment, "mitomycin" was replaced with "intravesical chemotherapy." A corresponding footnote k was added, "The most commonly used options for intravesical chemotherapy are mitomycin and gemcitabine."**
- **Footnote m was added, "Cystectomy is generally reserved for residual T1, high grade, and muscle-invasive disease at resection."**

BL-3

- **Follow-up results,**
  - **Last pathway was clarified, "*Cystoscopy suspicious for* recurrence post-intravesical *therapy* ~~treatment with BCG or mitomycin~~; no more than 2 consecutive cycles."**
- **Treatment**
  - **Cystoscopy positive, the treatment was clarified, "Adjuvant intravesical therapy *or cystectomy* based on tumor *stage* and grade."**
  - **Cytology positive..., the treatment for bladder, prostate and upper tract negative were all combined.**

BL-4

- **After additional workup, "positive nodes" was changed to "cN1-3" and a corresponding footnote s, "Clinically suspicious nodes" was added. (Also for BL-5 and BL-6)**
- **Primary treatment,**
  - **2nd option was revised, ~~Segmental (~~Partial~~)~~ cystectomy..."**

BL-7

- **Metastatic, additional workup**
  - **4th bullet was changed from 24-hr urine creatinine clearance, if calculated GFR <60 mL/min" to "Estimate GFR to assess eligibility for cisplatin."**

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Updates in Version 2.2017 of the NCCN Guidelines for Bladder Cancer from Version 2.2016 include:

BL-A

- Principles of Imaging for Bladder/Urothelial Cancer
  - PET/CT was clarified as category 2B on all appropriate pages along with a statement, "PET/CT should not be used to delineate the anatomy of the upper urinary tract."
  - Non-muscle Invasive Bladder Cancer
    - ◊ Abdominal and Pelvic Imaging (BL-A 1 of 5)
      - – 1st bullet, 2nd sub-bullet was revised by adding, "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."
      - – 1st bullet, 4th sub-bullet was added, "Ureteroscopy."
      - – 2nd bullet was revised, "Upper tract (CTU, MRU, or retrograde with CT or US) and abdominal/pelvic imaging at baseline. For high-risk patients, UT imaging also performed at 12 mo and every 1–2 y thereafter up to 10 y."
  - Muscle Invasive Bladder Cancer (BL-A 3 of 5)
    - ◊ Abdominal and Pelvic Imaging
      - – Staging, 1st bullet, 4th sub-bullet was added, "Ureteroscopy."
      - – Staging, 1st bullet, 6th sub-bullet was added, "CT or MRI of the abdomen and pelvis with IV contrast if not performed with initial evaluation."
    - ◊ Follow-up, 1st sub-bullet, "Upper tract *and abdominal/pelvic* imaging as defined previously at 3- to 6-month intervals for 2 years. Then ~~at 1-year intervals~~ *abdominal/ pelvic imaging annually up to 5 y and as indicated thereafter*."
    - ◊ Evaluation of Suspected Bone Metastasis
      - – 2nd bullet was revised by adding, "... may be imaged with PET/CT *(category 2B) or bone scan*. PET/CT (category 2B) may also be considered in cases when additional sites of extraosseous metastatic disease are suspected or previously documented."
  - Urothelial Carcinoma of the Prostate/Primary Carcinoma of the Urethra (BL-A 4 of 5)
    - ◊ 2nd bullet, 4th sub-bullet was added, "Ureteroscopy."
    - ◊ 3rd bullet, 1st sub-bullet was revised, "*Low-risk T1 or* <T1 disease" and chest x-ray was removed as a follow-up option.

BL-B

- Principles of Surgical Management
  - This section was extensively revised.
  - Hyperlinks were added throughout the guidelines to BL-B

BL-F

- Principles of Intravesical Therapy
  - This page was extensively revised.

BL-G 1 of 4

- Principles of Systemic Therapy
  - Last bullet was revised, "For patients with borderline renal function, ~~24-hr urine creatine clearance should be assessed to estimate GFR~~ *estimate GFR to assess eligibility for cisplatin*.

BL-G 2 of 4

- Principles of Systemic Therapy
  - Heading was changed from "Second-line..." to "Subsequent systemic therapy..."
  - Subsequent systemic therapy
    - ◊ 1st bullet was revised, "~~No standard therapy exists in this setting; thus,~~ Participation in clinical trials of new agents is recommended."

BL-H 1 of 3

- Principles of Radiation Management of Invasive Disease,
  - Carcinoma of the Bladder
    - ◊ 14th bullet was revised by adding "with contrast" to "CT of chest/abdomen/pelvis."
    - ◊ Last bullet was added, "In highly selected T4b tumor cases, may consider intraoperative RT."
  - References were added to BL-H 3 of 3.

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Updates in Version 2.2017 of the NCCN Guidelines for Bladder Cancer from Version 2.2016 include:

Upper GU Tract Tumors

UTT-1

- **Workup**
  - **7th bullet was revised, "*Nuclear medicine* renal scan (optional)." (Also for UTT-2)**

UTT-2

- **Primary treatment**
  - **Mid, low grade, the 3rd option was revised, "Nephroureterectomy with cuff of bladder ~~and consider regional lymphadenectomy~~."**

UTT-3

- **Follow-up for renal pelvis and urothelial carcinoma of ureter**
  - **For both pT0, pT1 and pT2, pT3, pT4, pN+, the 2nd bullet was revised, "*Abdominal/pelvic* CT ~~scan~~ or MRI *with and without contrast."***
  - **"Chest x-ray" was removed.**

Primary Carcinoma of the Urethra

PCU-1

- **Workup,**
  - **3rd bullet was revised by adding, "MRI of pelvis *with and without contrast*."**

PCU-2

- **Primary treatment**
  - **RT preferably with chemotherapy was changed to "chemoradiotherapy (preferred) or RT" (Also for PCU-3)**
  - **Tis, Ta, T1, the recommendation was clarified, "Repeat TUR, Followed by intraurethral *chemo*therapy *or BCG* (selected cases)."**

PCU-3

- **Therapy for recurrence,**
  - **For T3, T4, palpable inguinal lymph nodes and distant metastasis, the first option was revised, Pelvic exenteration (category 2B) ± ~~en bloc~~ ilioinguinal lymphadenectomy."**

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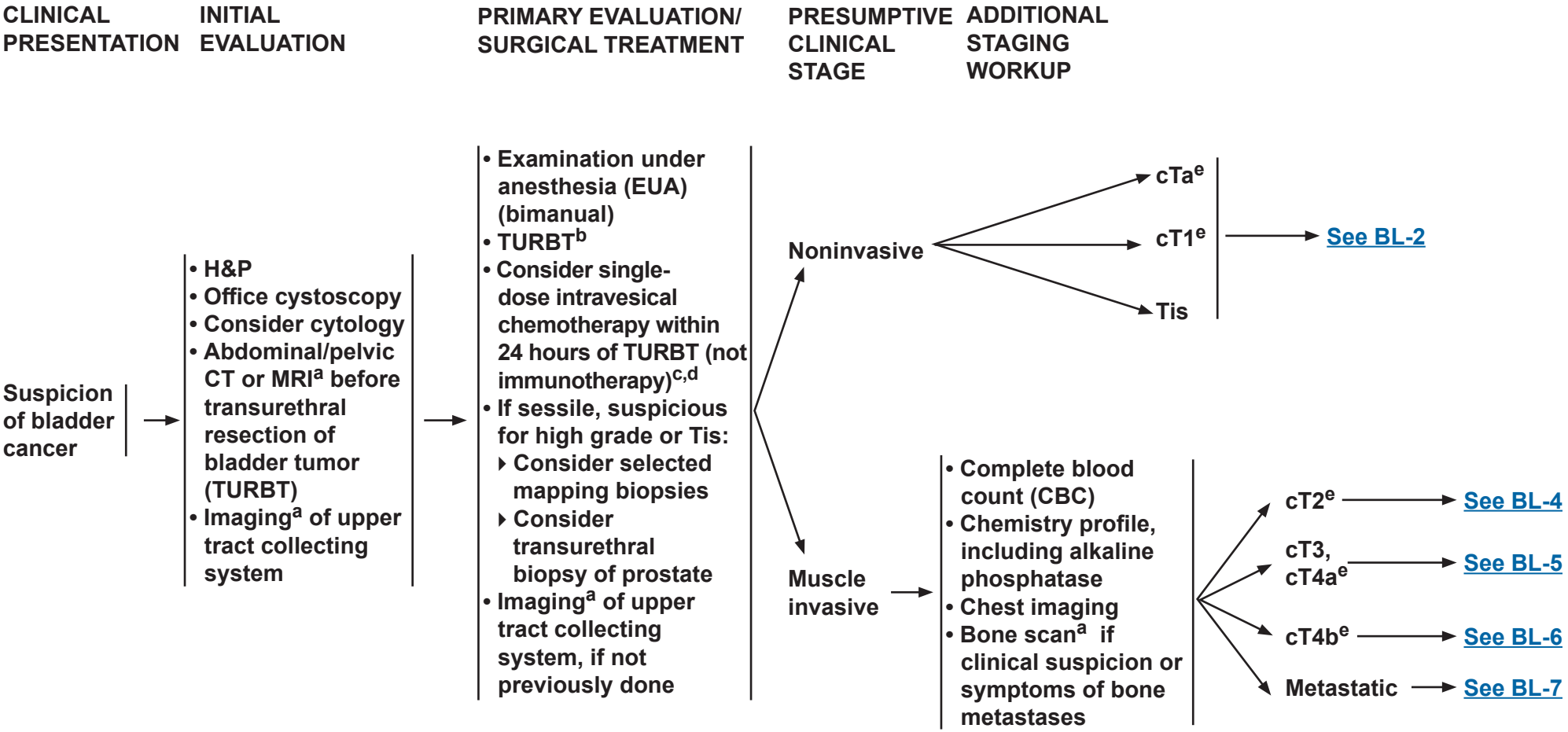

[a] See Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
[b] See Principles of Surgical Management (BL-B).
[c] Immediate intravesical chemotherapy, not immunotherapy, has been shown to decrease recurrence in select subgroups of patients.
[d] Although there is no standard for immediate perioperative intravesical chemotherapy, mitomycin is most commonly used.
[e] The modifier "c" refers to clinical staging based on bimanual examination under anesthesia and endoscopic surgery (biopsy or transurethral resection) and imaging studies. The modifier "p" refers to pathologic staging based on cystectomy and lymph node dissection.

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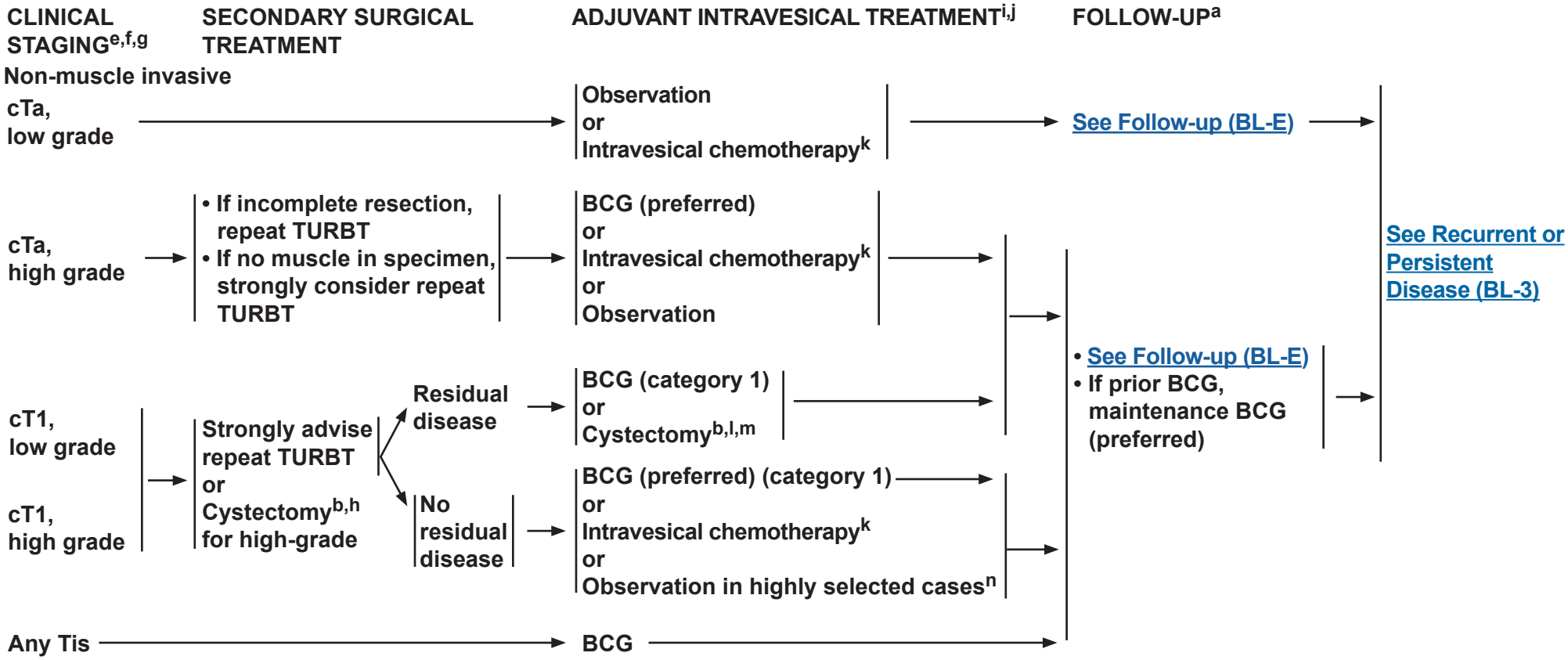
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



[a] See Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
[b] See Principles of Surgical Management (BL-B).
[e] The modifier "c" refers to clinical staging based on bimanual examination under anesthesia and endoscopic surgery (biopsy or transurethral resection) and imaging studies. The modifier "p" refers to pathologic staging based on cystectomy and lymph node dissection.
[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 Non-Urothelial Cell Carcinoma of the Bladder (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 mitomycin and gemcitabine.
[l] If not a cystectomy candidate, consider concurrent chemoradiotherapy (category 2B) or a clinical trial. See Principles of Systemic Therapy (BL-G 3 of 4).
[m] Cystectomy is generally reserved for residual T1, high grade, and muscle-invasive disease at re-resection.
[n] Highly selected cases with small-volume tumors with limited lamina propria invasion and no CIS.

