National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Bladder Cancer

Version 6.2021 — December 6, 2021

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

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For important information regarding the BCG shortage see MS-10. Also see the AUA BCG Shortage Notice.

National Comprehensive Cancer Network®

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***Thomas W. Flaig, MD †/Chair**
University of Colorado Cancer Center

***Philippe E. Spiess, MD, MS ¶ ϖ/Vice Chair**
Moffitt Cancer Center

Neeraj Agarwal, MD ‡ †
Huntsman Cancer Institute
at the University of Utah

Rick Bangs, MBA
Patient Advocate

Stephen A. Boorjian, MD ϖ
Mayo Clinic Cancer Center

Mark K. Buyyounouski, MD, MS §
Stanford Cancer Institute

Kevin Chan, MD ¶ ϖ
City of Hope National Medical Center

Sam Chang, MD, MBA ¶
Vanderbilt-Ingram Cancer Center

Tracy M. Downs, MD ϖ
University of Wisconsin Carbone Cancer Center

Terence Friedlander, MD †
UCSF Helen Diller Family
Comprehensive Cancer Center

Richard E. Greenberg, MD ϖ
Fox Chase Cancer Center

Khurshid A. Guru, MD ϖ
Roswell Park Comprehensive Cancer Center

Thomas Guzzo, MD, MPH ϖ
Abramson Cancer Center at the
University of Pennsylvania

Harry W. Herr, MD ϖ
Memorial Sloan Kettering Cancer Center

Jean Hoffman-Censits, MD †
The Sidney Kimmel Comprehensive
Cancer Center at Johns Hopkins

Brant A. Inman, MD, MSc ¶ ϖ
Duke Cancer Institute

Amar Kishan, MD §
UCLA Jonsson Comprehensive Cancer Center

Shilajit Kundu, MD ϖ
Robert H. Lurie Comprehensive Cancer Center
of Northwestern University

Subodh M. Lele, MD ≠
Fred & Pamela Buffett Cancer Center

Ronac Mamtani, MD ϖ
Abramson Cancer Center at the University of
Pennsylvania

Vitaly Margulis, MD ϖ
UT Southwestern Simmons
Comprehensive Cancer Center

Omar Y. Mian, MD, PhD §
Case Comprehensive Cancer Center/
University Hospitals Seidman Cancer Center
and Cleveland Clinic Taussig Cancer Institute

Jeff Michalski, MD, MBA §
Siteman Cancer Center at Barnes-
Jewish Hospital and Washington
University School of Medicine

Jeffrey S. Montgomery, MD, MHSA ϖ
University of Michigan Rogel Cancer Center

Lakshminarayanan Nandagopal, MD †
O'Neal Comprehensive Cancer Center at UAB

Lance C. Pagliaro, MD †
Mayo Clinic Cancer Center

Mamta Parikh, MD, MS ϖ
UC Davis Comprehensive Cancer Center

Anthony Patterson, MD ϖ
St. Jude Children's Research Hospital/
The University of Tennessee
Health Science Center

Elizabeth R. Plimack, MD, MS † Þ
Fox Chase Cancer Center

Kamal S. Pohar, MD ¶ ϖ
The Ohio State University Comprehensive
Cancer Center - James Cancer Hospital
and Solove Research Institute

Mark A. Preston, MD, MPH ϖ
Dana-Farber/Brigham and Women's
Cancer Center

Kyle Richards, MD ϖ
University of Wisconsin Carbone Cancer Center

Wade J. Sexton, MD ϖ
Moffitt Cancer Center

Arlene O. Siefker-Radtke, MD †
The University of Texas
MD Anderson Cancer Center

Jonathan Tward, MD, PhD §
Huntsman Cancer Institute
at the University of Utah

Jonathan L. Wright, MD, MS ϖ
Fred Hutchinson Cancer Research Center/
Seattle Cancer Care Alliance

NCCN
Lisa Gurski, PhD
Mary Dwyer, MS

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

NCCN Guidelines Panel Disclosures

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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/member_institutions.aspx.

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

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

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Updates in Version 5.2021 of the NCCN Guidelines for Bladder Cancer from Version 4.2021 include:

MS-1

- **The discussion has been updated to reflect the changes in the algorithm.**

Updates in Version 5.2021 of the NCCN Guidelines for Bladder Cancer from Version 4.2021 include:

BL-5 and BL-7

- **For stage II and IIIA, adjuvant treatment revised:**
  - **Based on pathologic risk**
    - **If no cisplatin neoadjuvant treatment given *and pT3, pT4a, or pN+***
      - **Adjuvant cisplatin-based chemotherapy *should be discussed (preferred)* or**
      - ***Consider adjuvant nivolumab***
    - ***If cisplatin neoadjuvant chemotherapy and ypT2-ypT4a or ypN+, consider nivolumab***
    - ***Consider* adjuvant RT *in selected patients* (T3–4, positive nodes/margins) (category 2B)**
- **Footnote added: Most appropriate for patients who value an opportunity to delay recurrence even if the chance of cure was not improved, and for whom the risk of side effects was acceptable.**

BL-G (1 of 7)

- **Neoadjuvant chemotherapy [preferred for bladder]**
  - **Preferred regimens:**
    - **Revised: DDMVAC (dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin) with growth factor support for ~~3 or 4~~ *3-6* cycles**
  - **Gemcitabine and cisplatin for 4 cycles moved to Other recommended regimens**
- **Other Recommended regimens:**
  - **Removed: CMV (cisplatin, methotrexate, and vinblastine) for 3 cycles**
- **Adjuvant therapy recommendations with the addition of nivolumab moved to a new table.**

BL-G (2 of 7)

- **First-line systemic therapy for locally advanced or metastatic disease, cisplatin ineligible revised: Pembrolizumab (~~only for patients whose tumors express PD-L1 or who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression~~ *for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for any platinum-containing chemotherapy*)**

UTT-3

- **Adjuvant Treatment revised:**
  - ***If no platinum neoadjuvant treatment given and pT3, pT4, or pN+***
    - ***Adjuvant platinum-based chemotherapy should be discussed or***
    - ***Consider adjuvant nivolumab (category 2B) or***
  - ***If platinum neoadjuvant chemotherapy given and ypT2-ypT4 or ypN+, consider adjuvant nivolumab***
  - ***± RT (T3, T4, or N+)***
- **Footnote added: *Most appropriate for patients who value an opportunity to delay recurrence even if the chance of cure was not improved, and for whom the risk of side effects was acceptable.***

Updates in Version 4.2021 of the NCCN Guidelines for Bladder Cancer from Version 3.2021 include:

BL-G (3 of 7)

- **Second-line systemic therapy for locally advanced or metastatic disease (Stage IV)**
  - **Post-platinum: Alternative preferred regimens, enfortumab vedotin-ejfv was added as a category 2A recommendation with a corresponding footnote g, "Indicated for cisplatin ineligible patients who have received one or more prior lines of therapy."**
  - **Post-checkpoint inhibitor: Preferred regimens for cisplatin ineligible, chemotherapy naïve disease, enfortumab vedotin-ejfv was added as a category 2A recommendation.**

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Updates in Version 3.2021 of the NCCN Guidelines for Bladder Cancer from Version 2.2021 include:

BL-G (4 of 7)
- Subsequent-line systemic therapy for locally advanced or metastatic disease (Stage IV)
  - Other recommended regimens, sacituzumab govitecan-hziy was added as a category 2A recommendation.

Updates in Version 2.2021 of the NCCN Guidelines for Bladder Cancer from Version 1.2021 include:

BL-G (3 of 7)
- Second-line systemic therapy for locally advanced or metastatic disease (Stage IV) (post-platinum)
  - Alternative preferred regimens, atezolizumab was removed as an option based on the voluntary withdrawal of the FDA indication.

Updates in Version 1.2021 of the NCCN Guidelines for Bladder Cancer from Version 6.2020 include:

Bladder Cancer

BL-1
- Initial Evaluation
  - 2nd bullet was revised, "Office cystoscopy*, enhanced if available*."
- Primary Evaluation/Surgical Treatment
  - Bullet removed, "If sessile, suspicious for high grade or Tis: Consider selected mapping biopsies."
- Footnote d was revised by adding: "...for selected patients. Most efficacious in patients with low-grade, low-volume Ta urothelial cancer."

BL-2 and **BL-3**
- The algorithms for non-muscle invasive bladder cancer were extensively revised to provide recommendations for management based on AUA risk stratification group.

BL-4
- The title of the page was clarified as "Management of Positive Urine Cytology."
- Evaluation
  - 1st bullet was added, "If initial positive cytology, consider repeating cytology test within 3 months."
  - 2nd bullet was added, "If repeated positive cytology," and the current recommendations were added as sub-bullets to this bullet.

BL-5
- Additional Workup
  - Last bullet was added: "Estimate GFR to assess eligibility for cisplatin" with footnote v: "For patients with borderline GFR consider timed urine collection, which may more accurately determine eligibility for cisplatin." Also for BL-7, BL-8, and BL-9.
- Primary Treatment
  - "Bladder preservation with" was added to "concurrent chemoradiotherapy (category 1)." Also for BL-7.
  - Reassessment bullet was revised: "Reassess tumor status 2-3 months after ~~full~~ treatment *completion*." (Also to BL-6, BL-7)
- Adjuvant Treatment of Cystectomy candidates was updated. Also for BL-7.
  - "Based on pathologic risk, consider
    - ◊ Adjuvant cisplatin-based chemotherapy if no neoadjuvant treatment, or
    - ◊ Adjuvant RT (pT3–4, ~~or~~ positive nodes/*margins* ~~or positive margins~~) (category 2B)
- Footnote z was revised: "Optimal candidates for bladder preservation with chemoradiotherapy include patients with tumors that present without *moderate/severe* hydronephrosis,..." Also for BL-7.
- Footnote was removed: There are data to support equivalent survival rates. Not all institutions have experience with these multidisciplinary treatment approaches, which require a dedicated team. Also for BL-7.

BL-6
- Adjuvant Treatment
  - Tumor pathway: "± intravesical therapy" was added to TURBT. Also for BL-7.

BL-8
- Footnote dd was revised: "...there is no evidence of distant disease on imaging reassessment, further cystoscopic assessment of tumor response in the bladder ~~is recommended~~ *may be considered*."

BL-9
- M1a Disease, Subsequent Treatment
  - CR option was revised from "Concurrent chemoradiotherapy or Cystectomy" to "Consider consolidative local therapy in selected cases."

BL-10
- After primary treatment, a link to "See Follow-up (BL-E)" was added.

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UPDATES

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Updates in Version 1.2021 of the NCCN Guidelines for Bladder Cancer from Version 6.2020 include:

Principles of Imaging for Bladder/Urothelial Cancer

BL-A (1 of 5)

- Abdominal and Pelvic Imaging, Staging, 2nd sub-bullet was revised: MR urography (MRU) may be appropriate *especially* in patients..."

BL-A (3 of 5)

- "Metastatic Disease - Patients Being Observed, See Follow-Up (BL-E 6 of 6)" was added.

BL-A (4 of 5)

- Urothelial Carcinoma of the Prostate/Primary Carcinoma of the Urethra, Staging, 1st bullet was revised: Staging: *Chest CT (preferred)* or PA and lateral chest x-ray ~~or chest CT~~.

Principles of Surgical Management

BL-B (1 of 4)

- TURBT/Maximal TURBT for Treatment, 1st bullet revised: ~~Bladder preservation with maximally complete and safe TURBT~~ *Maximally complete and safe TURBT is an essential part of bladder preservation. See Principles of Radiation Therapy (BL-H*) and sentence, "Concurrent chemoradiotherapy is generally most suitable for patients with solitary tumors, negative nodes, no extensive or multifocal CIS, no moderate/severe tumor-related hydronephrosis, and good pre-treatment bladder function" was moved and added as last bullet on BL-H.

BL-B (2 of 4)

- Partial Cystectomy, 1st bullet was revised: "May be used for cT2 muscle invasive disease with solitary lesion in location amenable to segmental resection with adequate margins, *particularly for purely non-urothelial histology*."
- Radical Cystectomy/Cystoprostatectomy,
  - 1st bullet was revised: In non-muscle invasive disease, radical cystectomy is generally reserved for residual high-grade cT1, *variant histology, lymphovascular invasion, concomitant CIS, and Bacillus Calmette-Guérin (BCG)-unresponsive disease*.
  - Last bullet was added: In appropriately selected female patients, approaches that preserve the uterus, vagina, and/or ovaries should be employed when feasible.
- Radical Nephroureterectomy with Cuff of Bladder
  - 3rd bullet was revised: Neoadjuvant chemotherapy should be considered in select patients with high-grade disease *or concerning radiographic findings.*
  - Last bullet was added: Adjuvant chemotherapy may also be considered in patients who did not receive neoadjuvant chemotherapy (Birtle A, et al. Lancet 2020;395:1268-1277).

BL-B (3 of 4)

- Urethrectomy, 6th bullet, first sub-bullet was updated: "with T2 primary carcinoma of the urethra may be treated with urethrectomy and cystectomy *with organ-sparing approaches when feasible in appropriately selected cases*."