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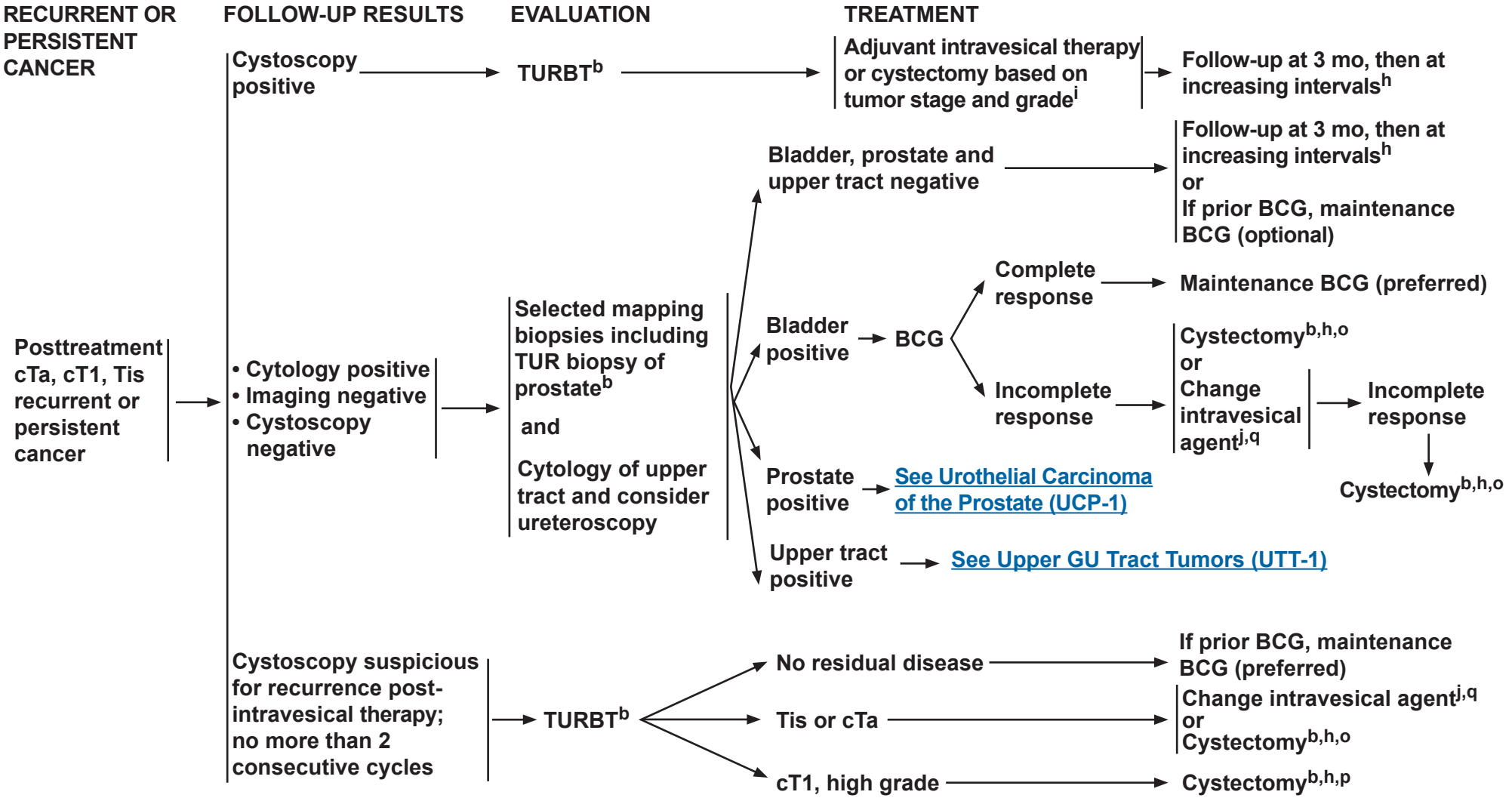

[b] See Principles of Surgical Management (BL-B).
[h] See Follow-Up (BL-E).
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[j] See Principles of Intravesical Treatment (BL-F).
[o] If not a cystectomy candidate, consider concurrent chemoradiotherapy (category 2B) or a clinical trial. See Principles of Systemic Therapy (BL-G 3 of 4).
[p] If not a cystectomy candidate, consider concurrent chemoradiotherapy (see Principles of Systemic Therapy [BL-G 3 of 4]), change in intravesical agent, or a clinical trial.
[q] Valrubicin is approved for BCG-refractory carcinoma in situ.

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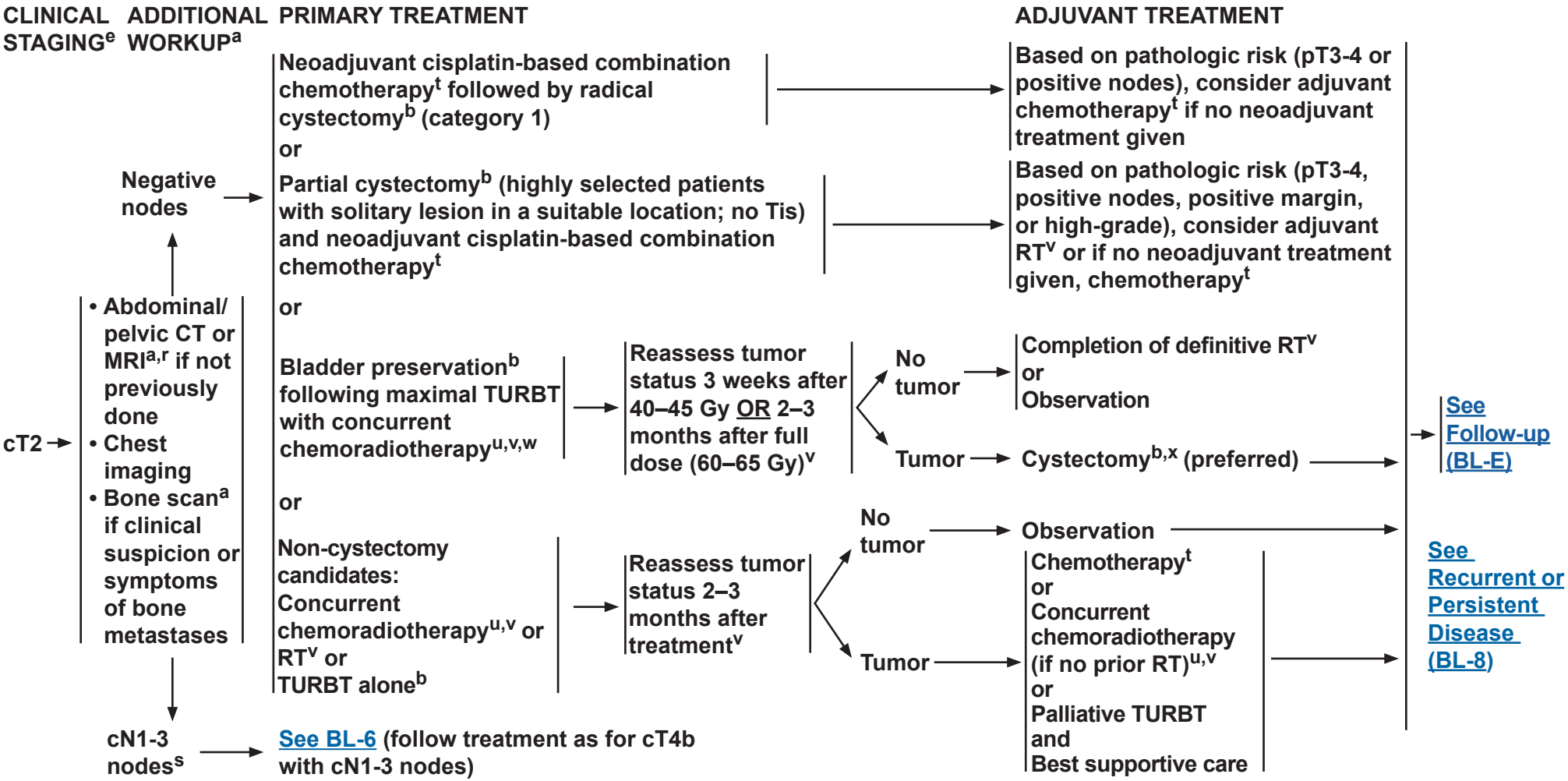

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[r] Consider PET/CT scan (category 2B).
[s] Clinically suspicious nodes.
[t] See Principles of Systemic Therapy (BL-G 1 of 4).
[u] See Principles of Systemic Therapy (BL-G 3 of 4).
[v] See Principles of Radiation Management of Invasive Disease (BL-H).
[w] There are data to support equivalent survival rates. Not all institutions have experience with these multidisciplinary treatment approaches, which require a dedicated team.
[x] Other options may include TURBT, best supportive care, or observation depending on patient and tumor characteristics.

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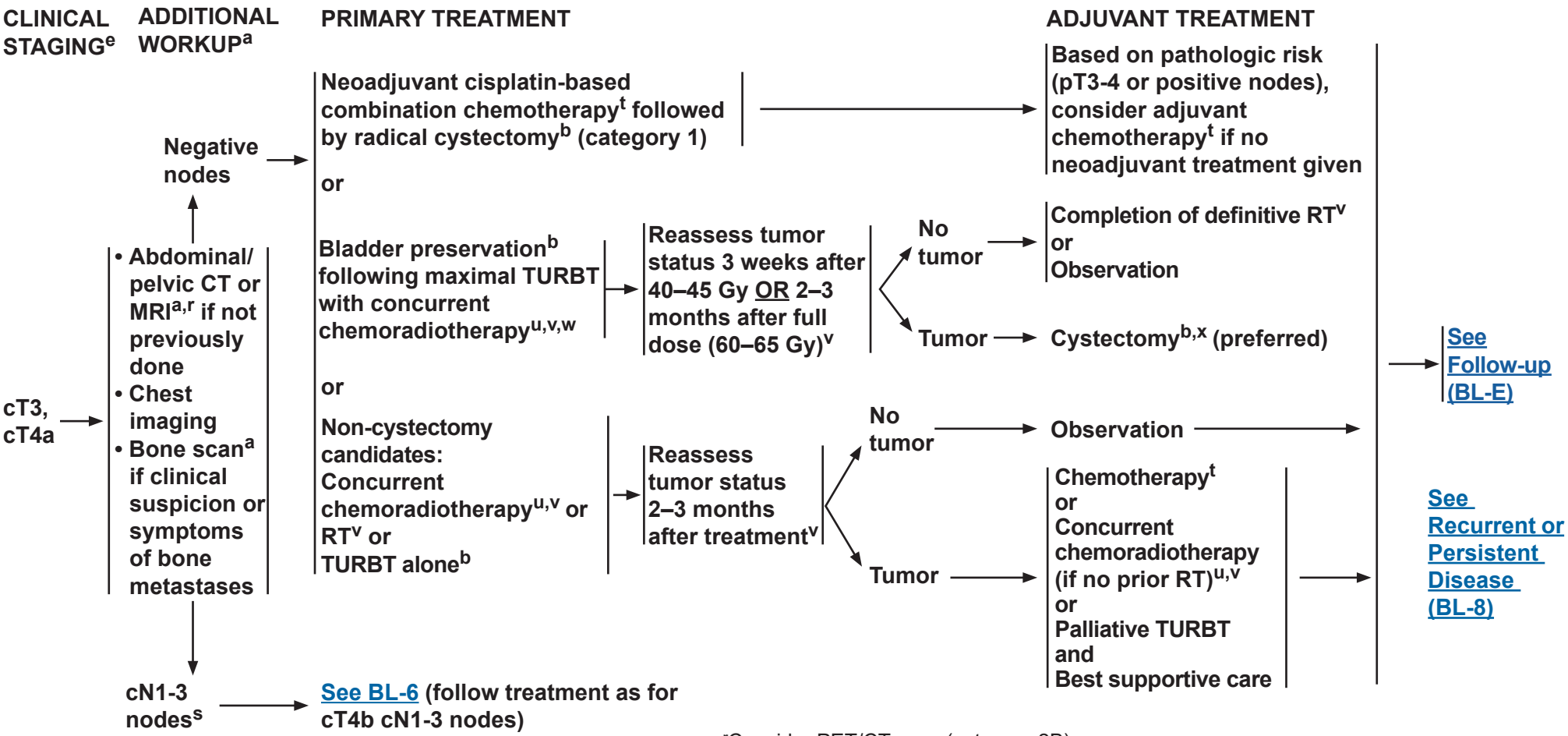