BL-B (4 of 4)

- 4th bullet, sub-bullet was removed: Hereditary predisposition (eg, hereditary nonpolyposis colon cancer [HNPCC])

Principles of Pathology Management

BL-C

- Section removed: Melanocytic tumors - Malignant melanoma, Naevus, Melanosis and Malignant melanoma was added to Miscellaneous tumors.
- Mesenchymal Tumors section was revised:
  - *Malignant* inflammatory myofibroblastic tumor
  - *Malignant* perivascular epithelioid cell tumor ~~- Benign, Malignant~~
  - *Malignant* solitary fibrous tumour ~~- Leiomyoma, Haemangioma, Granular cell tumour, Neurofibroma~~

Non-Urothelial And Urothelial With Variant Histology

BL-D (1 of 2)

- Mixed histology, 1st bullet was revised: Urothelial carcinoma plus squamous *differentiation*, adenocarcinoma *differentiation*,...
- Any Small-Cell Component (or neuroendocrine features), 1st bullet: "(See systemic therapy in NCCN Guidelines for Small Cell Lung Cancer)" was added.

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Updates in Version 1.2021 of the NCCN Guidelines for Bladder Cancer from Version 6.2020 include:

Follow-up

BL-E (6 of 6)

- Table 8 for Metastatic Disease that is being observed was added.

Principles of Intravesical Treatment

BL-F (1 of 3)

- Induction (Adjuvant) Intravesical Chemotherapy or BCG
  - 3rd bullet, 1st sub-bullet was revised: Other options include: *sequential gemcitabine/docetaxel*, epirubicin, valrubicin, docetaxel, or ~~sequential gemcitabine/docetaxel or~~ sequential gemcitabine/mitomycin.

BL-F (2 of 3)

- Intrapelvic and Intravesical Therapy for Upper Tract Tumors
  - Postsurgical, 2nd sub-bullet was revised: Perioperative intravesical chemotherapy with mitomycin or gemcitabine ~~may be given~~ *should be considered* following nephroureterectomy with cuff of bladder resection.

Principles of Systemic Therapy

BL-G (1 of 7)

- Table header was clarified: Perioperative chemotherapy (neoadjuvant *[preferred for bladder]* or adjuvant)
- 8th bullet, sub-bullet was added: Adjuvant therapy should be considered if neoadjuvant was not given for UTUC (Birtle A, et al. Lancet 2020;395:1268-1277).
- 9th bullet was revised: Carboplatin should not be substituted for cisplatin in the perioperative *bladder cancer* setting.

BL-G (2 of 7)

- First-line systemic therapy for locally advanced or metastatic disease (Stage IV)
  - Avelumab maintenance was clarified as a category 1 recommendation.

BL-G (3 of 7)

- Second-line systemic therapy for locally advanced or metastatic disease (Stage IV) (post-platinum)
  - Alternative preferred regimens, durvalumab was removed as an option based on the voluntary withdrawal of the FDA indication.
- Footnote e was added: Also for patients who received a therapy other than platinum or an immune checkpoint inhibitor in first-line.

BL-G (4 of 7)

- Subsequent-line systemic therapy for locally advanced or metastatic disease (Stage IV)
  - Preferred regimens, enfortumab vedotin was changed from a category 2A to a category 1 recommendation and corresponding reference was added: Powles T, Rosenberg JE, Sonpavde G, et al. Enfortumab vedotin in previously treated advanced urothelial carcinoma. N Engl J Med 2021. Online ahead of print.
- Footnote h was added: These therapies are appropriate for patients who received a first-line platinum-containing chemotherapy followed by avelumab maintenance therapy.

Principles of Radiation Management of Invasive Disease

BL-H

- 10th bullet was revised: Concurrent chemoradiotherapy *(preferred)* or RT alone should be considered as potentially curative therapy for medically inoperable patients. *Concurrent chemoradiotherapy or RT alone should be considered* for local palliation in patients with metastatic disease.
- 14th bullet was revised by removing the follow-up recommendations and directing to Table 7 on BL-E.

Upper GU Tract Tumors

UTT-1

- Workup: "or CT" was added to Chest x-ray. Also for UTT-2, UCP-1 and PCU-1.

UTT-3

- Adjuvant therapy for pT2, pT3, pT4, pN+
  - "± RT" was added to "Consider adjuvant chemotherapy."

Primary Carcinoma of the Urethra

PCU-3

- cN0, Primary Treatment.
  - Last option was revised, "~~Consolidative~~ Surgery alone for non-urothelial histology."

INTRODUCTION

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

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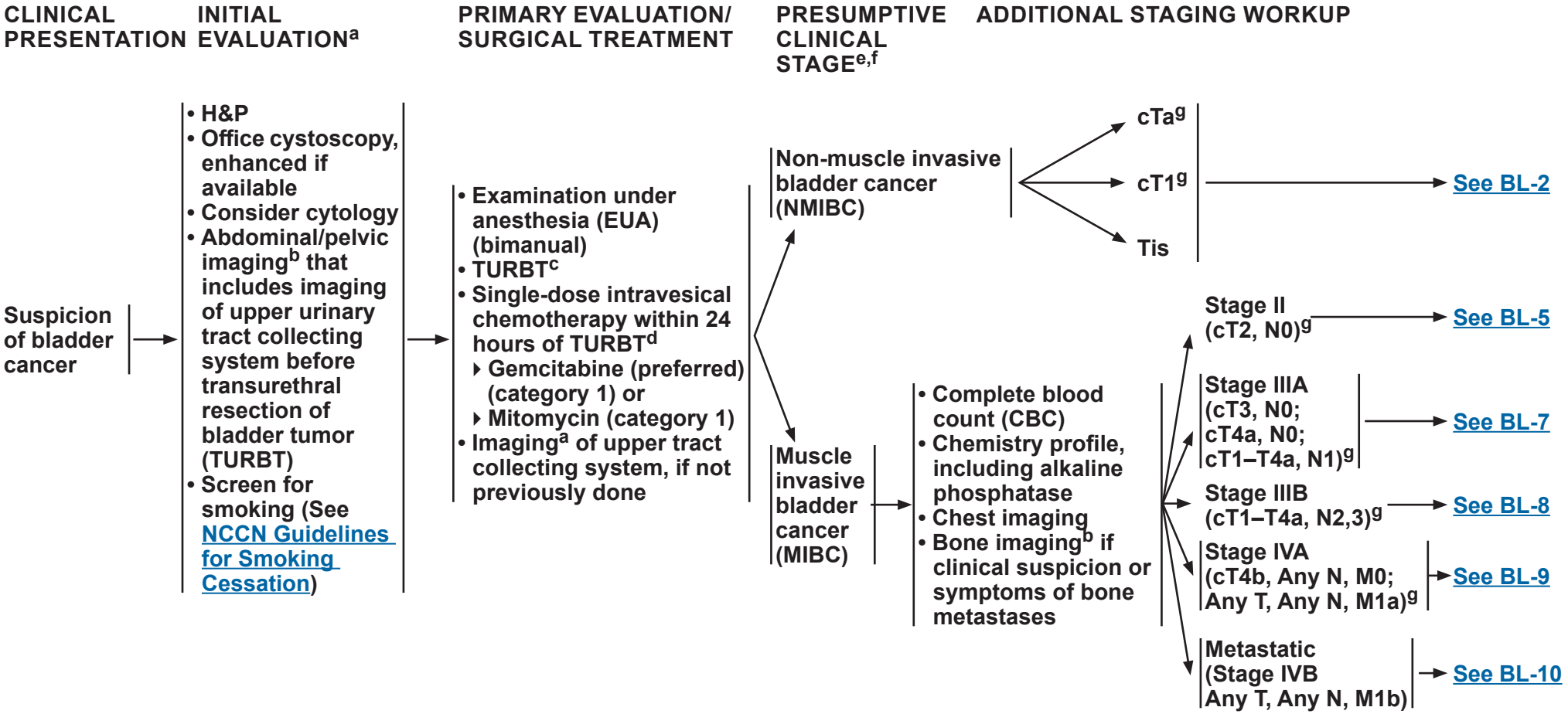
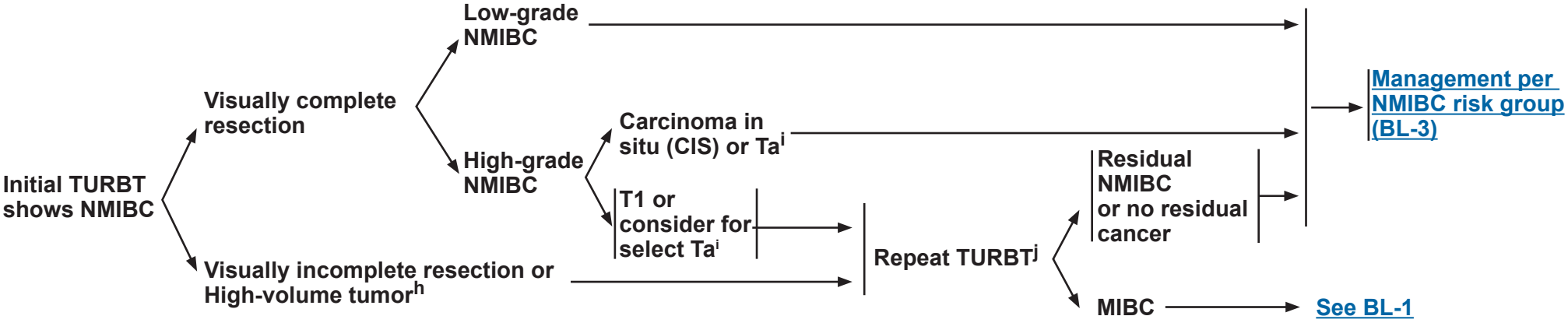


[a] For tools to aid optimal assessment and management of older adults with cancer, see NCCN Guidelines for Older Adult Oncology.
[b] See Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
[c] See Principles of Surgical Management (BL-B).
[d] Immediate intravesical chemotherapy reduces the recurrence rate by 35% for selected patients. Most efficacious in patients with low-grade, low-volume Ta urothelial cancer. See Principles of Intravesical Treatment (BL-F).
[e] See Principles of Pathology Management (BL-C).
[f] See Bladder Cancer: Non-Urothelial and Urothelial with Variant Histology (BL-D).
[g] The modifier "c" refers to clinical staging based on bimanual EUA, endoscopic surgery (biopsy or transurethral resection), and imaging studies. The modifier "p" refers to pathologic staging based on cystectomy and lymph node dissection.

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

RISK STRATIFICATION OF NMIBC



AUA Risk Stratification for Non-Muscle Invasive Bladder Cancer*

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

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

[h] High-volume tumors (large or highly multifocal) are at high risk of residual tumor.
[i] Consider repeat TURBT for high-grade Ta particularly if large, and/or no muscle in specimen.
[j] Muscle should be present in repeat TURBT pathology specimen if possible.
[k] Kamat AM, et al. J Clin Oncol 2016;34:1935-1944.
[l] Montironi R, et al. Int J Surg Pathol 2005;13:143-153.

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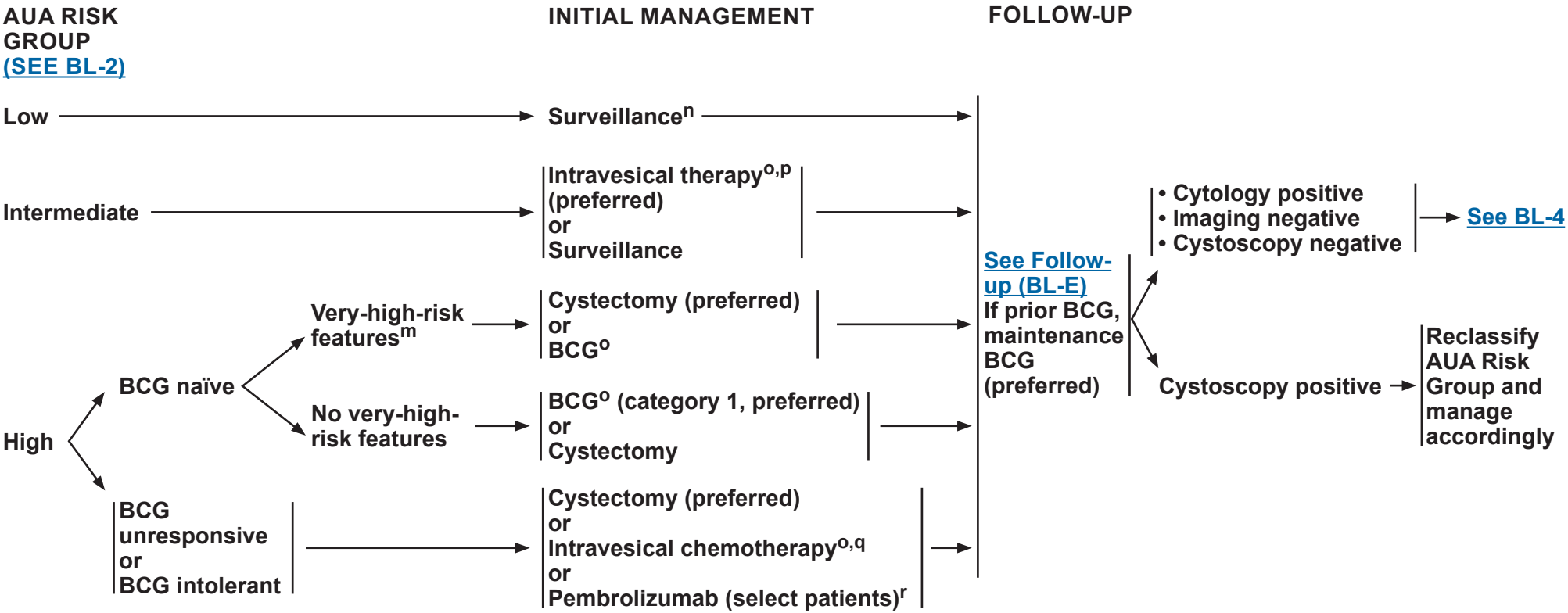
MANAGEMENT PER NMIBC RISK GROUP



[m] Lymphovascular invasion, prostatic urethral involvement of tumor, variant histology (eg, micropapillary, plasmacytoid, sarcomatoid), T1 with extensive CIS.
[n] Should consider single perioperative instillation of intravesical chemotherapy at time of TURBT.
[o] See Principles of Intravesical Therapy (BL-F).
[p] Options for intravesical therapy for intermediate-risk disease include BCG and chemotherapy; should consider BCG availability in decision-making.
[q] Valrubicin is approved for BCG-refractory CIS.
[r] Pembrolizumab is indicated for the treatment of patients with BCG-unresponsive, high-risk NMIBC with Tis (with or without papillary) tumors who are ineligible for or have elected not to undergo cystectomy.

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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Management of Positive Urine Cytology

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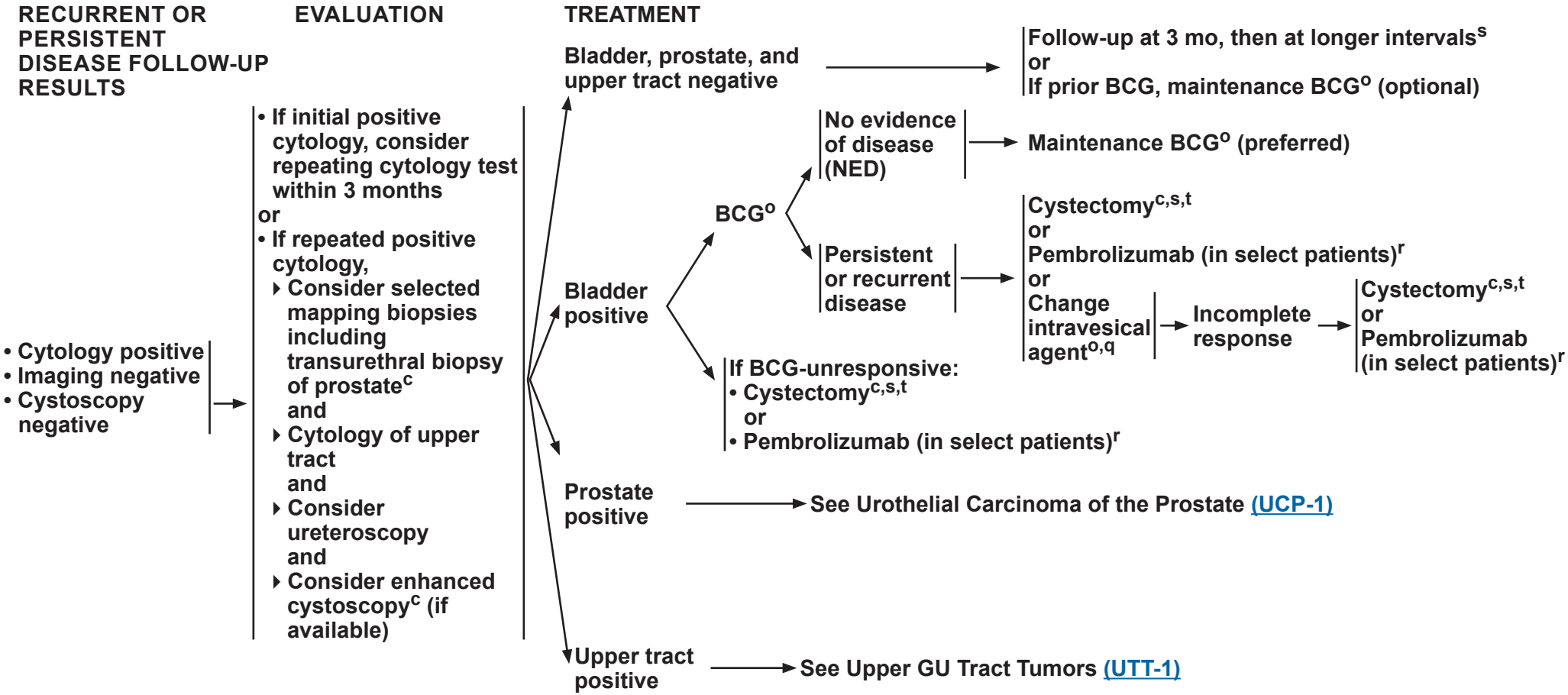

[c] See Principles of Surgical Management (BL-B).
[o] See Principles of Intravesical Treatment (BL-F).
[q] Valrubicin is approved for BCG-refractory CIS.
[r] Pembrolizumab is indicated for the treatment of patients with BCG-unresponsive, high-risk, non-muscle invasive bladder cancer with Tis (with or without papillary) tumors who are ineligible for or have elected not to undergo cystectomy.
[s] See Follow-up (BL-E).
[t] If not a cystectomy candidate, and recurrence is cTa or cT1, consider concurrent chemoradiotherapy (category 2B for cTa, category 2A for cT1) or a clinical trial. See Principles of Systemic Therapy (BL-G 5 of 7).

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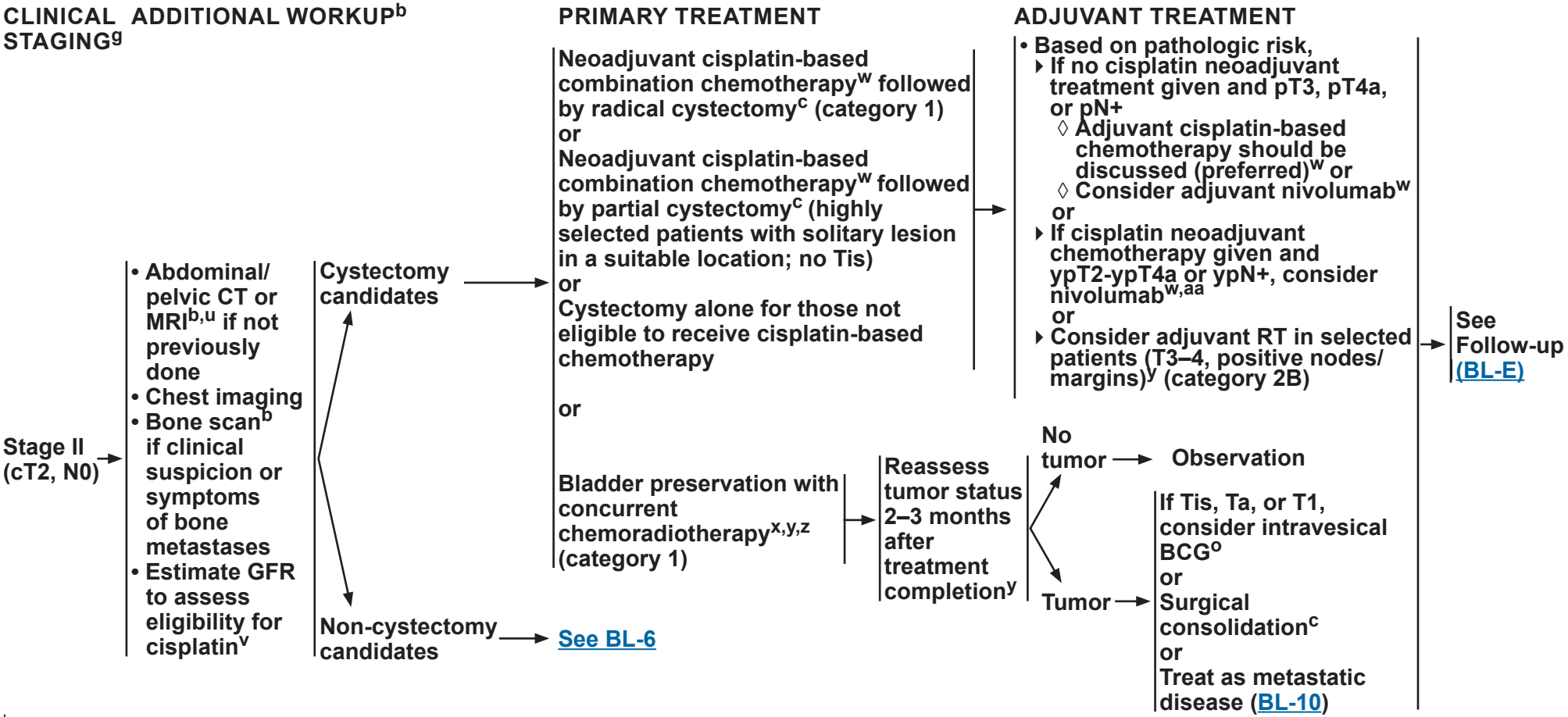

[b] See Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
[c] See Principles of Surgical Management (BL-B).
[g] The modifier "c" refers to clinical staging based on bimanual EUA, endoscopic surgery (biopsy or transurethral resection), and imaging studies. The modifier "p" refers to pathologic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

Note: All recommendations are category 2A unless otherwise indicated.
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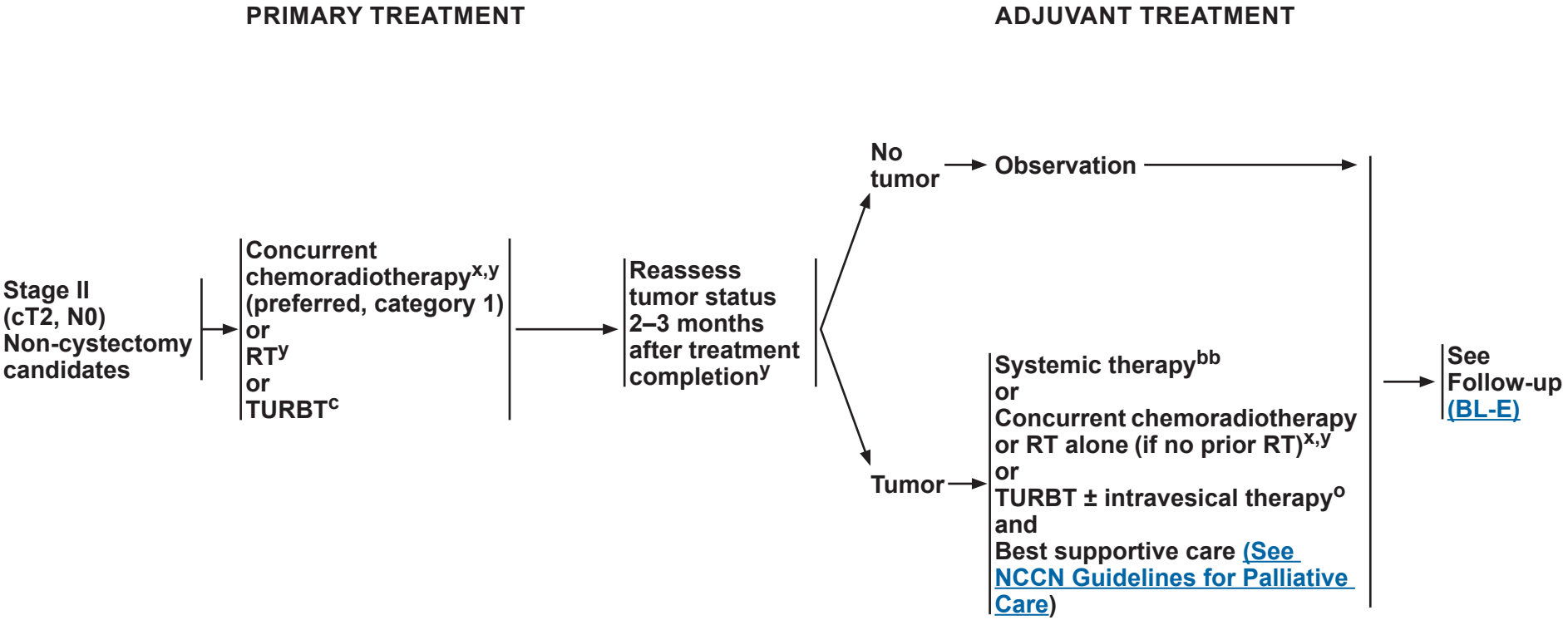
See Recurrent or Persistent Disease (BL-11)



[c] See Principles of Surgical Management (BL-B).
[o] See Principles of Intravesical Treatment (BL-F).
[x] See Principles of Systemic Therapy (BL-G 5 of 7).
[y] See Principles of Radiation Management of Invasive Disease (BL-H).
[bb] See Principles of Systemic Therapy (BL-G 2 of 7).