[a] See Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
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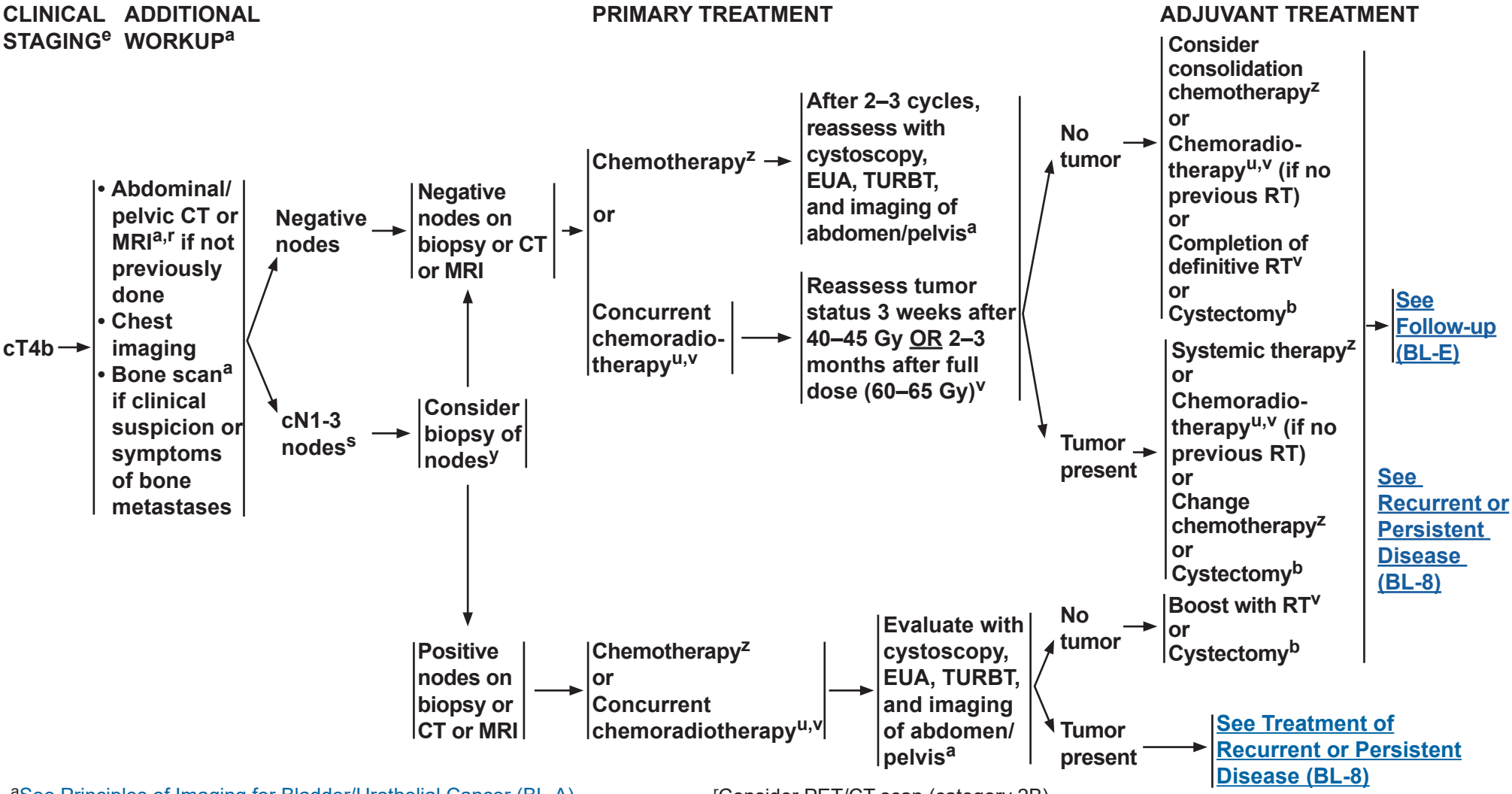

[a] See Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
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[r] Consider PET/CT scan (category 2B).
[s] Clinically suspicious nodes.
[u] See Principles of Systemic Therapy (BL-G 3 of 4).
[v] See Principles of Radiation Management of Invasive Disease (BL-H).
[y] If technically possible.
[z] See Principles of Systemic Therapy (BL-G 2 of 4).

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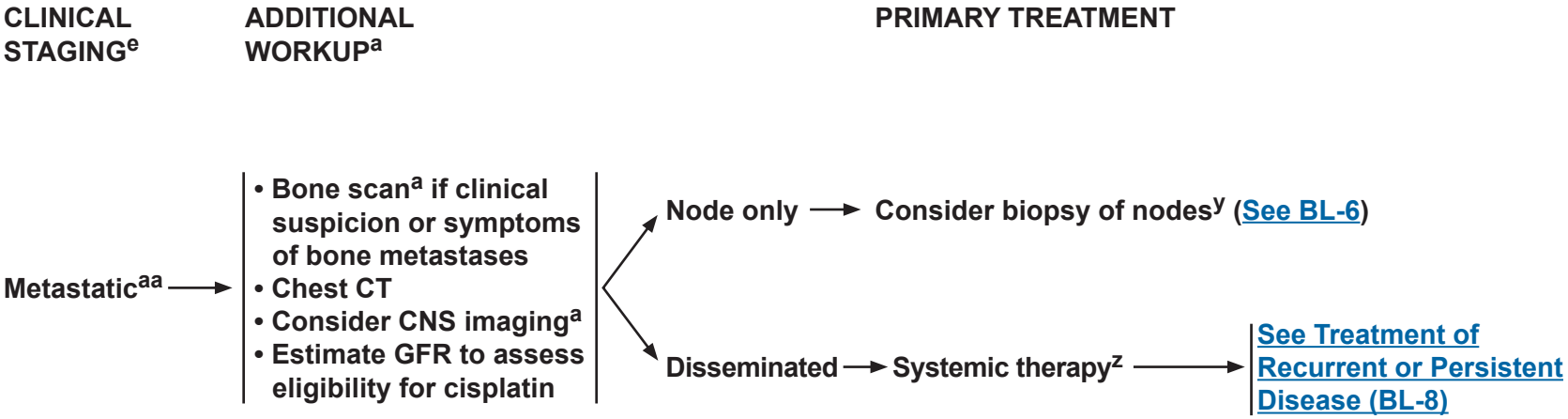

[a] See Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
[e] The modifier "c" refers to clinical staging based on bimanual examination under anesthesia and endoscopic surgery (biopsy or transurethral resection) and imaging studies. The modifier "p" refers to pathologic staging based on cystectomy and lymph node dissection.
[y] If technically possible.
[z] See Principles of Systemic Therapy (BL-G 2 of 4).
[aa] Consider molecular testing in a CLIA-approved laboratory. See Discussion.

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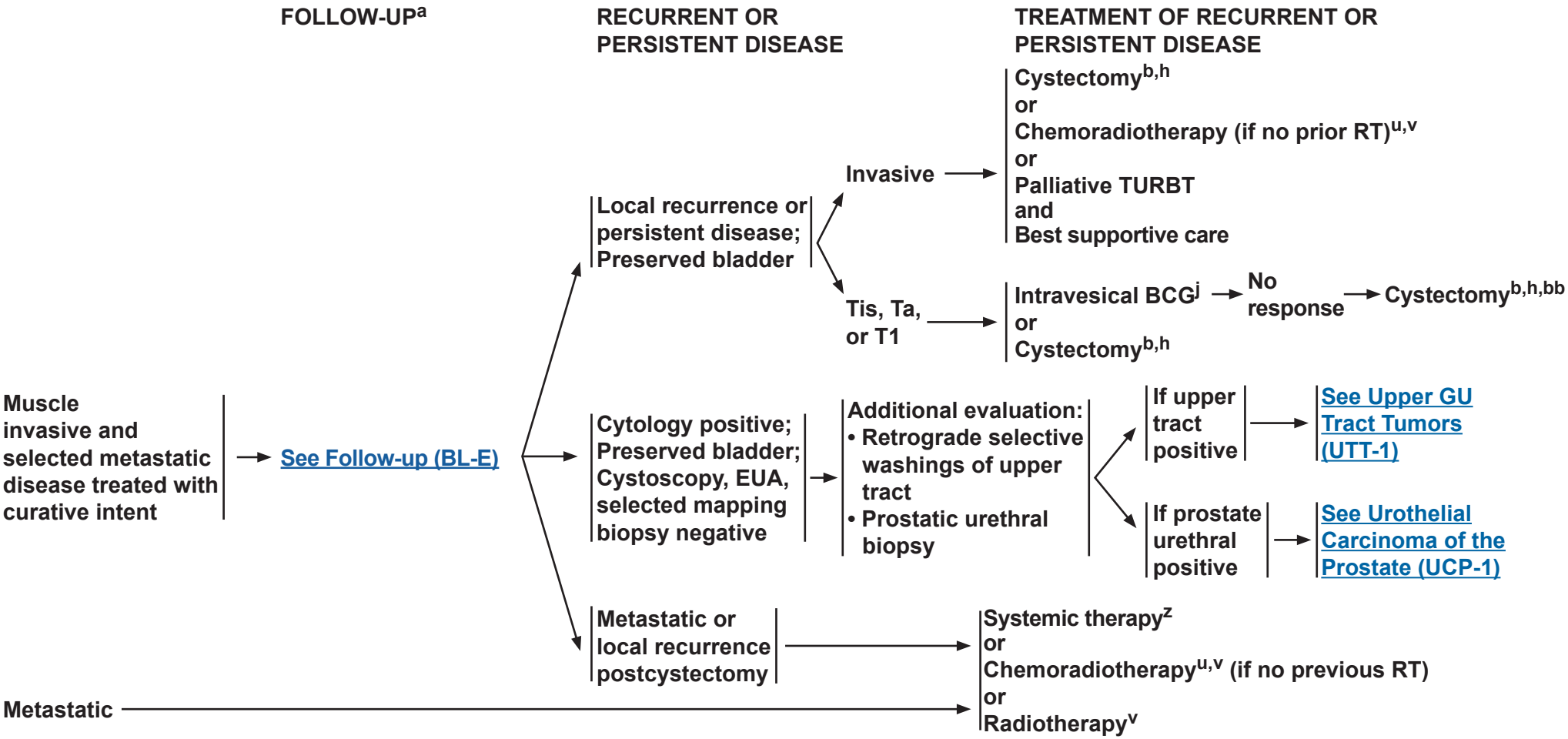

[a]See Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
[b]See Principles of Surgical Management (BL-B).
[h]See Follow-Up (BL-E).
[j]See Principles of Intravesical Treatment (BL-F).
[u]See Principles of Systemic Therapy (BL-G 3 of 4).
[v]See Principles of Radiation Management of Invasive Disease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

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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

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.[7]**

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 evaluation in patients who cannot receive either iodinated or gadolinium-based contrast material.**
  - **Ureteroscopy**
  - **Consider: In sessile or high-grade tumors, MR of the pelvis without and with IV 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.[8,9]**
- **Follow-up of NMIBC: (See BL-E)**
  - **Upper tract (CTU, MRU, or retrograde with CT or US) and abdominal/pelvic imaging at baseline. For high-risk patients, UT imaging also performed at 12 mo and every 1–2 y thereafter up to 10 y.**

Evaluation for Suspected Bone Metastasis

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

Neurologic/Brain Imaging[1,11]

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

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References on BL-A 5 of 5

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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.

Muscle Invasive Bladder Cancer

Chest Imaging

- Chest imaging may be performed with plain film radiography with posteroanterior (PA) and lateral views in early-stage disease. If an abnormality is seen, then CT of the chest may then be performed.
- Staging:[1]
  - PA and lateral chest x-ray, or
  - CT of the chest without contrast when the chest x-ray is equivocal or there is an abnormality identified on chest x-ray or in selected high-risk patients. Chest CT with IV contrast could be considered in patients undergoing concurrent imaging of the abdomen and pelvis.[2]
  - PET/CT (category 2B) may be beneficial in selected patients with T2 (muscle-invasive disease) and in patients with ≥cT3 disease. Will also include abdomen and pelvis if performed.[3-6] 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, or
  - Chest CT with IV contrast when the chest x-ray is equivocal or there is an abnormality identified on chest x-ray.
    - ◊ 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.
  - 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. 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, or
  - Chest CT with IV contrast (preferred) or when the chest x-ray is equivocal or there is an abnormality identified on chest x-ray.
    - ◊ 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.
  - PET/CT (category 2B) may be performed if not previously done or in high-risk patients in whom metastatic disease is suspected. Could also be used to guide biopsy in certain patients. PET/CT should not be used to delineate the anatomy of the upper urinary tract.

Continued on next page
References on BL-A 5 of 5

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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).[10]**
  - **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 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**
  - **PET/CT (category 2B) may be useful in selected patients with ≥cT2 disease and may change management in patients with ≥cT3 disease.[7] 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**
  - **MR of the pelvis without and with IV for local staging**
    - **May be performed in addition to CTU.**
    - **May also be performed without contrast if there is a contraindication to contrast.[7]**
- **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 up to 5 y and as indicated thereafter**
  - **PET/CT (category 2B) may be performed if not previously done or in high-risk patients in whom metastatic disease is suspected. Could also be used to guide biopsy in certain patients. PET/CT should not be used to delineate the anatomy of the upper urinary tract.**

Evaluation for Suspected Bone Metastasis

- **Symptomatic, high-risk patients or those with laboratory indicators of bone metastasis may be imaged with PET/CT (category 2B) or bone scan. 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[1,11]

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

Continued on next page

References on BL-A 5 of 5

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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.
  - Chest CT may be performed if chest x-ray equivocal or "high-risk" patients ≥T1 disease.
  - Consider abdominal CT or MRI in high-risk T1 disease or patients with ≥T2 disease.[13]
  - MR of the pelvis without and with IV 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
    - ◊ 1- to 2-year follow-up.
      - – MRI or CT of pelvis with and without IV contrast.

References on BL-A 5 of 5

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

TURBT/Maximal TURBT for Treatment

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

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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 urethra pathology.
- Postsurgical intraprostatic BCG is recommended (see Principles of Intravesical Therapy).

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

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

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

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

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PRINCIPLES OF SURGICAL MANAGEMENT

Urethrectomy

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

Regional Lymphadenectomy

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

Pelvic Exenteration (category 2B)

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

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PRINCIPLES OF PATHOLOGY MANAGEMENT

- **Classification of Urothelial Neoplasia (WHO/ISUP Consensus 2004):**
  - **Flat urothelial neoplastic lesion:**
    - ◊ **Urothelial carcinoma in situ**
  - **Papillary urothelial neoplastic lesions:**
    - ◊ **Urothelial papilloma**
    - ◊ **Papillary urothelial neoplasm of low malignant potential**
    - ◊ **Papillary urothelial carcinoma, low-grade**
    - ◊ **Papillary urothelial carcinoma, high-grade**
- **The pathology report on biopsy/TURBT specimens should specify:**
  - **If muscularis propria (detrusor muscle) is present and, if present, whether this structure is invaded by tumor**
  - **Presence or absence of lamina propria invasion**
  - **Presence or absence of lymphovascular space invasion**
  - **Presence or absence of subjacent carcinoma in situ**
- **Urothelial tumors with an inverted growth pattern should be graded similar to the WHO(2004)/ISUP system for exophytic tumors as detailed above.**
- **Variant histology should be stated if present:**
  - **Urothelial carcinoma with divergent differentiation (squamous/glandular).**
    - ◊ **Percentage of divergent differentiation may be stated. Eg, "urothelial carcinoma with glandular (35%) differentiation."**
  - **Micropapillary variant of urothelial carcinoma.**
    - ◊ **Percentage of micropapillary component should be stated. However, no percentage limitation is required for diagnosis.**
  - **Nested variant of urothelial carcinoma.**
  - **Lymphoepithelioma-like carcinoma.**
  - **Sarcomatoid carcinoma.**
  - **Undifferentiated carcinoma with trophoblastic giant cells.**
  - **Undifferentiated carcinoma (including giant cell carcinoma)**
  - **Squamous cell carcinoma (comprised almost entirely of keratin-forming squamous carcinoma)**
    - ◊ **Squamous cell carcinoma (non-verrucous and non-schistosomal)**
    - ◊ **Verrucous squamous carcinoma**
    - ◊ **Squamous cell carcinoma, associated with precedent or concurrent infection with schistosomal species.**
  - **Adenocarcinoma**
    - ◊ **Primary adenocarcinoma**
      - **– Enteric pattern (acinar, villous, cribriform, or solid)**
      - **– Mucinous or colloid carcinoma**
      - **– Signet-ring cell carcinoma**
      - **– Mixed pattern**
    - ◊ **Urachal carcinoma (majority are adenocarcinoma)**
      - **– Clear cell adenocarcinoma**
  - **Neuroendocrine carcinoma**
    - ◊ **Small cell carcinoma**
    - ◊ **Large cell neuroendocrine carcinoma**
    - ◊ **Mixed patterns**

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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 fashion 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, 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):
- 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.

References on BL-D 2 of 2

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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: Non-Muscle Invasive Bladder Cancer

Test	AUA Risk Category	Year (at month intervals)						
		1	2	3	4	5	5–10	>10
Cystoscopy	Low risk	3, 12	Annually				As clinically indicated	
	Intermediate risk	3, 6, 12	Every 6 mo	Annually			As clinically indicated	
	High risk	Every 3 mo		Every 6 mo			Annually	As clinically indicated
Imaging	Low risk	UT baseline AP baseline	As clinically indicated					
	Intermediate risk	UT baseline AP baseline	As clinically indicated					
	High risk	Consider: UT baseline, 12 AP baseline	UT every 1–2 y					As clinically indicated
Blood tests	Low risk	N/A						
	Intermediate risk							
	High risk							
Urine Tests	Low risk	N/A						
	Intermediate risk	UC 3, 6, 12	UC every 6 mo	Annually			As clinically indicated	
	High risk	UC every 3 mo Consider urinary urothelial tumor markers (category 2B)		UC every 6 mo			Annually	As clinically indicated

See Table Legend on BL-E 4 of 4
See Recurrent or Persistent Disease (BL-8)
See Post-Cystectomy or Post-Bladder Sparing (BL-E 2 of 4)

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Table 2: Post-cystectomy or Post-bladder Sparing (Partial cystectomy chemoradiation)

<table>
<tr><th rowspan="2">Test</th><th rowspan="2">Risk Category</th><th colspan="7">Year (at month intervals)</th></tr>
<tr><th>1</th><th>2</th><th>3</th><th>4</th><th>5</th><th>5-10</th><th>>10</th></tr>
<tr><td rowspan="3">Cystoscopy</td><td>Post-cystectomy NMIBC</td><td colspan="7">N/A</td></tr>
<tr><td>Post-cystectomy MIBC</td><td colspan="7">N/A</td></tr>
<tr><td>Post-bladder sparing (ie, partial cystectomy or chemoradiation)</td><td colspan="2">Every 3 mo</td><td colspan="2">Every 6 mo</td><td colspan="2">Annually</td><td>As clinically indicated</td></tr>
<tr><td colspan="9"></td></tr>
<tr><td rowspan="3">Imaging</td><td>Post-cystectomy NMIBC</td><td>AP/UT 3, 12</td><td colspan="3">AP/UT Annually</td><td colspan="2">R annually</td><td>As clinically indicated</td></tr>
<tr><td>Post-cystectomy MIBC</td><td colspan="2">AP/UT every 3–6 mo
C every 3–6 mo</td><td colspan="3">AP annually
C annually</td><td colspan="2">R annually</td><td>As clinically indicated</td></tr>
<tr><td>Post-bladder sparing (ie, partial cystectomy or chemoradiation)</td><td colspan="2">AP/UT every 3–6 months for MIBC
C every 3–6 months for MIBC</td><td colspan="3">AP annually
C annually</td><td colspan="2">As clinically indicated</td></tr>
</table>

See Table Legend on BL-E 4 of 4

See Recurrent or Persistent Disease (BL-8)

Table 2 continued on next page

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FOLLOW-UP

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Table 2 (continued): Post-cystectomy or Post-bladder sparing (Partial cystectomy chemoradiation)

Test	Risk Category	Year (at month intervals)						
		1	2	3	4	5	5-10	>10
Blood tests	Post-cystectomy NMIBC or Post-cystectomy MIBC	• R every 3–6 mo • LFT every 3–6 mo • CBC, CMP every 3–6 mo if received chemotherapy	• R annually • LFT annually • B12 annually				As clinically indicated	
	Post-bladder sparing (ie, partial cystectomy or chemoradiation)	• R every 3–6 mo • LFT every 3-6 mo • CBC, CMP every 3–6 mo if received chemotherapy	R as clinically indicated LFT as clinically indicated					
Urine Tests	Post-cystectomy NMIBC Intermediate risk	UC every 6–12 mo Consider UW every 6–12 mo*	UC as clinically indicated UW as clinically indicated					
	Post-bladder sparing (ie, partial cystectomy or chemoradiation)	UC every 6–12 mo	UC as clinically indicated					

See Table Legend on BL-E 4 of 4

See Recurrent or Persistent Disease (BL-8)

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FOLLOW-UP

Table Legend

Imaging studies:
UT = upper tract imaging: CT urography, MR urography, IVP, retrograde pyelography, or ureteroscopy
AP = abdominal-pelvic imaging: CT, MRI, or PET/CT (PET/CT not recommended for NMIBC)
AP/UT = CT urography or MR urography (image upper tracts + axial imaging of abdomen/pelvis)
R = renal imaging to look for hydronephrosis: renal ultrasound
C = chest imaging: Chest x-ray (preferred), CT chest, or PET/CT

Blood tests:
B = bone testing: calcium, magnesium, phosphate, alkaline phosphatase
CMP = complete metabolic panel
LFT = liver function testing: AST, ALT, bilirubin, alkaline phosphatase
R = renal function testing: electrolytes, creatinine

Urine tests:
UC = urine cytology, done at time of cystoscopy if bladder in situ
UA = urinalysis (to assess for microhematuria)
UW = urethral wash cytology, reserved for high-risk patients: positive urethral margin, multifocal CIS, prostatic urethral invasion

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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

- Consider for patients following initial TURBT. See Clinical Presentation and Initial Evaluation (BL-1)
- The most commonly used agent is mitomycin.
- Initiated within 24 hours after TURBT.
- Treatment should not be given if extensive TURBT or if suspected bladder perforation.
- Immediate intravesical chemotherapy, not BCG, has been shown to decrease recurrence in select subgroups of patients.

Induction (Adjuvant) Intravesical Chemotherapy or BCG

- Treatment option for NMIBC (See BL-2, BL-3, and BL-8).
- The most commonly used agents are BCG, mitomycin, and gemcitabine.
- Initiated 3–4 weeks after TURBT with or without maintenance.
- Weekly instillations during induction are given for approximately 6 weeks.
- Maximum of 2 consecutive cycles 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 three weekly instillations at months 3, 6, 12, 18, 24, 30, and 36.[1]
- 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.[1]

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Note: 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.

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)**
- **Initiated 3–4 weeks after TURP**
- **Induction (adjuvant) BCG should be followed with maintenance BCG**
- **Data indicate a reduction in recurrence in the prostate in patients with superficial disease[2-8]**

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 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 Intrapelvic Therapy for Upper Tract Tumors

- **Consider for patients with non-metastatic, low-grade tumors of the renal pelvis. See Upper Tract Tumors: Renal Pelvis (UTT-1)**
- **Induction (adjuvant) therapy initiated 3–4 weeks after endoscopic resection**
- **The most commonly used agents are BCG, mitomycin C, and gemcitabine**
- **Role of maintenance in this context is uncertain**
- **Efficacy of this treatment in upper urinary tract cancer has not been established[9-11]**

References on BL-F 3 of 3

Note: All recommendations are category 2A unless otherwise indicated.
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PRINCIPLES OF INTRAVESICAL TREATMENT

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PRINCIPLES OF SYSTEMIC THERAPY

Perioperative chemotherapy (neoadjuvant or adjuvant)

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

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

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References on BL-G 4 of 4

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PRINCIPLES OF SYSTEMIC THERAPY

First-line chemotherapy for locally advanced or metastatic disease

	Standard regimens	Alternate regimens for select patients
Cisplatin eligible	• Gemcitabine and cisplatin[4] (category 1) • DDMVAC with growth factor support (category 1)[2,8]	
Cisplatin ineligible with poor kidney function or poor PS	• Gemcitabine and carboplatin[11]	• Gemcitabine[12] • Gemcitabine and paclitaxel[13]
Cisplatin ineligible due to hearing/ neuropathy but with good kidney function, and good PS		• Ifosfamide, doxorubicin, and gemcitabine[14]

- The presence of both visceral metastases and ECOG performance score ≥2 strongly predict poor outcome with chemotherapy. Patients without these adverse prognostic factors have the greatest benefit from chemotherapy.
- For most patients, the risks of adding paclitaxel to gemcitabine and cisplatin outweigh the limited benefit seen in the randomized trial.[15]
- A substantial proportion of patients cannot receive cisplatin-based chemotherapy due to renal impairment or other comorbidities.
  - Participation in clinical trials of new or more tolerable therapy is recommended.

Subsequent systemic therapy for locally advanced or metastatic disease

- Participation in clinical trials of new agents is recommended.

Standard regimens	Alternate regimens for select patients
• Atezolizumab[16] • Nivolumab[17] • Paclitaxel or docetaxel[18] • Gemcitabine[12] • Pemetrexed[19]	• Nab-paclitaxel[20] • Ifosfamide[21] • Methotrexate • Ifosfamide, doxorubicin, and gemcitabine[14] • Gemcitabine and paclitaxel[13] • Gemcitabine and cisplatin[4] • DDMVAC[2]

Continued on BL-G 3 of 4

References on BL-G 4 of 4

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PRINCIPLES OF SYSTEMIC THERAPY

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

- **First-line chemotherapy**

Standard regimens (doublet chemotherapy is preferred)	Alternate regimens
• Cisplatin[a] and 5-FU[22] • Cisplatin[a] and paclitaxel[22,23] • 5-FU and mitomycin[24]	• Cisplatin[a] alone[25] • Low-dose gemcitabine[26,27] (category 2B)

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

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

References on BL-G 4 of 4

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

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PRINCIPLES OF SYSTEMIC THERAPY

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PRINCIPLES OF RADIATION MANAGEMENT OF INVASIVE DISEASE

Carcinoma of the Bladder:

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

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PRINCIPLES OF RADIATION MANAGEMENT OF INVASIVE DISEASE

Carcinoma of the Urethra:

- **Data support the use of radiation therapy for urothelial carcinoma and squamous cell carcinoma of the urethra (case series and experience treating these carcinomas arising from other disease sites); radiation can also be considered for adenocarcinomas of the urethra.**
- **Definitive Radiation Therapy (organ preservation)**
  - **cT2 cN0**
    - ◊ **66 to 70 Gy EBRT delivered to gross disease with a margin to encompass areas of potential microscopic spread. Concurrent chemotherapy with regimens used for bladder cancer is encouraged for added tumor cytotoxicity.**
    - ◊ **Strongly consider prophylactic radiation treatment of regional-nodal basins (inguinal and low pelvic nodes for female and distal male tumors; pelvic lymph nodes for proximal male tumors).**

  - **cT3-T4, or lymph node positive**
    - ◊ **45 to 50.4 Gy EBRT delivered to gross disease with a margin to encompass areas of microscopic spread and to regional-nodal basins (inguinal and low pelvic nodes for female and distal male tumors; pelvic lymph nodes for proximal male tumors). Boost gross primary disease to 66 to 70 Gy and gross nodal disease to 54 to 66 Gy, if feasible. Dose delivered to gross nodal disease may be limited secondary to normal tissue dose constraints. Concurrent chemotherapy should be administered for added tumor cytotoxicity.**

  - **Postoperative Adjuvant Radiation Therapy**
    - ◊ **Treatment field should encompass areas at risk for harboring residual microscopic disease based on pathologic findings at resection and may include resection bed, inguinal lymph nodes, and pelvic lymph nodes. Areas at risk for harboring residual microscopic disease should receive 45 to 50.4 Gy EBRT. Involved resection margins and areas of extranodal extension should be boosted to 54 to 60 Gy if feasible based on normal tissue constraints. Areas of gross residual disease should be boosted to 66 to 70 Gy, if feasible based on normal tissue constraints. Concurrent chemotherapy with regimens used for bladder cancer should be considered for added tumor cytotoxicity.**

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PRINCIPLES OF RADIATION MANAGEMENT OF INVASIVE DISEASE

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Upper GU Tract Tumors

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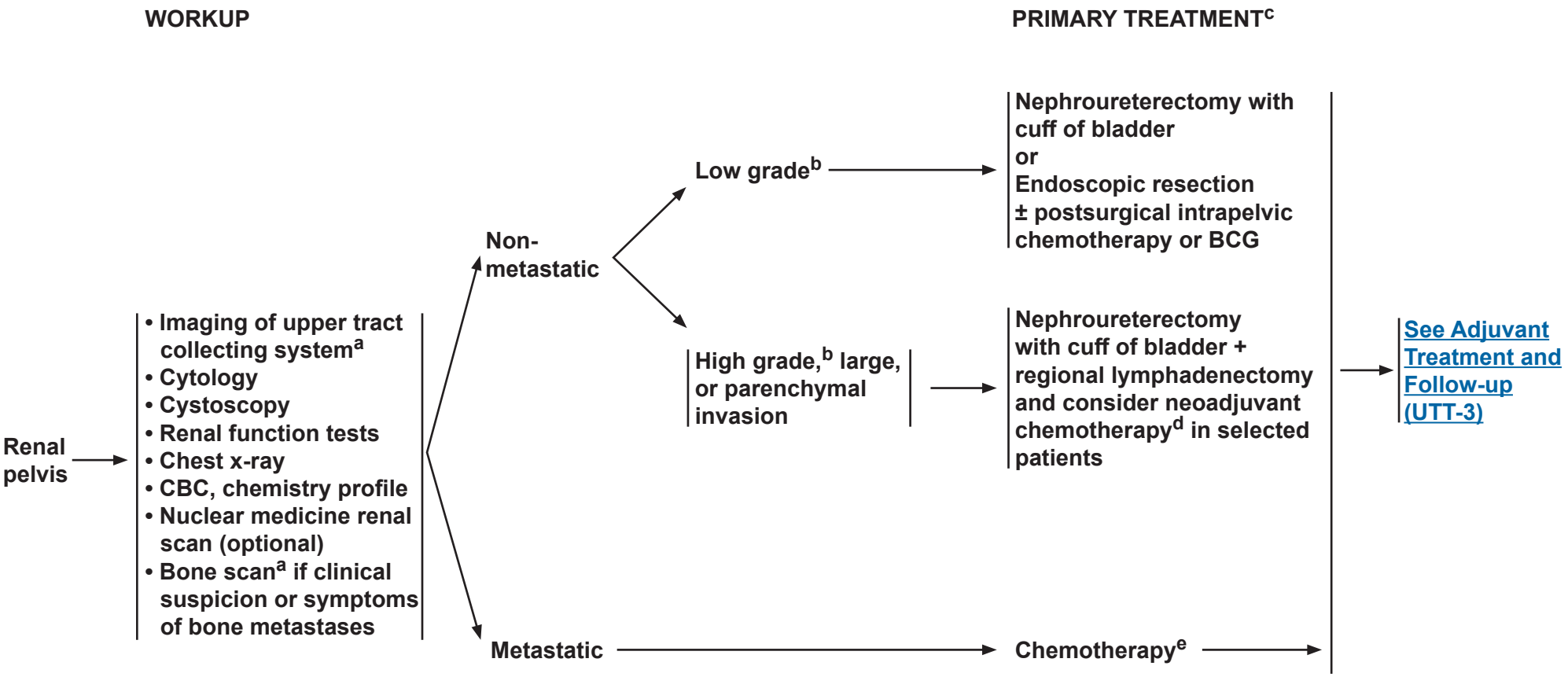