See Recurrent or Persistent Disease (BL-11)

Note: All recommendations are category 2A unless otherwise indicated.
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Muscle Invasive Bladder Cancer

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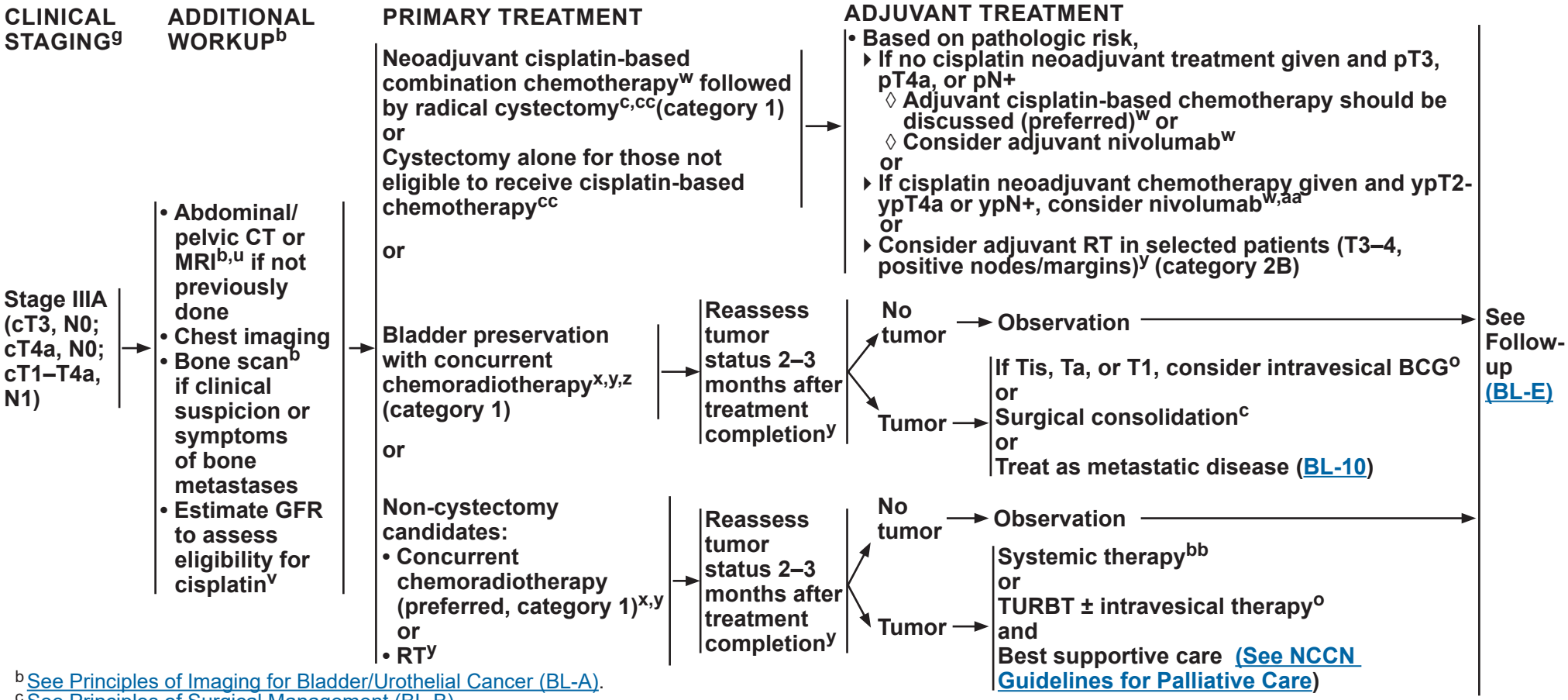

[b] See Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
[c] See Principles of Surgical Management (BL-B).
[g] The modifier "c" refers to clinical staging based on bimanual EUA, endoscopic surgery (biopsy or transurethral resection), and imaging studies. The modifier "p" refers to pathologic staging based on cystectomy and lymph node dissection.
[o] See Principles of Intravesical Treatment (BL-F).
[u] Consider FDG-PET/CT scan (skull base to mid-thigh) (category 2B).
[v] For patients with borderline GFR consider timed urine collection, which may more accurately determine eligibility for cisplatin.
[w] See Principles of Systemic Therapy (BL-G 1 of 7).
[x] See Principles of Systemic Therapy (BL-G 5 of 7).
[y] See Principles of Radiation Management of Invasive Disease (BL-H).
[z] Optimal candidates for bladder preservation with chemoradiotherapy include patients with tumors that present without moderate/severe hydronephrosis, are without concurrent extensive or multifocal Tis, and are <6 cm. Ideally, tumors should allow a visually complete or maximally debulking TURBT. See Principles of Radiation Management of Invasive Disease (BL-H).
[aa] Most appropriate for patients who value an opportunity to delay recurrence even if the chance of cure was not improved, and for whom the risk of side effects was acceptable.
[bb] See Principles of Systemic Therapy (BL-G 2 of 7).
[cc] Patients with cN1 disease have better outcomes if they are given neoadjuvant chemotherapy and have a response.

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See Recurrent or Persistent Disease (BL-11)

National Comprehensive Cancer Network®

NCCN Guidelines Version 6.2021
Muscle Invasive Bladder Cancer

NCCN Guidelines Index
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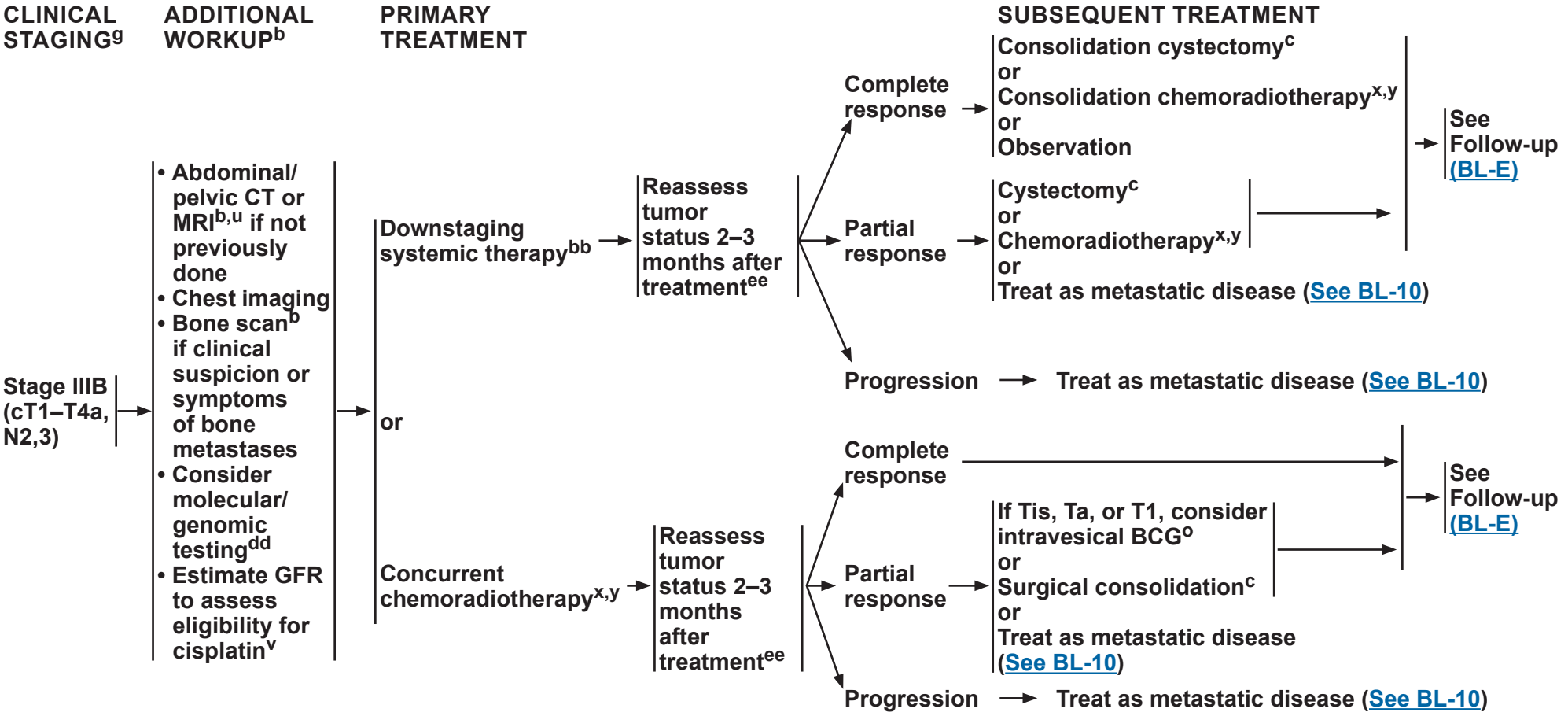
Discussion



[b] See Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
[c] See Principles of Surgical Management (BL-B).
[g] The modifier "c" refers to clinical staging based on bimanual EUA, 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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[u] Consider FDG-PET/CT scan (skull base to mid-thigh) (category 2B).
[v] For patients with borderline GFR consider timed urine collection, which may more accurately determine eligibility for cisplatin.
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[y] See Principles of Radiation Management of Invasive Disease (BL-H).
[bb] See Principles of Systemic Therapy (BL-G 2 of 7).
[dd] Molecular/genomic testing in a CLIA-approved laboratory, including FGFR RGQ RT-PCR for *FGFR3* or *FGFR2* genetic alterations. See Discussion.
[ee] Imaging with CT of chest/abdomen/pelvis with contrast. If there is no evidence of distant disease on imaging reassessment, further cystoscopic assessment of tumor response in the bladder may be considered.

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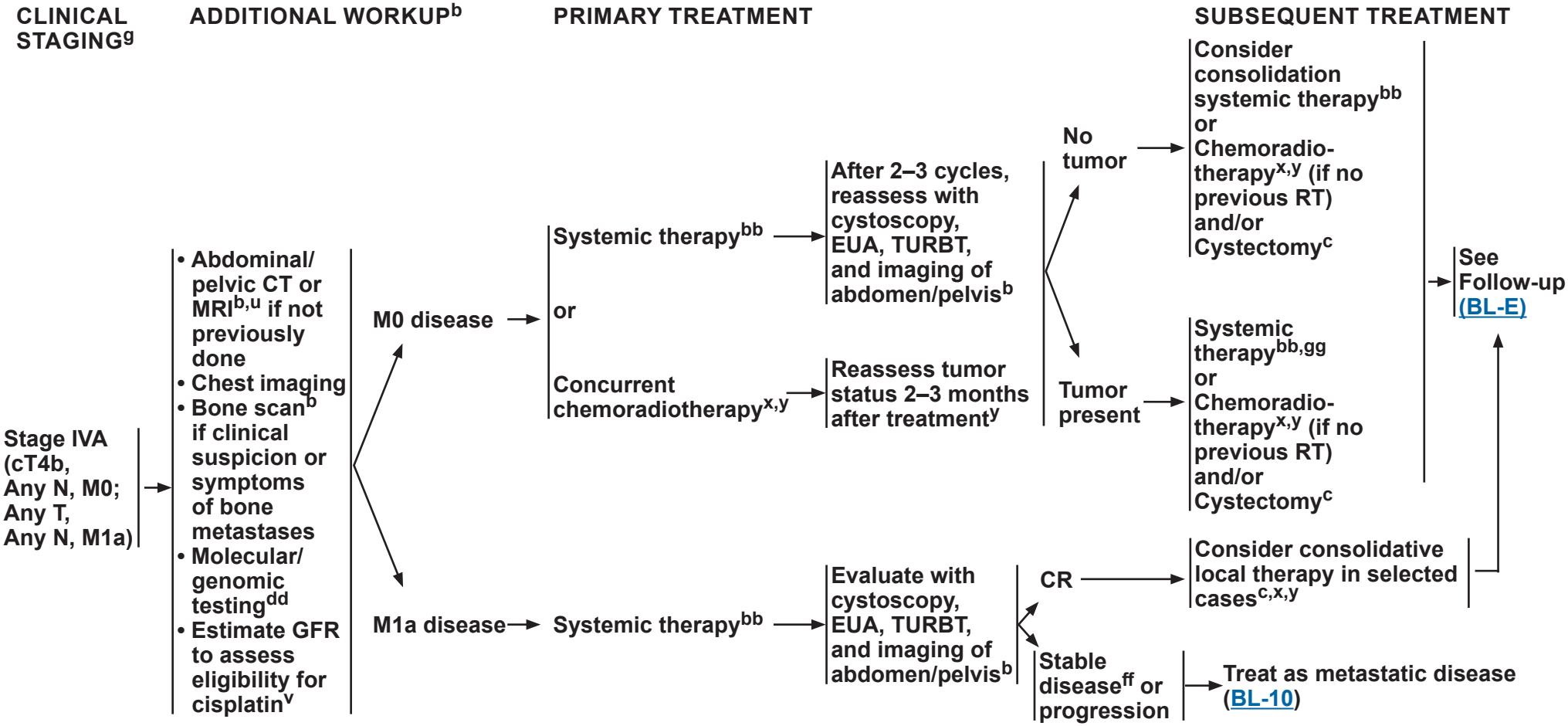

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[dd] Molecular/genomic testing in a CLIA-approved laboratory, including FGFR RGQ RT-PCR for *FGFR3* or *FGFR2* genetic alterations. See Discussion.
[ff] Non-bulky disease and no significant clinical progression.
[gg] See Principles of Systemic Therapy (BL-G 3 of 7 and 4 of 7).

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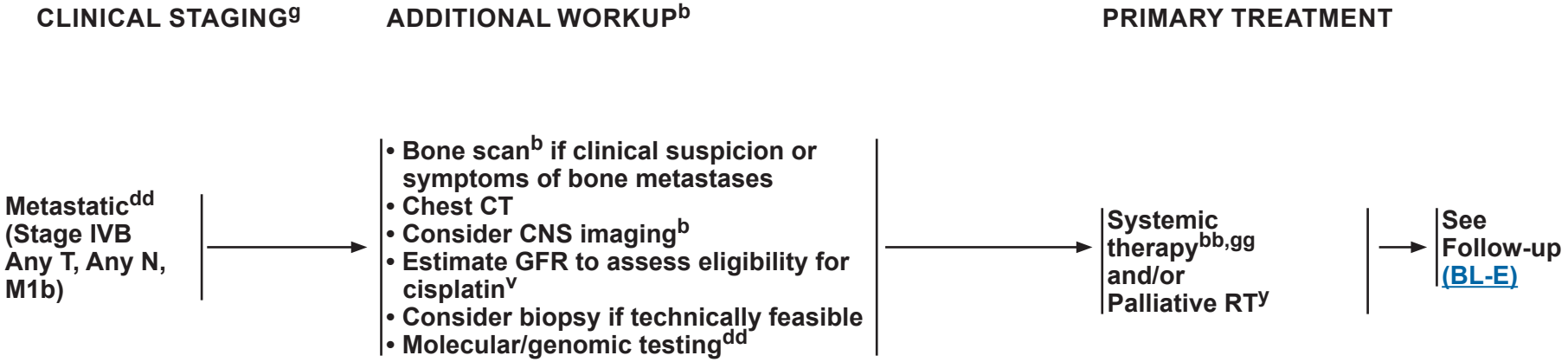
See Recurrent or Persistent Disease (BL-11)



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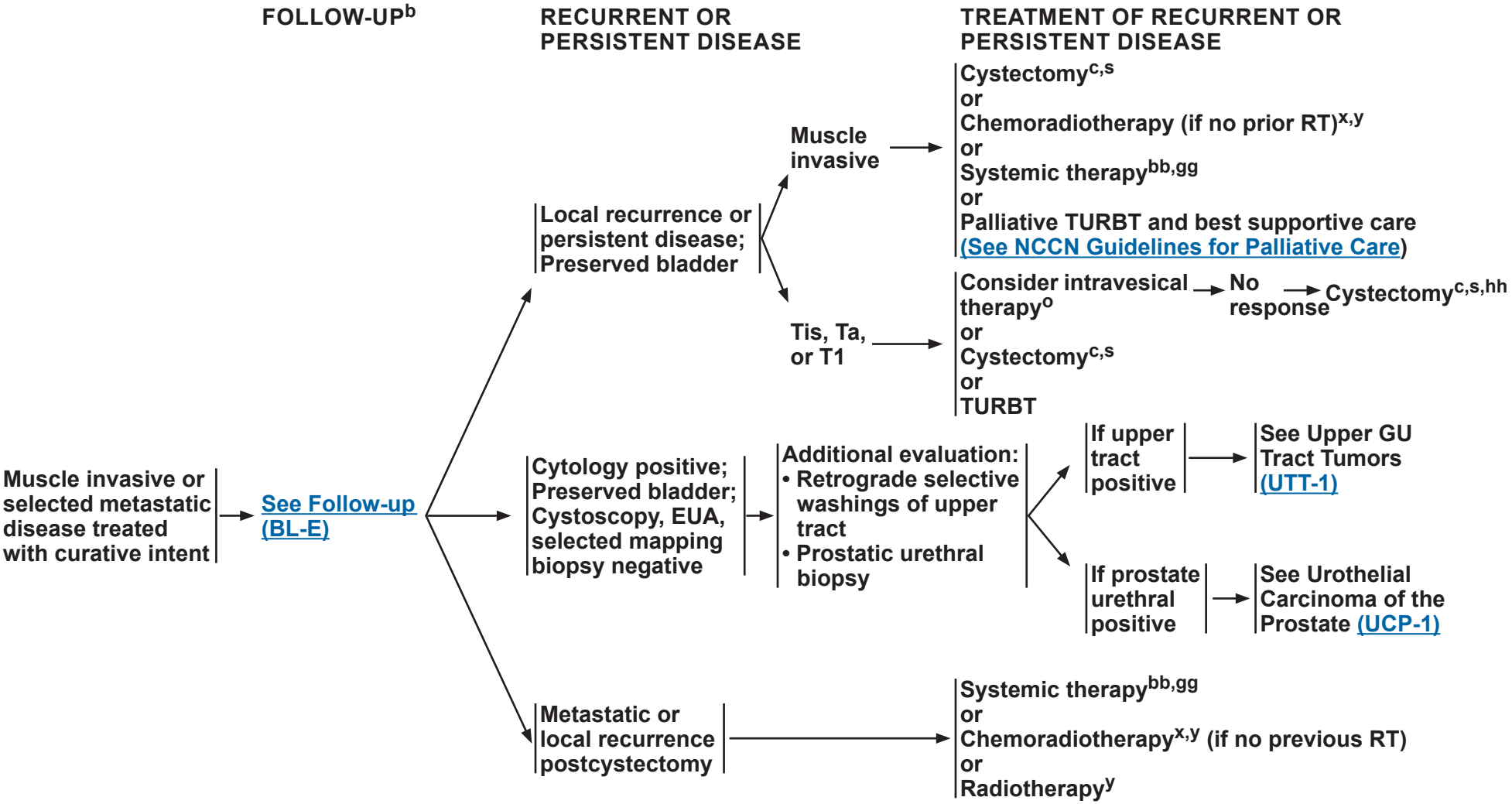

[b] See Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
[c] See Principles of Surgical Management (BL-B).
[o] See Principles of Intravesical Treatment (BL-F).
[s] See Follow-Up (BL-E).
[x] See Principles of Systemic Therapy (BL-G 5 of 7).
[y] See Principles of Radiation Management of Invasive Disease (BL-H).
[bb] See Principles of Systemic Therapy (BL-G 2 of 7).
[gg] See Principles of Systemic Therapy (BL-G 3 of 7 and 4 of 7).
[hh] If not a cystectomy candidate, consider concurrent chemoradiotherapy (See BL-G 5 of 7) (if no prior RT), change in intravesical agent, or a clinical trial.

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PRINCIPLES OF IMAGING FOR BLADDER/UROTHELIAL CANCER

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

Non-Muscle Invasive Bladder Cancer (NMIBC)

Chest Imaging

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

Abdominal and Pelvic Imaging

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

Evaluation for Suspected Bone Metastasis

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

Neurologic/Brain Imaging[4,5]

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

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Continued
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PRINCIPLES OF IMAGING FOR BLADDER/UROTHELIAL CANCER

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Muscle Invasive Bladder Cancer (MIBC)

Chest Imaging

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

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

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

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Continued
References

PRINCIPLES OF IMAGING FOR BLADDER/UROTHELIAL CANCER

Muscle Invasive Bladder Cancer (continued)

Abdominal and Pelvic Imaging

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

Evaluation for Suspected Bone Metastasis

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

Metastatic Disease - Patients Being Observed

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

Neurologic/Brain Imaging[4,5]

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

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Continued
References

PRINCIPLES OF IMAGING FOR BLADDER/UROTHELIAL CANCER

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

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

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

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

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

References

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PRINCIPLES OF IMAGING FOR BLADDER/UROTHELIAL CANCER
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[8] Goodfellow H, Viney Z, Hughes P, et al. Role of fluorodeoxyglucose positron emission tomography (FDG PET)-computed tomography (CT) in the staging of bladder cancer. BJU Int 2014;114:389-395.
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[11] Zhang J, Gerst S, Lefkowitz RA, et al. Imaging of bladder cancer. Radiol Clin North Am 2007;45:183-205.
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[13] Gakis G, Witjes JA, Compérat E, et al. EAU guidelines on primary urethral carcinoma. Eur Urol 2013;64:823-830.

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

TURBT/Maximal TURBT for Treatment

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

Continued

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PRINCIPLES OF SURGICAL MANAGEMENT

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

Transurethral Resection (TUR) of the Urethral Tumor
- Primary treatment of Tis, Ta, T1 primary carcinoma of the urethra.
- Patients with a prior radical cystectomy and a cutaneous diversion should consider a total urethrectomy.
- Consider postsurgical intraurethral therapy [see Principles of Intravesical Treatment (BL-F)].

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

Radical Cystectomy/Cystoprostatectomy
- In non-muscle invasive disease, radical cystectomy is generally reserved for residual high-grade cT1, variant histology, lymphovascular invasion, concomitant CIS, and Bacillus Calmette-Guérin (BCG)-unresponsive disease.
- Cystectomy should be done within 3 months of diagnosis if no therapy is given.
- Primary treatment option for cT2, cT3, and cT4a disease. Highly select patients with cT4b disease that responds to primary treatment may be eligible for cystectomy.
- Should be given with neoadjuvant cisplatin-based combination chemotherapy for patients with cT2–cT4a disease. For patients who cannot receive neoadjuvant chemotherapy, radical cystectomy alone is an option.
- Bilateral pelvic lymphadenectomy should be performed and include common, internal iliac, external iliac, and obturator nodes.
- In appropriately selected female patients, approaches that preserve the uterus, vagina, and/or ovaries should be employed when feasible.

Radical Nephroureterectomy with Cuff of Bladder
- Primary treatment option for non-metastatic high-grade upper GU tract tumors.
- For upper GU tract urothelial carcinoma, strongly consider single-dose immediate postoperative intravesical chemotherapy, as randomized trials have shown a decrease in intravesical recurrence. The most commonly used option for intravesical chemotherapy is mitomycin; gemcitabine is being utilized in select patients.
- Neoadjuvant chemotherapy should be considered in select patients with high-grade disease or concerning radiographic findings.
- Adjuvant chemotherapy may also be considered in patients who did not receive neoadjuvant chemotherapy (Birtle A, et al. Lancet 2020;395:1268-1277).

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PRINCIPLES OF SURGICAL MANAGEMENT

Regional Lymphadenectomy

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

Urethrectomy

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

Pelvic Exenteration (category 2B)

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

Continued

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PRINCIPLES OF SURGICAL MANAGEMENT

Endoscopic Management of Upper Tract Urothelial Cancer (UTUC)

- Favorable clinical and pathologic criteria for nephron preservation:
  - Low-grade tumor based on cytology and biopsy
  - Papillary architecture
  - Tumor size <1.5 cm
  - Unifocal tumor
  - Cross-sectional imaging showing no concern for invasive disease
- For favorable tumors - ureteroscopic and percutaneous management provide similar survival outcomes compared to nephroureterectomy
- Less favorable clinical and pathologic criteria for nephron preservation:
  - Multifocal tumors
  - Flat or sessile tumor architecture
  - Tumor size >1.5 cm
  - High-grade tumors
  - cT2–T4 tumors
  - Mid and proximal ureteral tumor due to technical challenges
  - Tumor crossing in fundibulum or ureteropelvic junction
- Imperative indications for conservative therapy of UTUC
  - Bilateral renal pelvis and/or urothelial carcinoma of the ureter
  - Solitary or solitary functioning kidney
  - Chronic kidney disease/renal insufficiency
- Percutaneous or ureteroscopic surgical procedures
  - Tumor fulguration/cautery
  - Tumor resection incorporating electrical energy, baskets, or cold cup devices with fulguration of the tumor bed
  - Laser therapies (Nd:YAG – penetration 4–6 mm; Ho:YAG – shallow penetration <0.5 mm)
- Extirpative surgical procedures
  - Segmental ureterectomy ± ureteral reimplantation for distal ureteral tumors
  - Complete ureterectomy with ileal ureter replacement (proximal/mid ureteral tumors)
- Topical immunotherapy and chemotherapy management
  - BCG, mitomycin
  - Route of administration might include percutaneous antegrade (preferred) or retrograde ureteral catheters
  - Induction and maintenance therapy regimens, similar to intravesical therapy, can be used
- Patients with renal pelvis and urothelial carcinoma of the ureter managed with nephron-preserving procedures and adjunctive therapies require long-term surveillance, including cross-sectional urography or endoscopic visualization. Treatment can be associated with patient anxiety, tumor seeding, and the need for multiple procedures and ultimate nephroureterectomy with bladder cuff. Clinical/pathologic understaging is problematic. Recurrence or tumor persistence might be life-threatening due to disease progression.