[a] See Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
[b] Montironi R, Lopez-Beltran A. The 2004 WHO classification of bladder tumors: A summary and commentary. Int J Surg Pathol 2005;13:143-153.
See Principles of Pathology Management (BL-C).
[c] See Principles of Surgical Management (PN-B).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

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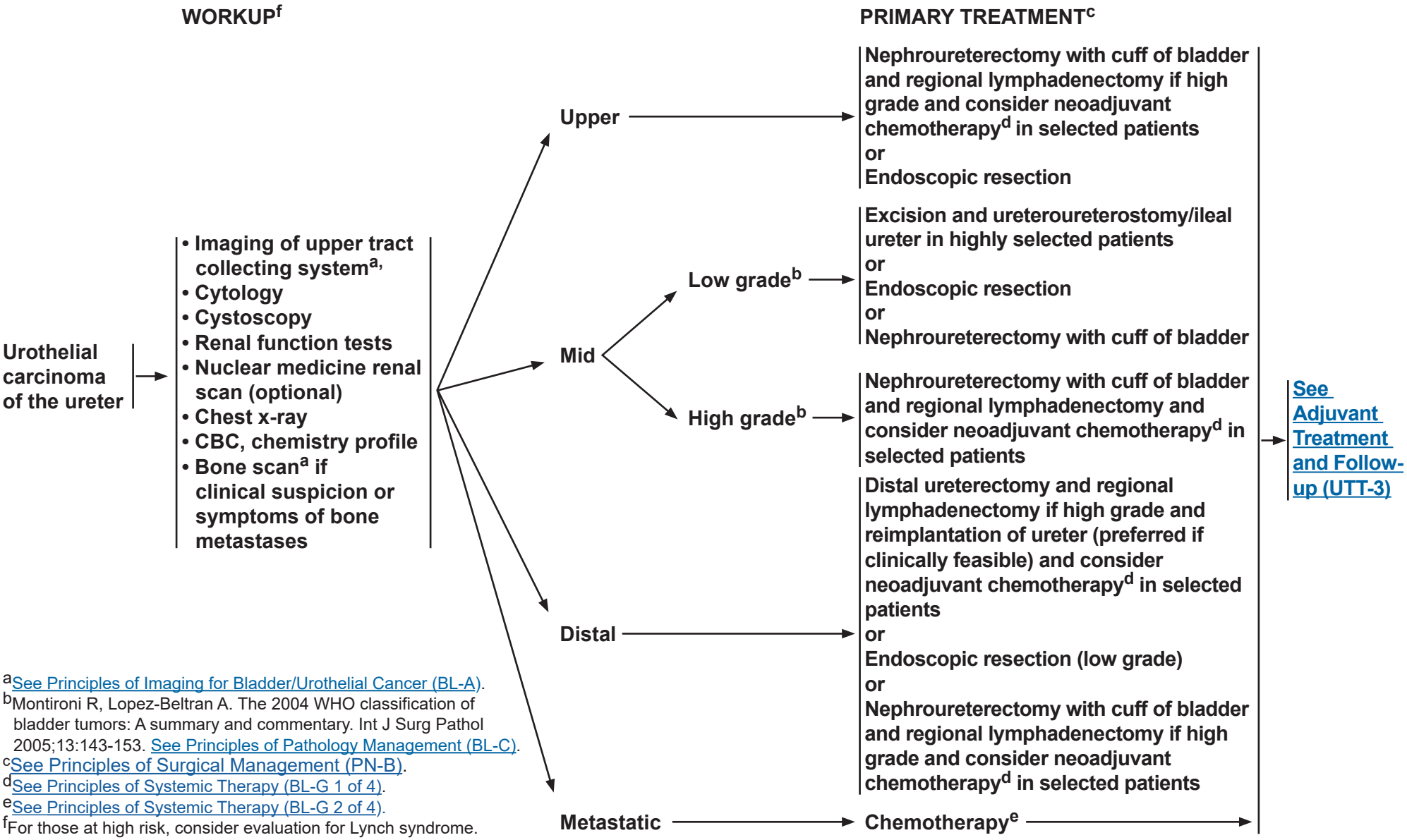

[a] See Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
[b] Montironi R, Lopez-Beltran A. The 2004 WHO classification of bladder tumors: A summary and commentary. Int J Surg Pathol 2005;13:143-153. See Principles of Pathology Management (BL-C).
[c] See Principles of Surgical Management (PN-B).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

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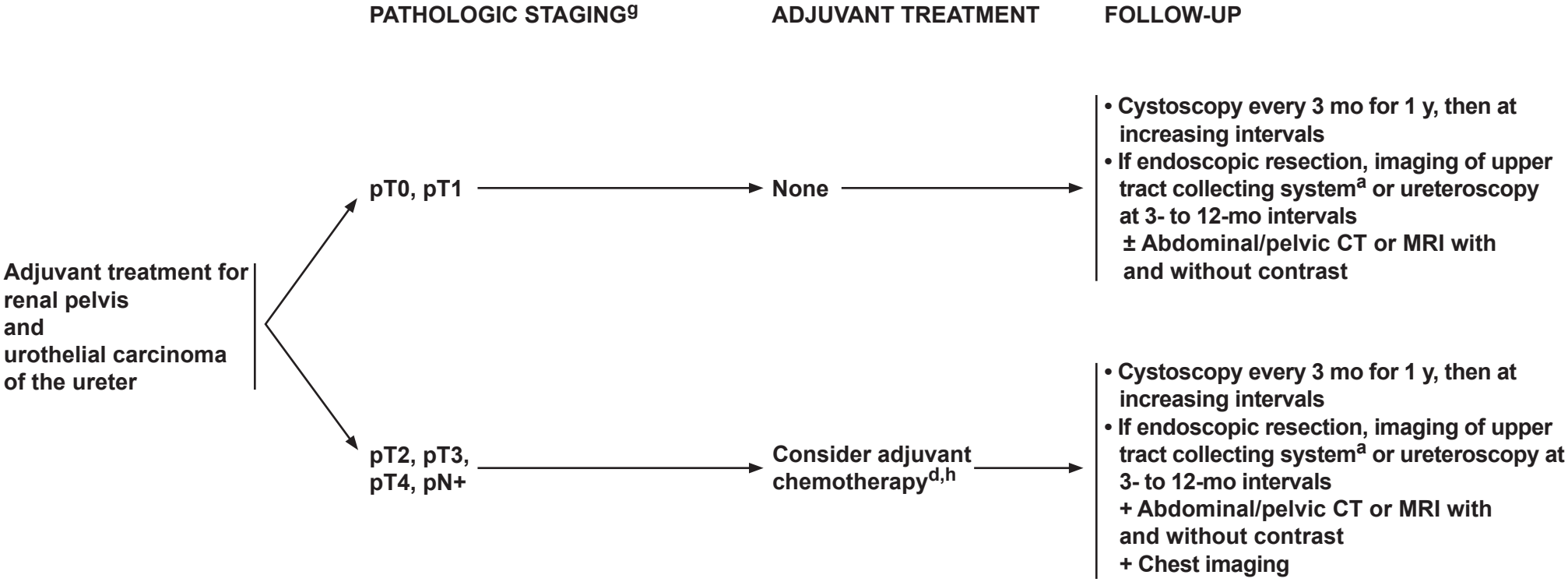

[a] See Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
[d] See Principles of Systemic Therapy (BL-G 1 of 4).
[g] The modifier "p" refers to pathologic staging based on cystectomy and lymph node dissection.
[h] Follow recommendations for adjuvant chemotherapy after ensuring that patient is fully staged to rule out metastatic disease.

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Urothelial Carcinoma of the Prostate

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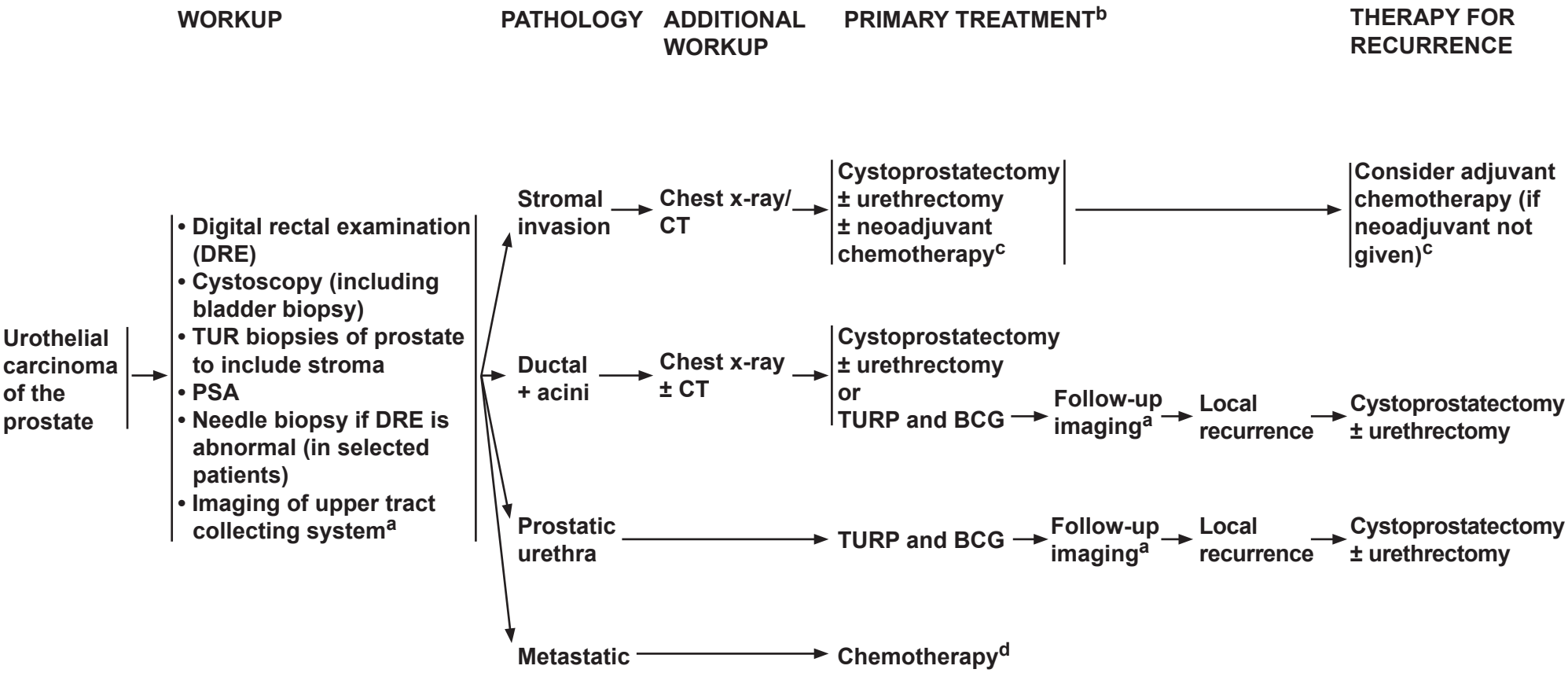

[a] See Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
[b] See Principles of Surgical Management (PN-B).
[c] See Principles of Systemic Therapy (BL-G 1 of 4).
[d] Principles of Systemic Therapy (BL-G 2 of 4).

Note: 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.