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

Urothelial Tumors
- Infiltrating urothelial carcinoma
  - Infiltrating urothelial carcinoma
  - Infiltrating urothelial carcinoma with divergent differentiation
    - ◊ Squamous differentiation
    - ◊ Glandular differentiation
    - ◊ Trophoblastic differentiation
    - ◊ Müllerian differentiation
  - Infiltrating urothelial carcinoma, variants:
    - ◊ Nested, including large nested
    - ◊ Microcystic
    - ◊ Micropapillary
    - ◊ Lymphoepithelioma-like
    - ◊ Plasmacytoid/ signet ring cell/diffuse
    - ◊ Sarcomatoid
    - ◊ Giant cell
    - ◊ Poorly differentiated
    - ◊ Lipid-rich
    - ◊ Clear cell
- Noninvasive urothelial neoplasms
  - Urothelial CIS
  - Noninvasive papillary urothelial carcinoma, low grade
  - Noninvasive papillary urothelial carcinoma, high-grade
  - Papillary urothelial neoplasm of low malignant potential
  - Urothelial papilloma
  - Inverted urothelial papilloma
  - Urothelial proliferation of uncertain malignant potential
  - Urothelial dysplasia[a]

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

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

Urachal Carcinoma

Tumors of Müllerian Type
- Clear cell carcinoma
- Endometrioid carcinoma

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

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

Urothelial Tract Hematopoietic and Lymphoid Tumors

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

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

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Continued

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PRINCIPLES OF PATHOLOGY MANAGEMENT

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

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BLADDER CANCER: NON-UROTHELIAL AND UROTHELIAL WITH VARIANT HISTOLOGY

Mixed Histology:
- Urothelial carcinoma plus squamous differentiation, adenocarcinoma differentiation, micropapillary, nested, plasmacytoid, and sarcomatoid should be identified because of the potential to have a more aggressive natural history.
- These are usually treated in a similar manner to pure urothelial carcinoma of the bladder.
- Micropapillary,[1,2] plasmacytoid,[3] and sarcomatoid histologies are generally at higher risk for progression to muscle invasive disease and a more aggressive approach should be considered.

Pure Squamous:
- No proven role for neoadjuvant/adjuvant chemotherapy for pure squamous cell carcinoma of the bladder.
- Local control with surgery or RT and best supportive care (See NCCN Guidelines for Palliative 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 Carcinoma:
- 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 (See NCCN Guidelines for Palliative Care) recommended.
- For urachal carcinoma with localized disease, a partial or complete cystectomy with en bloc resection of the urachal ligament with umbilicus and lymph node dissection is recommended.
- For node-positive disease, consider chemotherapy with colorectal regimen (FOLFOX [oxaliplatin, leucovorin, and 5-FU] or GemFLP [5-FU, leucovorin, gemcitabine, and cisplatin]). Consider post-chemotherapy surgical consolidation in responding disease.
- For advanced disease, clinical trial preferred. For selected patients, combination chemotherapy with a 5-FU–based regimen (FOLFOX or GemFLP) or ITP (paclitaxel, ifosfamide, and cisplatin). Alternatively, combination paclitaxel and platinum may be considered.[4,6]
- For non-urachal pure adenocarcinoma, consider additional metastatic workup. See NCCN Guidelines for Occult Primary.

Any Small Cell Component (or neuroendocrine features):
- Concurrent chemoradiotherapy or neoadjuvant chemotherapy followed by local treatment (cystectomy or radiotherapy) is recommended for any patient with small cell component histology with localized disease regardless of stage. (See Principles of Systemic Therapy in NCCN Guidelines for Small Cell Lung Cancer)
- 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

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

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

Low Risk	Intermediate Risk	High Risk
• Papillary urothelial neoplasm of low malignant potential • Low grade urothelial carcinoma ▸ Ta and ▸ ≤3 cm and ▸ Solitary	• Low grade urothelial carcinoma ▸ T1 or ▸ >3 cm or ▸ Multifocal or ▸ Recurrence within 1 year • High grade urothelial carcinoma ▸ Ta and ▸ ≤3 cm and ▸ Solitary	• High grade urothelial carcinoma ▸ CIS or ▸ T1 or ▸ >3 cm or ▸ Multifocal • Very high risk features (any): ▸ BCG unresponsive ▸ Variant histologies ▸ Lymphovascular invasion ▸ Prostatic urethral invasion

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

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

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

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

[1] See AUA Risk Stratification for Non-Muscle Invasive Bladder Cancer definitions on BL-2.
[2] Upper tract imaging includes CTU, MRU, intravenous pyelogram (IVP), retrograde pyelography, or ureteroscopy.
[3] Abdominal/pelvic imaging includes CT or MRI.
[4] See Principles of Imaging for Bladder/Urothelial Cancer (BL-A).

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See NCCN Guidelines for Survivorship

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

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

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

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

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

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

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

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

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

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Table 6: Post-Cystectomy Muscle Invasive Bladder Cancer

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

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

See Recurrent or Persistent Disease (BL-11)

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

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

Test	Year						
	1	2	3	4	5	5–10	>10
Cystoscopy	Every 3 mo		Every 6 mo		Annually		As clinically indicated
Imaging[4]	• CTU or MRU (image upper tracts + axial imaging of abdomen/pelvis) every 3–6 mo for MIBC • Chest x-ray or CT chest every 3–6 mo for MIBC or • FDG PET/CT (category 2B) only if metastatic disease suspected		• Abdominal/pelvic CT or MRI annually • Chest x-ray or CT chest annually or • FDG PET/CT (category 2B) only if metastatic disease suspected[9]			As clinically indicated	
Blood tests	• Renal function testing (electrolytes and creatinine) every 3–6 mo • LFT[7] every 3–6 mo • CBC, CMP every 3–6 mo if received chemotherapy	• Renal function testing (electrolytes and creatinine) as clinically indicated • LFT[7] as clinically indicated					
Urine tests	Urine cytology[5] every 6–12 mo		Urine cytology[5] as clinically indicated				

[4] See Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
[5] Urine cytology should be done at time of cystoscopy if bladder in situ.
[7] Liver function testing includes AST, ALT, bilirubin, and alkaline phosphatase.
[9] PET/CT not recommended for NMIBC.

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Table 8: Metastatic Disease: Observation

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

[4] See Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
[5] Urine cytology should be done at time of cystoscopy if bladder in situ.

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PRINCIPLES OF INTRAVESICAL TREATMENT

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

Intravesical Therapy for Bladder Cancer

Immediate Postoperative Intravesical Chemotherapy

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

Induction (Adjuvant) Intravesical Chemotherapy or BCG

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

Maintenance Intravesical BCG

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

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Continued
References

PRINCIPLES OF INTRAVESICAL TREATMENT

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

Topical or Percutaneous Administration of Chemotherapy or BCG

- **Although the target site differs, the principles of this treatment are similar to intravesical therapy. Topical chemotherapeutic agents are delivered by instillation. Administration can be percutaneous or through a retrograde approach using a catheter. There is no standard regimen and patients should be referred to an institution with experience in this treatment or a clinical trial.**

Postsurgical Intraprostatic BCG for Urothelial Carcinoma of the Prostate

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

Postsurgical Intraurethral Therapy for Primary Carcinoma of the Urethra

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

Intrapelvic and Intravesical Therapy for Upper Tract Tumors

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

References

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PRINCIPLES OF INTRAVESICAL TREATMENT
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PRINCIPLES OF SYSTEMIC THERAPY

Neoadjuvant chemotherapy [preferred for bladder]
Preferred regimen • DDMVAC (dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin) with growth factor support for 3-6 cycles[1,2] **Other recommended regimens** • Gemcitabine and cisplatin for 4 cycles[3,4]

Adjuvant therapy	
No previous platinum-based neoadjuvant therapy (pT3, pT4a, pN+)	**Preferred regimen** • DDMVAC with growth factor support for 3-6 cycles[1,2] **Other recommended regimens** • Gemcitabine and cisplatin for 4 cycles[3,4] • Nivolumab[5]
Previous platinum-based neoadjuvant therapy (ypT2-ypT4a or ypN+)	**Other recommended regimen** • Nivolumab[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 MIBC.[1,6,7]
- Meta-analysis suggests overall survival benefit with adjuvant cisplatin-based chemotherapy for pathologic T3, T4 or N+ disease at cystectomy, if it was not given as neoadjuvant.[7]
- Neoadjuvant chemotherapy is preferred over adjuvant-based chemotherapy on a higher level of evidence data.
- DDMVAC is preferred over standard MVAC based on category 1 evidence for metastatic disease showing DDMVAC to be better tolerated and more effective than conventional MVAC in advanced disease.[2,8] Based on these data, the traditional dose and schedule for MVAC is no longer recommended.
- Perioperative gemcitabine and cisplatin is a reasonable alternative to DDMVAC based on category 1 evidence for metastatic disease showing equivalence to conventional MVAC in the setting of advanced disease.[4,9]
- For gemcitabine/cisplatin, a 21-day cycle is preferred. Better dose compliance may be achieved with fewer delays in dosing using the 21-day schedule.[10]
- Neoadjuvant chemotherapy may be considered for select patients with UTUC, particularly for higher stage and/or grade tumors, as renal function will decline after nephroureterectomy and may preclude adjuvant therapy.
  - Adjuvant therapy should be considered if neoadjuvant therapy was not given for UTUC (Birtle A, et al. Lancet 2020;395:1268-1277).
- Carboplatin should not be substituted for cisplatin in the perioperative bladder cancer setting.
  - For patients with borderline renal function or minimal dysfunction, a split-dose administration of cisplatin may be considered (such as 35 mg/m^2 on days 1 and 2 or days 1 and 8) (category 2B). While safer, the relative efficacy of the cisplatin-containing combination administered with such modifications remains undefined.
- For patients with borderline renal function, estimate GFR to assess eligibility for cisplatin. Consider timed urine collection, which may more accurately determine eligibilty for cisplatin.

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Continued
References

PRINCIPLES OF SYSTEMIC THERAPY

First-line systemic therapy for locally advanced or metastatic disease (Stage IV)	
Cisplatin eligible	**Preferred regimens** • Gemcitabine and cisplatin[4] (category 1) followed by avelumab maintenance therapy (category 1)[a,11] • DDMVAC with growth factor support (category 1)[2,8] followed by avelumab maintenance therapy (category 1)[a,11]
Cisplatin ineligible	**Preferred regimens** • Gemcitabine and carboplatin[12] followed by avelumab maintenance therapy (category 1)[a,11] • Atezolizumab[13] (only for patients whose tumors express PD-L1[b] or who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression) • Pembrolizumab[14] (for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for any platinum-containing chemotherapy) **Other recommended regimens** • Gemcitabine[15] • Gemcitabine and paclitaxel[16] **Useful under certain circumstances** • Ifosfamide, doxorubicin, and gemcitabine[17] (for patients with good kidney function and good PS)

- The presence of both non-nodal metastases and ECOG performance score ≥2 strongly predict poor outcome with chemotherapy. Patients without these adverse prognostic factors have the greatest benefit from chemotherapy. The impact of these factors in relation to immune checkpoint inhibition is not fully defined, but they remain poor prognostic indicators in general.
- For most patients, the risks of adding paclitaxel to gemcitabine and cisplatin outweigh the limited benefit seen in the randomized trial.[18]
- A substantial proportion of patients cannot receive cisplatin-based chemotherapy due to renal impairment or other comorbidities.
  - Participation in clinical trials of new or more tolerable therapy is recommended.

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

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References

PRINCIPLES OF SYSTEMIC THERAPY

Second-line systemic therapy for locally advanced or metastatic disease (Stage IV) (post-platinum)[c,d] Participation in clinical trials of new agents is recommended.	
Preferred regimen • Pembrolizumab (category 1)[19]	**Other recommended regimens** • Paclitaxel[25] or docetaxel[26] • Gemcitabine[15]
Alternative preferred regimens • Immune checkpoint inhibitor ▸ Nivolumab[20] ▸ Avelumab[21,22] • Erdafitinib[e,23] • Enfortumab vedotin-ejfv[f,24]	**Useful in certain circumstances based on prior medical therapy** • Ifosfamide, doxorubicin, and gemcitabine[17] • Gemcitabine and paclitaxel[16] • Gemcitabine and cisplatin[4] • DDMVAC with growth factor support[2]

Second-line systemic therapy for locally advanced or metastatic disease (Stage IV) (post-checkpoint inhibitor) Participation in clinical trials of new agents is recommended.	
Preferred regimens for cisplatin ineligible, chemotherapy naïve • Enfortumab vedotin-ejfv[24] • Gemcitabine/carboplatin	**Other recommended regimens** • Erdafitinib[e,23] • Paclitaxel or docetaxel[26] • Gemcitabine[15]
Preferred regimens for cisplatin eligible, chemotherapy naïve • Gemcitabine and cisplatin[4] • DDMVAC with growth factor support[2]	**Useful in certain circumstances based on prior medical therapy** • Ifosfamide, doxorubicin, and gemcitabine[17] • Gemcitabine and paclitaxel[16]

[c] If PFS >12 months after platinum (eg, cisplatin or carboplatin), consider re-treatment with platinum if the patient is still platinum eligible.
[d] Also for patients who received a therapy other than platinum or an immune checkpoint inhibitor in first-line.
[e] Only for patients with susceptible *FGFR3* or *FGFR2* genetic alterations.
[f] Indicated for cisplatin ineligible patients who have received one or more prior lines of therapy.

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References

PRINCIPLES OF SYSTEMIC THERAPY

Subsequent-line systemic therapy for locally advanced or metastatic disease (Stage IV)[g,h] Participation in clinical trials of new agents is recommended.	
Preferred regimens • Enfortumab vedotin-ejfv (category 1)[27,28] • Erdafitinib[e]	**Other recommended regimens** • Gemcitabine[15] • Paclitaxel[25] or docetaxel[26] • Ifosfamide, doxorubicin, and gemcitabine[17] • Gemcitabine and paclitaxel[16] • Gemcitabine and cisplatin[4] • DDMVAC with growth factor support[2] • Sacituzumab govitecan-hziy[29]

[e] Only for patients with susceptible *FGFR3* or *FGFR2* genetic alterations.
[g] Patient should have already received platinum and a checkpoint inhibitor, if eligible.
[h] These therapies are appropriate for patients who received a first-line platinum-containing chemotherapy followed by avelumab maintenance therapy.

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References

PRINCIPLES OF SYSTEMIC THERAPY

Radiosensitizing chemotherapy regimens for organ-preserving chemoradiation
Preferred regimens (doublet chemotherapy is preferred when feasible) • Cisplatin and 5-FU[30,31] • Cisplatin and paclitaxel[30,32] • 5-FU and mitomycin[33] • Cisplatin[i] alone[34]
Other recommended regimen • Low-dose gemcitabine[31,35,36] (category 2B)

Radiosensitizing chemotherapy given concurrently with conventionally fractionated radiation with palliative intent for regional disease
Preferred regimen • Cisplatin[i]
Other recommended regimens • Taxane (docetaxel or paclitaxel) (category 2B) • 5-FU (category 2B) • 5-FU and mitomycin (category 2B) • Low-dose gemcitabine[31] (category 2B) • Capecitabine (category 3)

[i] 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 RADIATION MANAGEMENT OF INVASIVE DISEASE

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

- **Precede radiation therapy (RT) alone or concurrent chemoradiotherapy by maximal TUR of the tumor when safely possible.**
- **Simulating and treating patients when they have an empty bladder is preferred for daily reproducibility (bladder full for tumor boosts is acceptable with image guidance).**
- **Use multiple fields from high-energy linear accelerator beams.**
- **For invasive tumors, consider low-dose preoperative RT prior to segmental cystectomy (category 2B).**
- **Concurrent chemoradiotherapy or RT alone is most successful for patients without hydronephrosis and without extensive CIS associated with their muscle-invading tumor.**
- **For patients with stage Ta, T1, or Tis, external beam RT (EBRT) alone is rarely appropriate. For patients with recurrent Ta–T1 disease usually following BCG therapy but without extensive Tis who are not candidates for cystectomy, concurrent chemoradiotherapy may be considered as a potentially curative alternative to radical cystectomy, which is the standard treatment by NCCN Guidelines.**
- **Treat the whole bladder with or without pelvic nodal radiotherapy 39.6–50.4 Gy using conventional or accelerated hyperfractionation. Elective treatment to the lymph nodes is optional and should take into account patient comorbidities and the risks of toxicity to adjacent critical structures. Then boost either the whole or partial bladder between 60–66 Gy. For node-positive disease, consider boosting grossly involved nodes to the highest achievable dose that does not violate dose-volume histogram (DVH) parameters based on the clinical scenario. Reasonable alternatives to conventional fractionation include taking the whole bladder to 55 Gy in 20 fractions, or using simultaneous integrated boosts to sites of gross disease.**
- **When irradiating the bladder only or bladder tumor boost, consider daily image guidance.**
- **Concurrent chemoradiotherapy is recommended for added tumor cytotoxicity, and can be given without significant increased toxicity over RT alone. Concurrent 5-FU and mitomycin C or low-dose gemcitabine can be used instead of cisplatin-containing regimens in patients with low or moderate renal function. Such therapy is optimally given by dedicated multidisciplinary teams.**
- **Concurrent chemoradiotherapy (preferred) or RT alone should be considered as potentially curative therapy for medically inoperable patients. Concurrent chemoradiotherapy or RT alone should be considered for local palliation in patients with metastatic disease.**
- **When giving palliative radiation for metastatic bladder cancer or for recurrent pelvic tumor, combining radiation with radiosensitizing chemotherapy should be considered. See BL-G 5 of 7 for agents. Chemotherapy should not be used concurrently with high-dose (>3 Gy per fraction) palliative radiation.**
- **Treatment field should include whole bladder and all sites of gross disease plus or minus uninvolved regional lymph nodes. Regional lymph nodes include the hypogastric, obturator, internal and external iliac, perivesical, sacral, and presacral nodes. For involved nodal disease, the common iliac nodes are a site of secondary involvement.**
- **For patients with pT3/pT4 pN0–2 urothelial (pure urothelial or primary urothelial mixed with other subtypes) bladder cancer following radical cystectomy with ileal conduit, consider postoperative adjuvant pelvic RT (category 2B). Treatment field should encompass areas at risk for harboring residual microscopic disease based on pathologic findings at resection and may include cystectomy bed and pelvic lymph nodes with doses in the range of 45 to 50.4 Gy. Involved resection margins and areas of extranodal extension could be boosted to 54–60 Gy if feasible based on normal tissue constraints.**
- **Tumor status assessment after completion of full-dose primary chemoradiotherapy. See Table 7 on BL-E 5 of 6.**
- **In highly selected T4b tumor cases, may consider intraoperative RT.**
- **Concurrent chemoradiotherapy is generally most suitable for patients with solitary tumors, negative nodes, no extensive or multifocal CIS, no moderate/severe tumor-related hydronephrosis, and good pre-treatment bladder function.**

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References

PRINCIPLES OF RADIATION MANAGEMENT OF INVASIVE DISEASE

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

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

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

  - **Postoperative adjuvant radiation therapy**
    - ◊ **Treatment field should encompass areas at risk for harboring residual microscopic disease based on pathologic findings at resection and may include resection bed, inguinal lymph nodes, and pelvic lymph nodes. Areas at risk for harboring residual microscopic disease should receive 45–50.4 Gy EBRT. Involved resection margins and areas of extranodal extension should be boosted to 54–60 Gy if feasible based on normal tissue constraints. Areas of gross residual disease should be boosted to 66–70 Gy, if feasible based on normal tissue constraints. Concurrent chemotherapy with regimens used for bladder cancer should be considered for added tumor cytotoxicity.**
  - **Recurrent disease**
    - ◊ **Clinical target volume (CTV) should include gross disease in any suspected areas of spread at 66–74 Gy (higher dose up to 74 Gy for larger tumor and non-urothelial histology) and consideration can be given to elective regional-nodal basins (45–50.4 Gy) as discussed above, if feasible based on normal tissue constraints.**

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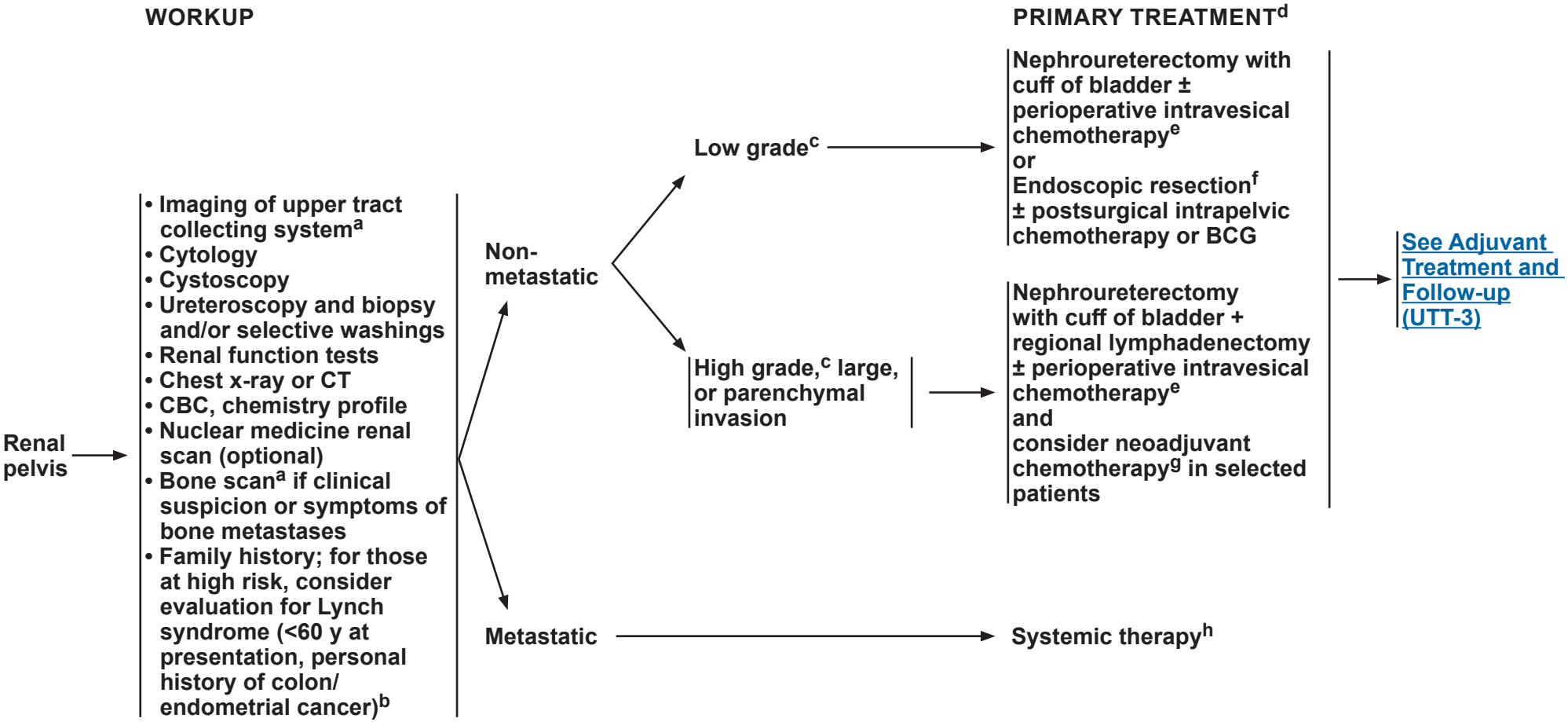