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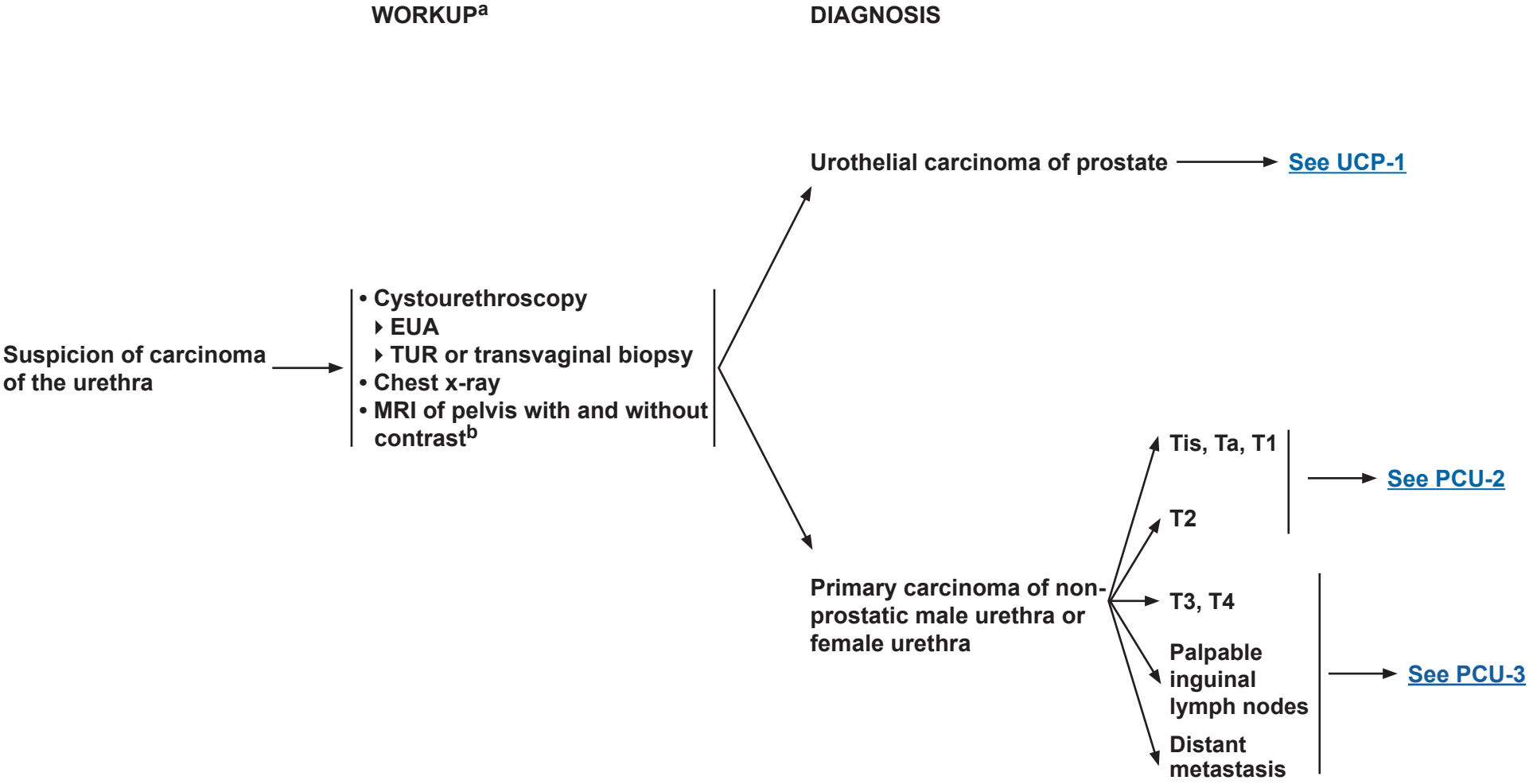

[a]Referral to a specialized center is recommended.
[b]See Principles of Imaging for Bladder/Urothelial Cancer (BL-A).

Note: 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.

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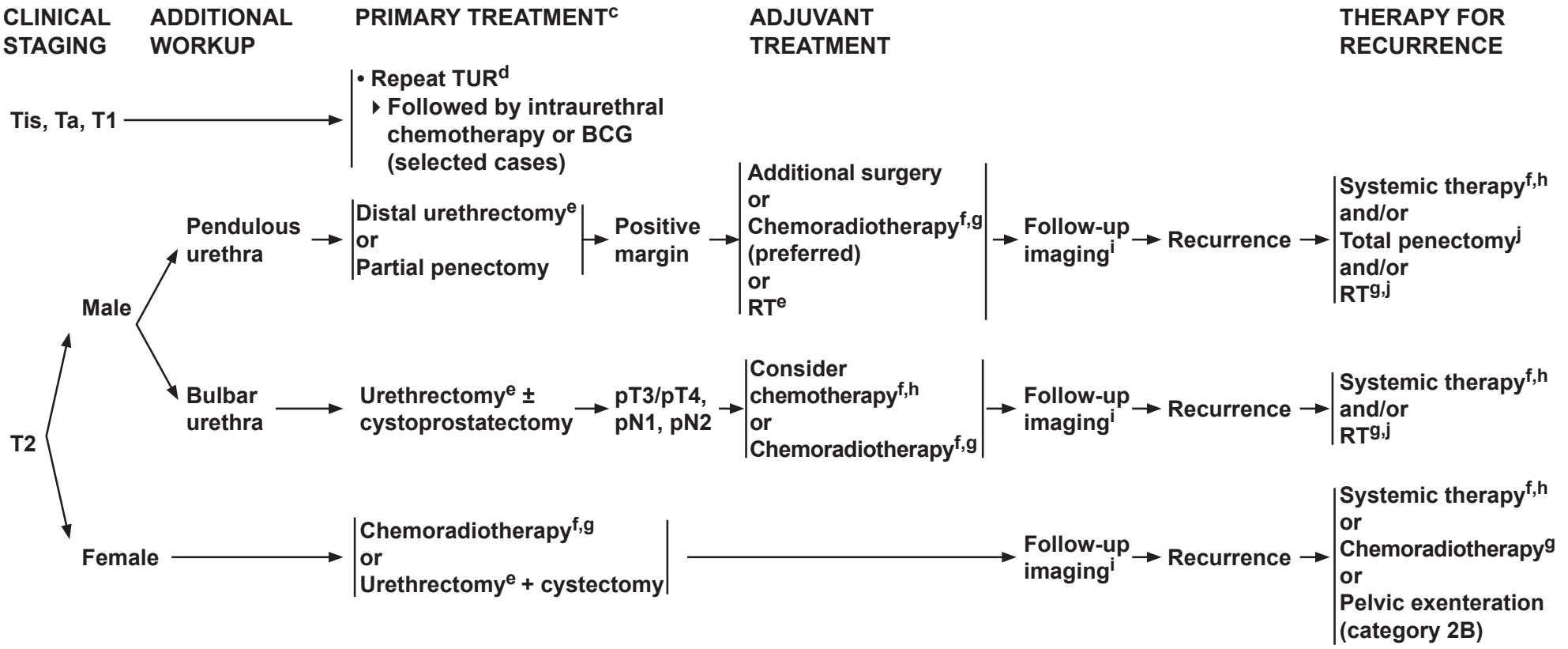

[c] See Principles of Surgical Management (PN-B).
[d] In patients with a prior radical cystectomy or a cutaneous diversion, consider a total urethrectomy.
[e] Consider neoadjuvant chemotherapy (category 2B) or chemoradiation.
[f] See Principles of Systemic Therapy (BL-G). Also see Non-Urothelial Cell and Urothelial with Variant Histology (BL-D).
[g] See Principles of Radiation Management of Invasive Disease-Carcinoma of Urethra (BL-H 2 of 3).
[h] 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.)
[i] See Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
[j] Consider for local recurrence (± chemotherapy).

Note: 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.

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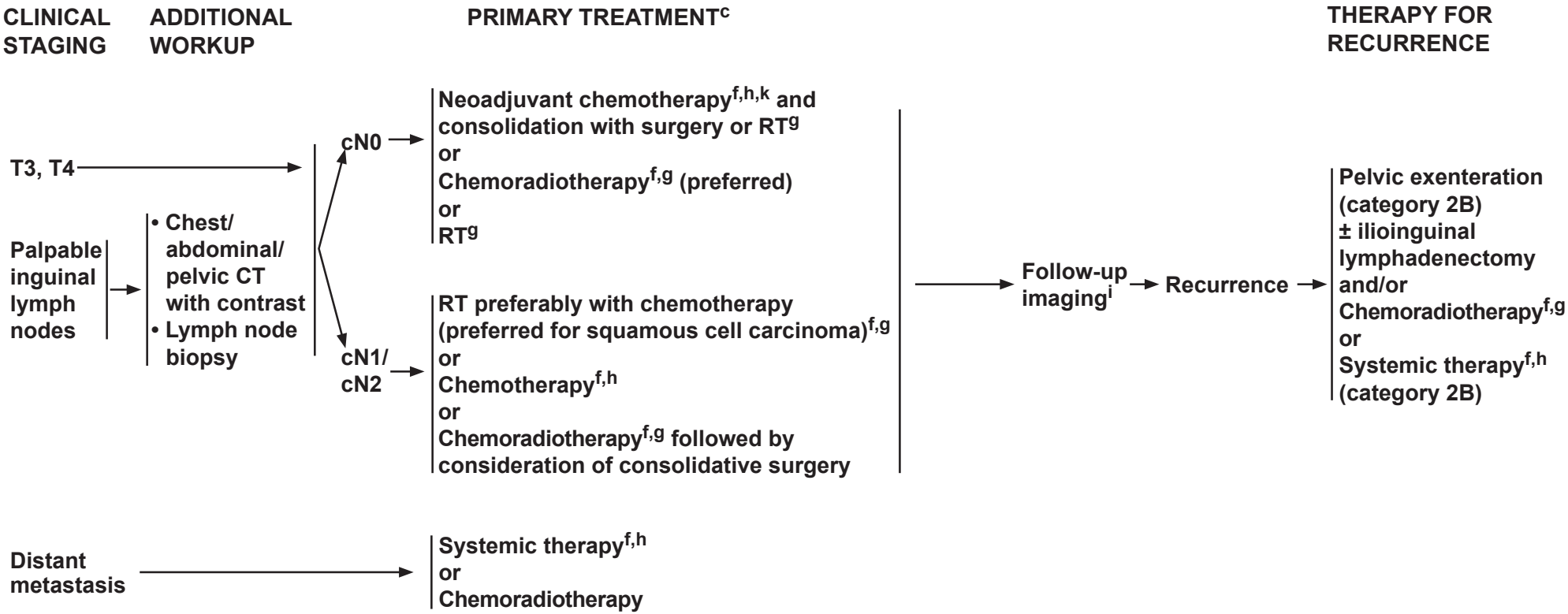

[c] See Principles of Surgical Management (PN-B).
[f] See Principles of Systemic Therapy (BL-G). Also see Non-Urothelial Cell and Urothelial with Variant Histology (BL-D).
[g] See Principles of Radiation Management of Invasive Disease-Carcinoma of Urethra (BL-H 2 of 3).
[h] Chemotherapy regimen based 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.)
[i] See Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
[k] Data support neoadjuvant chemotherapy only for urothelial carcinoma.

Note: 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.

NCCN Guidelines Version 2.2017 Staging
Bladder Cancer

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Table 1

American Joint Committee on Cancer (AJCC)
TNM Staging System for Bladder Cancer (7th ed., 2010)

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Noninvasive papillary carcinoma
Tis	Carcinoma in situ: "flat tumor"
T1	Tumor invades 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	Tumor invades any of the following: prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
T4a	Tumor invades prostatic stroma, uterus, vagina
T4b	Tumor invades pelvic wall, abdominal wall

Regional Lymph Nodes (N)

Regional lymph nodes include both primary and secondary drainage regions. All other nodes above the aortic bifurcation are considered distant lymph nodes.

NX	Lymph nodes cannot be assessed
N0	No lymph node metastasis
N1	Single regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node)
N2	Multiple regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node metastasis)
N3	Lymph node metastasis to the common iliac lymph nodes

Distant Metastasis (M)

M0	No distant metastasis
M1	Distant metastasis

ANATOMIC STAGE/PROGNOSTIC GROUPS

Stage 0a	Ta	N0	M0
Stage 0is	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2a	N0	M0
	T2b	N0	M0
Stage III	T3a	N0	M0
	T3b	N0	M0
	T4a	N0	M0
Stage IV	T4b	N0	M0
	Any T	N1-3	M0
	Any T	Any N	M1

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science+Business Media, LLC (SBM). (For complete information and data supporting the staging tables, visit www.springer.com.) Any citation or quotation of this material must be credited to the AJCC as its primary source. The inclusion of this information herein does not authorize any reuse or further distribution without the expressed, written permission of Springer SBM, on behalf of the AJCC.

Table 1 (Continued)

American Joint Committee on Cancer (AJCC) TNM Staging System for Bladder Cancer (7th ed., 2010)

Clinical Staging

Primary tumor assessment includes bimanual examination under anesthesia before and after endoscopic surgery (biopsy or transurethral resection) and histologic verification of the presence or absence of tumor when indicated. Bimanual examination following endoscopic surgery is an indicator of clinical stage. The finding of bladder wall thickening, a mobile mass, or a fixed mass suggests the presence of T3 and/or T4 disease, respectively. Appropriate imaging techniques for extravesical extension of the primary tumor and lymph node evaluation should be incorporated into clinical staging. When indicated, evaluation for distant metastases includes imaging of the chest, biochemical studies, and isotopic studies to detect common metastatic sites.

Pathologic Staging

Microscopic examination and confirmation of extent are required. Total cystectomy and lymph node dissection generally are required for this staging; however, a pathologic staging classification should be given for partial cystectomy specimens. Laterality does not affect the N classification.

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

If a grading system is not specified, generally the following system is used:

GX Grade cannot be assessed
G1 Well differentiated
G2 Moderately differentiated
G3 Poorly differentiated
G4 Undifferentiated

Histopathologic Type

The histologic types are as follows:

Urothelial (transitional cell) carcinoma
- In situ
- Papillary
- Flat
- With squamous differentiation
- With glandular differentiation
- With squamous and glandular differentiation

Squamous cell carcinoma
Adenocarcinoma
Undifferentiated carcinoma

The predominant cancer is urothelial (transitional cell) carcinoma. Histologic variants include micropapillary and nested subtypes.

Table 2

American Joint Committee on Cancer (AJCC)
TNM Staging System for Renal Pelvis and Ureter Cancer (7th ed., 2010)

Primary Tumor (T)

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 T3. (For ureter only) Tumor invades beyond muscularis into periureteric fat
T4	Tumor invades adjacent organs, or through the kidney into the perinephric fat.

Regional Lymph Nodes (N)*

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node, 2 cm or less in greatest dimension
N2	Metastasis in a single lymph node, more than 2 cm but not more than 5 cm in greatest dimension; or multiple lymph nodes, none more than 5 cm in greatest dimension
N3	Metastasis in a lymph node, more than 5 cm in greatest dimension

* Note: Laterality does not affect the N classification.

Distant Metastasis (M)

M0	No distant metastasis
M1	Distant metastasis

ANATOMIC STAGE/PROGNOSTIC GROUPS

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	N0	M0
	Any T	N1	M0
	Any T	N2	M0
	Any T	N3	M0
	Any T	Any N	M1

Table 2 (Continued)

American Joint Committee on Cancer (AJCC)
TNM Staging System for Renal Pelvis and Ureter Cancer (7th ed., 2010)

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

If a grading system is not specified, generally the following system is used:

GX Grade cannot be assessed
G1 Well differentiated
G2 Moderately differentiated
G3 Poorly differentiated
G4 Undifferentiated

Histopathologic Type
The histologic types are as follows:

Urothelial (transitional cell) carcinoma
- In situ
  - Papillary
  - Flat
  - With squamous differentiation
  - With glandular differentiation
  - With squamous and glandular differentiation

Squamous cell carcinoma
Adenocarcinoma
Undifferentiated carcinoma

The predominant cancer is urothelial (transitional cell) carcinoma.
Histologic variants include micropapillary and nested subtypes.

Table 3

American Joint Committee on Cancer (AJCC)
TNM Staging System for Urethral Carcinoma (7th ed., 2010)

Primary Tumor (T) (Male and Female)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Noninvasive papillary, polypoid, or verrucous carcinoma
Tis	Carcinoma in situ
T1	Tumor invades subepithelial connective tissue
T2	Tumor invades any of the following: corpus spongiosum, prostate, periurethral muscle
T3	Tumor invades any of the following: corpus cavernosum, beyond prostatic capsule, anterior vagina, bladder neck
T4	Tumor invades other adjacent organs

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node 2 cm or less in greatest dimension
N2	Metastasis in a single node more than 2 cm in greatest dimension, or in multiple nodes

Distant Metastasis (M)

M0	No distant metastasis
M1	Distant metastasis

Urothelial (Transitional Cell) Carcinoma of the Prostate

Tis pu	Carcinoma in situ, involvement of the prostatic urethra
Tis pd	Carcinoma in situ, involvement of the prostatic ducts
T1	Tumor invades urethral subepithelial connective tissue
T2	Tumor invades any of the following: prostatic stroma, corpus spongiosum, periurethral muscle
T3	Tumor invades any of the following: corpus cavernosum, beyond prostatic capsule, bladder neck (extraprostatic extension)
T4	Tumor invades other adjacent organs (invasion of the bladder)

ANATOMIC STAGE/PROGNOSTIC GROUPS

Stage 0a	Ta	N0	M0
Stage 0is	Tis	N0	M0
	Tis pu	N0	M0
	Tis pd	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

Table 3 (Continued)

American Joint Committee on Cancer (AJCC)
TNM Staging System for Urethral Carcinoma (7th ed., 2010)

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

If a grading system is not specified, generally the following system is used:

GX Grade cannot be assessed
G1 Well differentiated
G2 Moderately differentiated
G3 Poorly differentiated
G4 Undifferentiated

Histopathologic Type
The classification applies to urothelial (transitional cell), squamous, and glandular carcinomas of the urethra and to urothelial (transitional cell) carcinomas of the prostate and prostatic urethra. There should be histologic or cytologic confirmation of the disease.

Discussion

NCCN Categories of Evidence and Consensus

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

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

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

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

All recommendations are category 2A unless otherwise noted.

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Overview

An estimated 79,030 new cases of urinary bladder cancer (60,490 men and 18,540 women) will be diagnosed in the United States in 2017 with approximately 16,870 deaths (12,240 men and 4630 women) occurring during this same period.[1] Bladder cancer, the sixth most common cancer in the United States,[1] is rarely diagnosed in individuals younger than 40 years of age. Given that the median age at diagnosis is 65 years, medical comorbidities are a frequent consideration in patient management.

The clinical spectrum of bladder cancer can be divided into 3 categories that differ in prognosis, management, and therapeutic aims. The first category consists of non-muscle-invasive 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 quality of life. Numerous agents with different mechanisms of action have antitumor effects on this disease. The issue remains 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 published between August 20, 2014 and September 8, 2016**,** using the following search terms: bladder cancer OR urothelial carcinoma OR urothelial carcinoma of the ureter OR upper genitourinary tract tumor OR renal pelvic tumor OR urothelial carcinoma of the prostate OR primary carcinoma of the urethra. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.[2]

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial; Guideline; Meta-Analysis; Randomized Controlled Trial; Systematic Reviews; and Validation Studies.

The PubMed search resulted in 378 citations and their potential relevance was examined. 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 on the NCCN webpage.

Clinical Presentation and Workup

The most common presenting symptom in patients with bladder cancer is microscopic or gross hematuria, although urinary frequency from 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 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 pyelogram; 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 chemotherapy within 24 hours of TURBT should be considered if non-invasive disease is suspected (see *Intravesical Chemotherapy)*. Although there is no standard for immediate perioperative intravesical chemotherapy, mitomycin is most commonly used.

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, selected mapping biopsies and transurethral biopsy of prostate may be considered.

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 American Joint Committee on Cancer (AJCC)[3] (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 70% 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%).[4,5] 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.[6] 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 criteria 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.

Adjuncts to Traditional White Light 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 hem-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.[7-12] 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.[13] 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[14], 1345 patients with Ta, T1 or CIS disease showed improved detection of bladder tumors and a reduction in recurrence.[14] 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.[15]

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).[16] 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.[15] The limitations of BLC require judicious application of this additional diagnostic tool.

Narrow Band Imaging

NBI uses two narrow bands of light at 415nm and 540nm 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.[17-21]

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 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).[22] However, the small number of

patients in this study is limiting. An international multicenter randomized controlled trial to address the role of NBI was initiated in 2010,[23] though data are not yet available.

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. However, the current implementation of NBI into routine practice is hindered by the increase in false positives and the lack of data for long-term clinical benefit. Furthermore, technical expertise may limit its application. Additional studies are needed to provide insight into the role of NBI.

Histology

More than 90% of urothelial tract 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 non-invasive 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. 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.[24] Two review articles highlight the changes between the third and fourth additions of this classification.[25,26] The presence of histologic variants in urothelial carcinoma should be documented as data suggest that the subtype may reflect the risk of disease progression 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.[27] 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, urachal carcinomas, epithelial tumors of the upper urinary tract, and tumors arising in a bladder diverticulum. Glandular neoplasms include adenocarcinoma and villous adenoma. Adenocarcinomas often occur in the dome of the bladder in the embryonal remnant of the urachus or in the periurethral tissues. Tumors arising within the genitourinary tract but not of urothelial origin (eg, tumors of müllerian type, melanocytic tumors, mesenchymal tumors) are beyond the scope of these guidelines.

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. 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, not immunotherapy, has been shown to decrease recurrence in select subgroups of patients. A meta-analysis of 7 randomized trials demonstrated a decreased risk of recurrence by 11% (from 48% down to 37%) following immediate postoperative intravesical chemotherapy in patients having either single or multiple tumors.[28] Later studies had mixed results, with two reporting a decrease in recurrence and one finding no advantage.[29-31]

The most commonly used agent is mitomycin. For tumors with a low risk of progression, immediate instillation of chemotherapy may be the only treatment given and data show a decrease in recurrence in these patients. For tumors with an intermediate or high risk of progression, subsequent treatment with intravesical induction (adjuvant) therapy may be given. There are no studies that have evaluated whether the immediate instillation of chemotherapy in these patients provides an additional reduction in progression or recurrence. 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.[32] The most commonly used chemotherapy agents are mitomycin C and gemcitabine.

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.[33] 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.[34-37] 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.[38] 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.[39]

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.[40] 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.[41] Long-term data comparing BCG to epirubicin in combination with interferon[41,42] in patients with T1 disease showed a better reduction in recurrence with BCG; however, no differences in progression or adverse events were seen.[42] 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.[43] The 3-week timing of BCG has shown improved outcomes compared with epirubicin[42] or isoniazid.[41] 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.[44] 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.[45] 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.[32,34,35,43,46,47]

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.[48] 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.[48] However, the side effects are treatable in almost all cases[49] 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 adverse events.[50,51]

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.[52] 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 BCG was effective, side effects were not reduced. Conversely, other publications suggest that the one-third dose may reduce side effects.[53-55] 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.

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 observation and to strongly consider administering a single dose of immediate intravesicular chemotherapy within 24 hours of resection. The immediate intravesical chemotherapy may be followed by 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.[6] Meta-analyses have confirmed the efficacy of adjuvant intravesical chemotherapy in reducing the risk of recurrence.[56,57] 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.[58] 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.[59] Repeat resection is recommended if there is incomplete resection, or should be strongly considered if there is no muscle in the specimen.

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.[34-37] 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.[60] 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.[61] 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.[62]

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.[63,64]

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. If the patient is unable to tolerate BCG, intravesical chemotherapy may be considered, but data supporting this approach are limited.

Surveillance

Consideration may be given to FDA-approved urinary biomarker testing by fluorescence in situ hybridization (FISH) or nuclear matrix protein 22 in monitoring for recurrence.[65,66]

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 increasing 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.[67] Most of these tests have a better sensitivity for detecting bladder cancer than urinary cytology, but specificity is lower. 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.

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 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 increasing 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.[68] 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.[69]

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.[70] 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 Genitourinary Tract Tumors*).

If the transurethral biopsies of the bladder, prostate, and upper tract are negative, follow-up at 3 months and then at increasing 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 and a bone scan in patients with symptoms or clinical suspicion of bone metastasis (eg, elevated alkaline phosphatase). Imaging studies help assess the extent of local tumor invasion and the spread to lymph nodes or distant organs.[71] An abdominal/pelvic CT or MRI may be used to assess local invasion if not previously done. 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 required for muscle-invasive tumors. Different treatment modalities are discussed below. These include radical cystectomy, partial cystectomy, neoadjuvant or adjuvant therapy, bladder-preserving approaches, and chemotherapy for advanced disease.

Radical Cystectomy

The appropriate surgical procedure involves a cystoprostatectomy in men and a cystectomy and commonly a hysterectomy in women, followed by the formation of a urinary diversion. 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, with drainage to the abdominal wall or the urethra. Relative contraindications to urethral drainage include Tis in the prostatic ducts or positive urethral margin. Orthotopic diversion or a neobladder provides bladder function similar to that of a native bladder with some increased risk for nighttime incontinence or urinary retention requiring intermittent self-catheterization.

Unfortunately, the accuracy of the staging cystoscopy and TURBT is modest, with under-staging frequently encountered. 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 is associated with better survival and a lower pelvic recurrence rate.[72-76] 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 approximately 5% of cases, an initial invasive tumor develops in an area of the bladder where an adequate margin of soft tissue and a minimum of 2 cm 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.

Similar to radical cystectomy, partial cystectomy begins with a laparotomy (intraperitoneal) and resection of the pelvic lymph nodes. 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), 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 T2, T3, and T4a lesions.[77-82] In a SWOG randomized trial of 307 patients with muscle-invasive disease, radical cystectomy alone versus 3 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.[77] Another trial randomized 196 patients with invasive bladder cancer to 2 cycles of neoadjuvant MVAC before radical cystectomy or cystectomy only.[83] Neoadjuvant chemotherapy resulted in more patients achieving pT0 than cystectomy alone (34% vs. 9%; $P < .01$). OS was higher in the neoadjuvant group, although it did not reach statistical significance.[83] In a meta-analysis of 11 trials involving 3005 patients, cisplatin-based multi-agent neoadjuvant chemotherapy was associated with improved 5-year OS and DFS (5% and 9% absolute improvement, respectively).[84]

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 dosing of MVAC (11% vs. 25%; 2-sided $P = .006$).[85] 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.[86] 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 start of chemotherapy.[86] A separate single-arm phase II study also reported pathologic downstaging in 49% of patients receiving neoadjuvant ddMVAC with a similar safety profile.[87] 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.[88] 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.[82]

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,[89-91] but no randomized comparisons of adequate sample size have definitively shown a survival benefit in large part due to poor accrual.[92] 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.[93-95] 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 undergo chemotherapy, which is not typical of more contemporary series. Many 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.[96] Interestingly, the follow-up analysis included 3 more studies for a total of 9 trials (N = 945 patients).[91] 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.[91] An observational study evaluated 5653 patients of which 23% received adjuvant chemotherapy post-cystectomy.[90] Patients who received adjuvant chemotherapy had an improved OS (HR, 0.70; 95% CI, 0.06–0.76).[90] 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 Panel strengthened the recommendations for neoadjuvant chemotherapy for patients with cT2, cT3, and cT4a bladder cancer and for adjuvant chemotherapy for patients with pT3 or pT4 disease or positive nodes (see *cT2 Primary and Adjuvant Treatment* and *cT3, cT4a Primary and Adjuvant Treatment* in the algorithm). Neoadjuvant chemotherapy followed by radical cystectomy is a category 1 recommendation. Patients with hearing loss or neuropathy, poor performance status, or renal insufficiency may not be eligible for cisplatin-based chemotherapy. If neoadjuvant cisplatin-based chemotherapy cannot be given, neoadjuvant chemotherapy is not recommended. For patients with borderline renal function or minimal dysfunction, a split-dose administration of cisplatin may be considered (category 2B). Although split-dose is a safer alternative, the relative efficacy remains undefined. Adjuvant chemotherapy may be given in 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 three cycles of a cisplatin-based combination, such as ddMVAC, GCM, or CMV, may be used in patients undergoing perioperative chemotherapy. Regimen and dosing recommendations are mainly based on studies in advanced disease.[77,82,97-99] 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

Data on radiation or chemoradiation following cystectomy are scarce and further prospective studies are needed to evaluate their efficacy and potential toxicity. 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.[100] A retrospective series similarly demonstrated improved cancer-specific survival with adjuvant radiotherapy for patients with pT2 to T4a disease.[101]

A phase III, multicenter, randomized trial evaluated the safety and non-inferiority of reduced high-dose volume radiation to standard volume radiation.[102] A radiation dose equivalent to 80% of the standard

dose (standard dose defined as either 55 Gy/20 fractions over 4 weeks or 64 Gy/32 fractions over 6.5 weeks) was given to the uninvolved areas. Patients receiving concurrent chemotherapy received 5-FU (500 mg/m^2/24 hours continuous infusion during fractions 1 through 5 and fractions 16 through 20 of radiation therapy) and mitomycin C (12 mg/m^2 intravenous bolus dose on day 1). Primary endpoints of late toxicity and time to locoregional recurrence were measured. No statistical difference between groups was seen in late side effects; non-inferiority could not be concluded, but the low rates of relapse and toxicity suggest that reduced radiation may be a treatment option.[102] The safety of radiation doses, especially in the setting of a neobladder, needs to be further studied.

Because local recurrence rates are high for some patients after cystectomy (32% for pT3-T4 patients and 68% for patients with positive surgical margins),[74] adjuvant radiation therapy is reasonable to consider in these patients. Radiotherapy to 40 to 45 Gy, with or without concurrent cisplatin, may be used. Since pT3a to pT4a patients are also at high risk of developing metastatic disease, they are treated with first-line multidrug chemotherapy if their renal function is adequate for cisplatin. Radiation and multidrug chemotherapy should not be given concurrently.

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 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. It is also endorsed by the International Consultation on Urologic Diseases-European Association of Urology evidence-based guidelines.[103] There is an apparent underutilization of aggressive bladder-preserving therapies for non-cystectomy candidates, especially the elderly and racial minorities.[104] 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.

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). An early report indicated that up to a third of bladders may be understaged.[105,106] 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.[107] 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 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.[108,109] Maximal TURBT with concurrent chemoradiotherapy should be given as primary treatment for these patients. For non-cystectomy candidates,

bladder-preserving strategies include concurrent chemoradiotherapy, radiotherapy, or TURBT alone.

For patients who have tumor after reassessment, cystectomy, if feasible, is preferred. Close cystoscopic observation alone, chemotherapy alone, and concurrent chemoradiotherapy (if no previous RT) are potential treatment options. When possible, bladder-sparing options should be chosen in the context of clinical trials.

Radiotherapy with Concurrent Chemotherapy Following TURBT

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 and for survival.[110,111]

Radiation Therapy Oncology Group protocol 89-03 compared concurrent cisplatin and radiotherapy with or without 2 cycles of induction MCV (methotrexate, cisplatin, and vinblastine) chemotherapy.[109] No difference in complete clinical response or 5-year OS was observed between the treatment arms. Other studies also reported no significant survival benefit for neoadjuvant chemotherapy before bladder-preserving chemotherapy with radiation therapy.[111,112]

Conversely, results from several prospective trials have demonstrated the effectiveness of this approach. In the RTOG 89-03 trial in which 123 patients with clinical stage T2-T4a were treated with radiotherapy plus concurrent cisplatin, with or without induction MCV chemotherapy, 5-year OS was approximately 49% in both arms.[109] The subsequent RTOG 95-06 trial treated 34 patients with twice-daily irradiation and concurrent cisplatin and 5-FU and reported a three-year OS of 83%.[113] The RTOG 97-06 trial treated 47 patients with twice-daily irradiation and concurrent cisplatin; patients also received adjuvant chemotherapy with CMV.[114] 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%.[115] Taken together, the complete response rates ranged from 59% to 81%. An alternative approach involves twice-daily radiation with concurrent paclitaxel plus cisplatin or 5-FU plus cisplatin.[116]

Up to about 80% of long-term survivors maintain an intact bladder, while other patients ultimately require radical cystectomy.[108-115] A combined analysis of survivors from these 4 trials, with a median follow-up of 5.4 years, showed that combined-modality therapy was associated with low rates of late grade 3 toxicity (5.7% genitourinary and 1.9% gastrointestinal).[117] No late grade 4 toxicities or treatment-related deaths were recorded.

Chemotherapy Following TURBT

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%.[77] A higher proportion of bladders can be rendered tumor-free and therefore preserved when chemotherapy is combined with concurrent radiotherapy.

Radiotherapy Following TURBT

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.[118,119] 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.[119] Hence, radiotherapy alone is only indicated for those who cannot tolerate a cystectomy or chemotherapy because of medical comorbidities.

TURBT Alone

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.[120]

If considered for TURBT alone, patients should undergo an aggressive re-resection of the site within 4 weeks of the primary procedure to ensure that no residual disease is present. If the repeat TURBT is negative for residual tumor, 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.

Treatment of T2, T3, and T4a Tumors

The critical issues in the management and prognosis of these patients are whether a palpable mass is appreciated at EUA and if the tumor has extended through the bladder wall. Tumors that are organ-confined (T2) have a better prognosis than those that have extended through the bladder wall into the perivesical fat (T3) and beyond. T4a tumors involve the prostatic stroma, uterus, or vagina and are typically surgically managed similar to T3 tumors.

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

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

Bladder preservation with maximal TURBT followed by concurrent chemoradiotherapy may be considered in patients who are medically fit. 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 as a radiosensitizer is the most common and well-studied chemoradiation method used to treat muscle-invasive bladder cancer.[107-111,118,119,121] The following radiosensitizing regimens are recommended: cisplatin plus 5-FU; cisplatin plus paclitaxel; and 5-FU plus mitomycin C. Doublet chemotherapy is preferred. Cisplatin alone or low-dose gemcitabine (category 2B) may be considered as alternative regimens.

After a complete TURBT, 65 to 70 Gy of external beam radiotherapy is administered, typically with a 4-field technique. Two doses of concurrent radiosensitizing chemotherapy are given on weeks 1 and 4. Alternatively, a partial dose of 40 to 45 Gy radiotherapy may be given following complete TURBT. The overall tumor status should be reassessed 3 weeks after radiation if 40 to 45 Gy was initially administered or 2 to 3 months after if the full dose of 60 to 65 Gy was

delivered. If no residual tumor is detected, appropriate options include observation or completion of radiation up to 66 Gy. If residual disease is present, cystectomy is preferred.

In patients with extensive comorbid disease or poor performance status who are non-cystectomy candidates, treatment options include concurrent chemoradiation, radiotherapy, or TURBT alone. Based on high-level evidence showing superiority to radiotherapy alone, the NCCN Panel recommends chemoradiotherapy with cisplatin alone or 5-FU and mitomycin C.[118,119] 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 T4b Disease or Positive Nodes

For patients with negative nodes on abdominal/pelvic CT or MRI scans or biopsy, the primary treatment recommendation includes 2 to 3 courses of chemotherapy with or without radiotherapy followed by evaluation with cystoscopy, EUA, TURBT, and imaging of the abdomen and pelvis. If no evidence of tumor is present after primary treatment, consolidation chemotherapy or completion of definitive RT may be considered. If a partial radiation dose of 40-45 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, cT4b disease is considered unresectable. However, in patients with disease that responds to treatment, cystectomy may be an option if the tumor becomes technically resectable.

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

For patients with abnormal nodes documented by imaging, a biopsy should be considered, if technically possible, to confirm nodal spread. Patients with positive nodes should receive chemotherapy with or without radiation and should be evaluated with cystoscopy, EUA, TURBT, and abdominal/pelvic imaging. If no residual tumor is detected, patients may receive a radiation boost or a cystectomy. If tumor is still present following primary therapy, these 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.[122] 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 tracts, 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, 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.

Recurrence or Persistent Disease

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

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

For patients with a preserved bladder, local recurrence or persistent disease should be evaluated as a new cancer. Recurrences are treated based on the extent of disease at relapse, with consideration of prior treatment. As previously discussed Tis, Ta, or T1 tumors are generally managed with intravesical 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 external-beam radiotherapy and has bulky residual disease. For these patients, chemoradiotherapy (if no prior radiotherapy) or 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 radiotherapy (see *Follow-up, Recurrent or Persistent Disease* in the algorithm and *Metastatic Disease* below).

Metastatic Urothelial Bladder Cancer

Approximately 4% of patients have metastatic disease at the time of diagnosis.[123] 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.

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.

Gemcitabine plus cisplatin (GC)[124,125] and ddMVAC[85,97] 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 MVAC.[99] 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 inferior to MVAC in terms of survival (OS, 13.0% vs. 15.3%; progression-free survival [PFS], 9.8% vs. 11.3%, respectively).[125] Another large, randomized, phase III trial compared ddMVAC to standard MVAC.[85,97] 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, standard MVAC is inferior to ddMVAC in terms of toxicity and efficacy, and is inferior to GC in terms of toxicity; therefore, standard 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 with a glomerular filtration rate (GFR) less than 60 mL/min, carboplatin may be substituted for cisplatin. A phase II/III study assessed 2 carboplatin-containing regimens in medically unfit patients (performance status 2).[126] 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.[127] 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,[128] gemcitabine/paclitaxel,[129] cisplatin/gemcitabine/paclitaxel,[130] carboplatin/gemcitabine/paclitaxel,[131] and cisplatin/gemcitabine/docetaxel,[132] have shown modest activity in patients with bladder cancer in phase I-II trials.

Although current data are insufficient to recommend the above alternative regimens as routine first-line options, non-cisplatin-containing regimens may be considered in patients who cannot tolerate cisplatin because of renal impairment or other comorbidities (see *Principles of Systemic Therapy* in the algorithm). 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.

Data for subsequent-line systemic therapy for locally advanced or metastatic disease are highly variable and the NCCN Panel recommends enrollment in a clinical trial. The available options depend on what was offered as first line. Regimens used in this setting include checkpoint inhibitors, and the following chemotherapies: docetaxel, paclitaxel, gemcitabine, or pemetrexed monotherapy.[133-136] Other options include Nab-paclitaxel; ifosfamide; methotrexate; ifosfamide, doxorubicin, and gemcitabine; gemcitabine and paclitaxel; GC; and ddMVAC.

Chemoradiotherapy for Metastatic Disease

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

Targeted Therapies

Platinum-based chemotherapy has been the standard of care in patients with metastatic disease with an OS of 9 to 15 months.[125,137] However, in patients with disease that relapses after this type of chemotherapy, the median survival is reduced to 5 to 7 months.[138] Several new agents for the treatment of metastatic urothelial carcinoma are being advanced in clinical trials and data suggest improved outcomes compared to standard therapies. Emerging data are encouraging for the effectiveness of checkpoint inhibitors for the treatment of urothelial carcinoma. Cancers with higher rates of somatic mutations have been shown to respond better to checkpoint inhibitors.[139-144] Data from the Cancer Genome Atlas rank bladder cancer as the third highest mutated cancer,[145,146] suggesting that checkpoint inhibitors may have a substantial impact as a treatment option for this cancer.

PD-1 and PD-L1 checkpoint inhibitors have garnered attention based on clinical trial data and the FDA approval of the PD-L1 inhibitor atezolizumab and the PD-1 inhibitor nivolumab for patients with urothelial carcinoma. Atezolizumab and nivolumab are both 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.

Data from a single-arm, multicenter, phase II trial evaluating atezolizumab in 310 post-platinum metastatic urothelial carcinoma patients, showed a significantly improved objective response rate compared to historical controls (15% vs. 10%; $P = .0058$).[147] Notably and consistent to observation of checkpoint inhibitors in other cancer

types, responses tended to 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 adverse events occurred in 16% and 5% of patients, respectively. Furthermore, there were no treatment-related deaths in this trial suggesting good tolerability. Atezolizumab marks the first immunotherapy to be approved for patients with advanced urothelial carcinoma, a setting that has had a dearth of new therapies.

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 overall objective response 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.[148] Out of the 270 patients enrolled in the study, grade 3 or 4 treatment-related adverse events were reported in 18% of patients. Three patient deaths were the result of treatment.[148] 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 early phase I/II data that reported an objective response rate of 24% (95% CI, 15.3%–35.4%) that was unaffected by PD-1 tumor status.[149] Out of the 78 patients enrolled in this study, 2 experienced grade 5 treatment-related adverse events, and grade 3 or 4 treatment-related adverse events were reported in 22% of patients.[149]

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.[150,151] The ORR was 25% in this trial with 7 of the 22 patients reporting a complete or partial response.[152] Grade 3 to 4 adverse events occurred in 15% of patients.[152] Two supplemental biologics license applications have been submitted for the use of pembrolizumab for first-line use in patients who are ineligible for cisplatin-containing therapy and for second-line use for patients with disease progression on or after platinum-containing therapy.

Durvalumab and avelumab are two other PD-L1 inhibitors that are in clinical trials to evaluate their activity in the treatment of bladder cancer. Early results from a phase I/II multicenter study of 61 patients has led to FDA breakthrough therapy designation of durvalumab for 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. In this study 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.[153] Median duration of response for 12 of the 13 patients was not yet reached at time of publication (range, 4.1–49.3 weeks). Results from the phase 1b trial for patients with platinum-refractory disease or who are ineligible for cisplatin-based chemotherapy demonstrated an ORR of 18.2% that consisted of 2 complete responses and 6 partial responses following treatment with avelumab.[154] A higher PFS was seen in patients with positive PD-L1 tumor cells versus patients who did not express PD-L1 (58.3% vs. 16.6% at 24 weeks), though PD-L1 negative tumors in some patients did respond to treatment.

The value of checkpoint inhibitors is reflected in the unanimous decision by the NCCN Panel to include atezolizumab and nivolumab as second-line systemic therapy options for locally advanced or metastatic disease after platinum-based therapy (see *Systemic Therapy* in the algorithm).

Treatment 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 estimate GFR should be obtained to assess patient eligibility for cisplatin. If the evidence of spread is limited to nodes, nodal biopsy should be considered and patients should be managed as previously outlined for positive nodal disease (see *Treatment of cT4b or Positive Nodes* in the discussion and *cT4b Primary and Adjuvant Treatment* in the algorithm). Patients who present with disseminated metastatic disease are generally treated with systemic chemotherapy. Management of persistent disseminated disease may involve chemotherapy, radiation, or a combination of the two.

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, radiation therapy, 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.[155-158] 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 radiation therapy 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 Genitourinary Tract Tumors

Upper tract tumors, including those that originate in the renal pelvis or in the ureter, are relatively uncommon. The treatment recommendations discussed below are based on the most common variant 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 pyelogram.

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 pyelogram; or ureteroscopy. 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.

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, a nephron-sparing procedure through a transureteroscopic approach, or a percutaneous approach 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. 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.[77-79] If metastatic disease is documented or associated comorbid conditions are present, treatment should include systemic chemotherapy 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.

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 increasing 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.

Patients with pT2, pT3, pT4, or nodal disease should be considered for adjuvant chemotherapy. 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. 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.[159]

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 cuff of bladder.

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.

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 prostatic urethra with no acinar or stromal invasion can be managed with TURP and intraprostatic 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, or 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.[77-79] Adjuvant chemotherapy may be advised for stromal invasion after primary treatment if neoadjuvant therapy was not given. Alternatively, TURP and intraprostatic 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.[160] The 5-year OS is 42%.[161,162] Stage and disease location are the most important prognostic factors for male patients, while tumor size and histology are prognostically significant for female patients.[160,162] 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 versus 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 or 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 was associated with a high urethral recurrence rate.[163] At recurrence, the patient may receive systemic therapy or chemoradiotherapy (both category 2A) or pelvic exenteration (category 2B).

A multimodal treatment approach (ie, surgery, chemotherapy, 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.[164] Combined chemoradiation with 5-FU and mitomycin C has shown efficacy in a series of male patients with squamous cell carcinoma of the urethra.[165] Patients receiving surgery after chemoradiation had a higher 5-year DFS rate (72%) than those receiving chemoradiation alone (54%). If chemotherapy 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. If positive nodes are present, radiation preferably with chemotherapy is the preferred treatment for squamous cell carcinoma. Chemotherapy or chemoradiotherapy followed by consideration of 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 systemic therapy or chemoradiotherapy based on histology.

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 tract 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 radiation therapy. 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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