[a] See Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
[b] See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.
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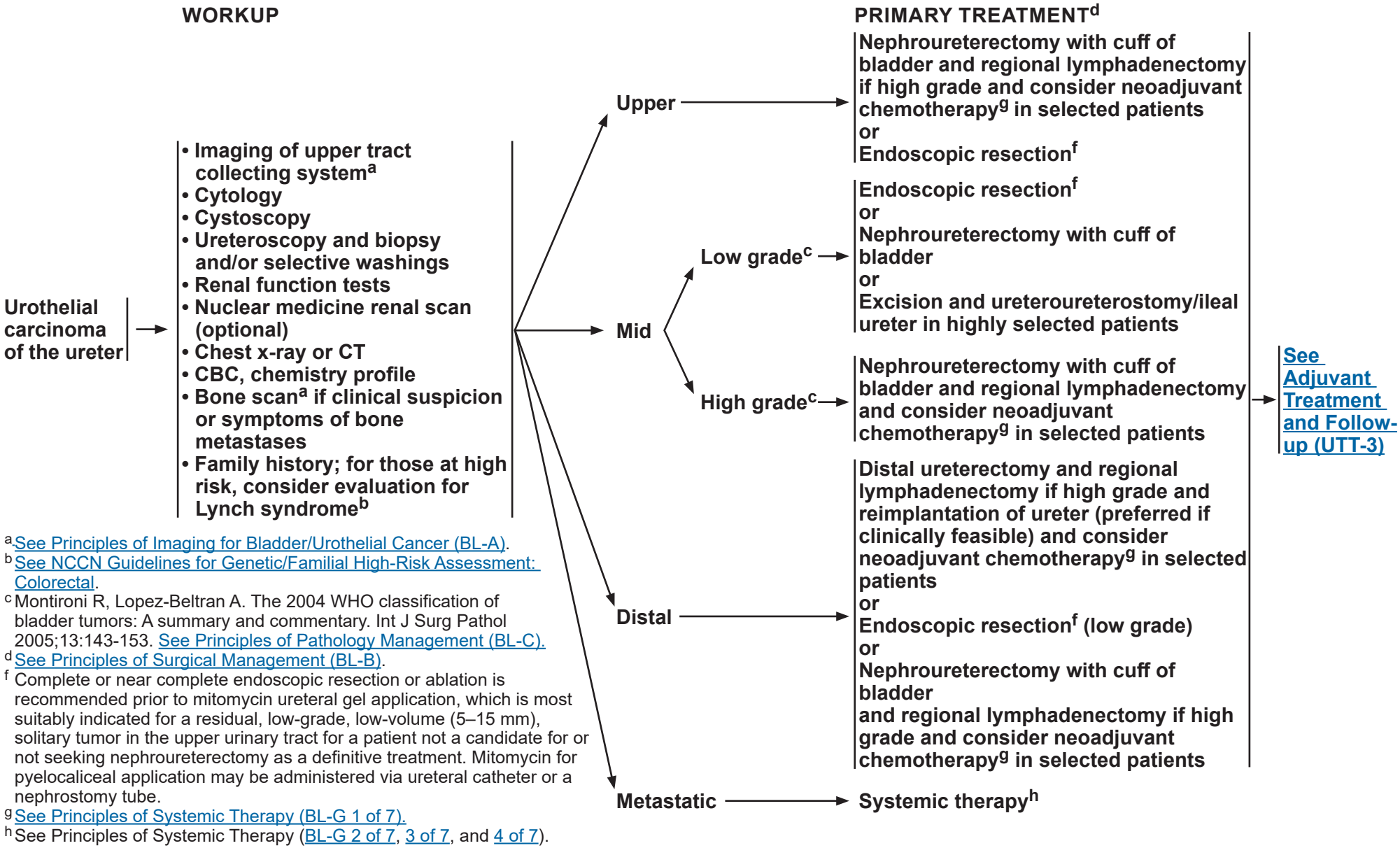
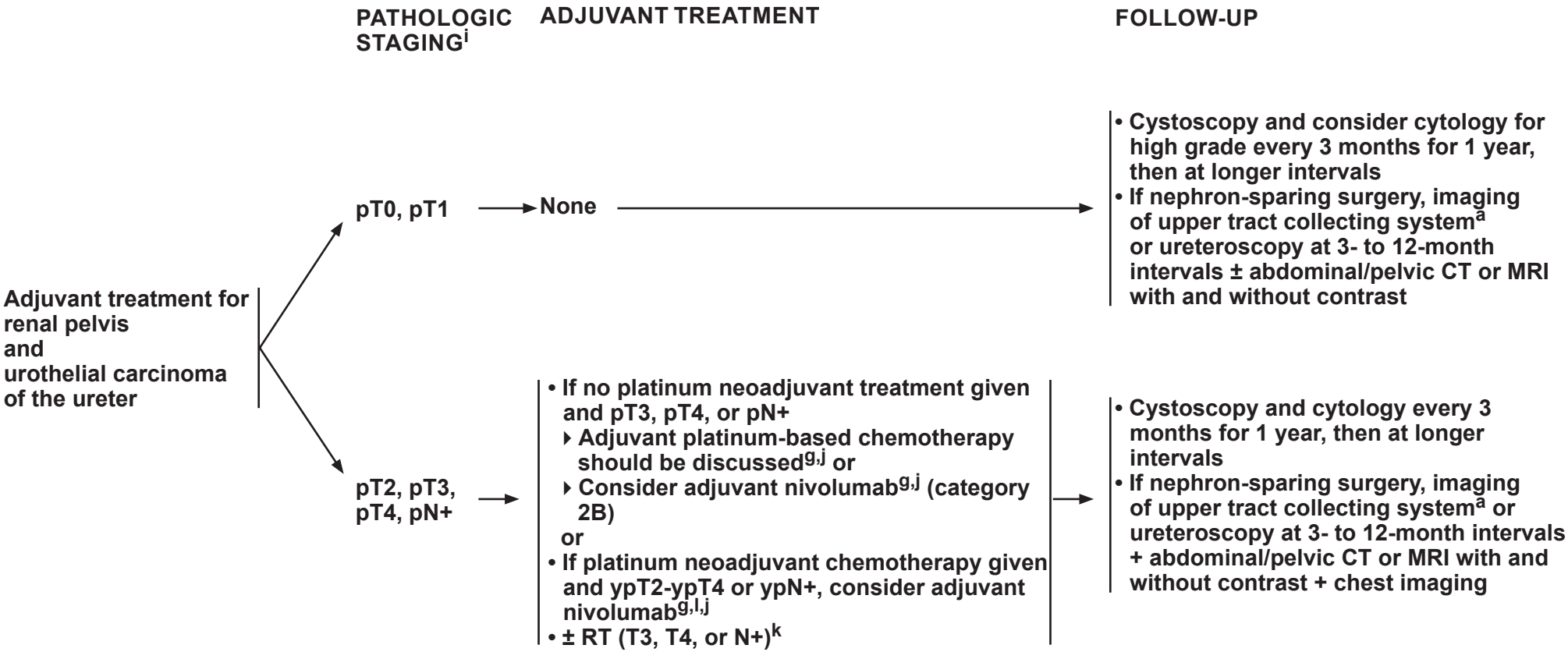
[d] See Principles of Surgical Management (BL-B).
[e] See Principles of Intravesical Treatment (BL-F).
[f] Complete or near complete endoscopic resection or ablation is recommended prior to mitomycin ureteral gel application, which is most suitably indicated for a residual, low-grade, low-volume (5–15 mm), solitary tumor in the upper urinary tract for a patient not a candidate for or not seeking nephroureterectomy as a definitive treatment. Mitomycin for pyelocaliceal application may be administered via ureteral catheter or a nephrostomy tube.
[g] See Principles of Systemic Therapy (BL-G 1 of 7).
[h] See Principles of Systemic Therapy (BL-G 2 of 7, 3 of 7, and 4 of 7).

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



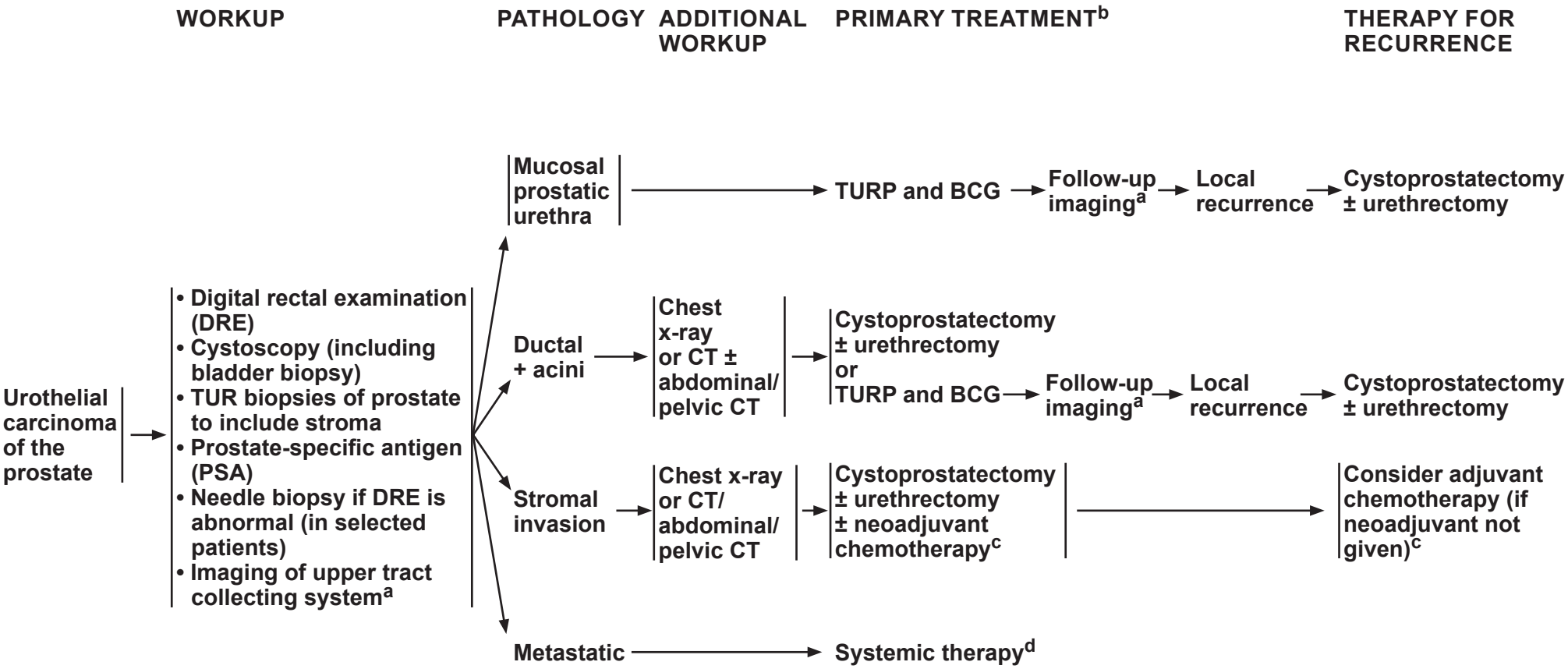
[a] See Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
[b] See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.
[c] Montironi R, Lopez-Beltran A. The 2004 WHO classification of bladder tumors: A summary and commentary. Int J Surg Pathol 2005;13:143-153. See Principles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

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



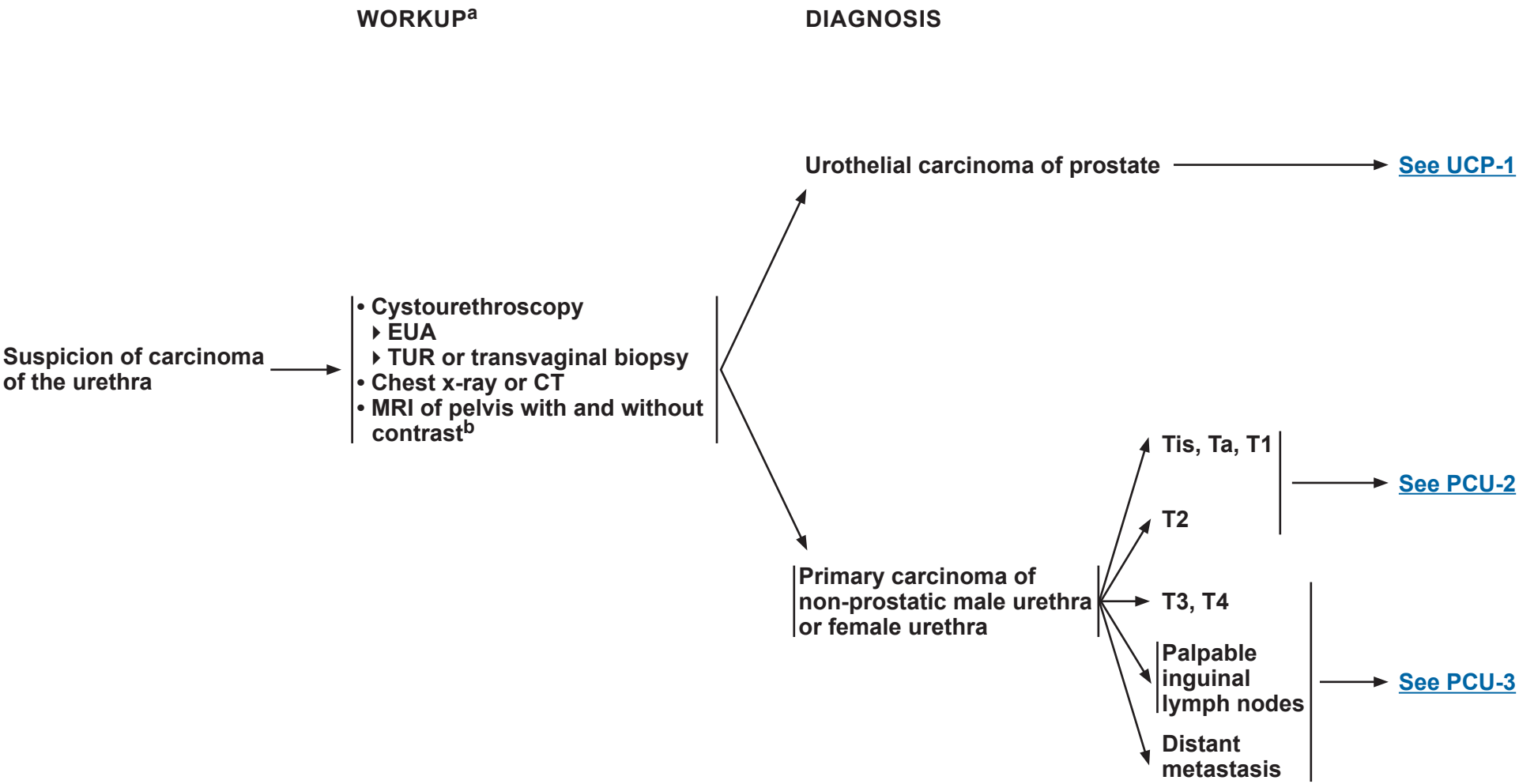
[a] See Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
[g] See Principles of Systemic Therapy (BL-G 1 of 7).
[i] The modifier “p” refers to pathologic staging based on surgical resection and lymph node dissection.
[j] Follow recommendations for adjuvant chemotherapy after ensuring that patient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

Note: All recommendations are category 2A unless otherwise indicated.
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).
[c] See Principles of Systemic Therapy (BL-G 1 of 7).
[d] See Principles of Systemic Therapy (BL-G 2 of 7, 3 of 7, and 4 of 7).

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.



[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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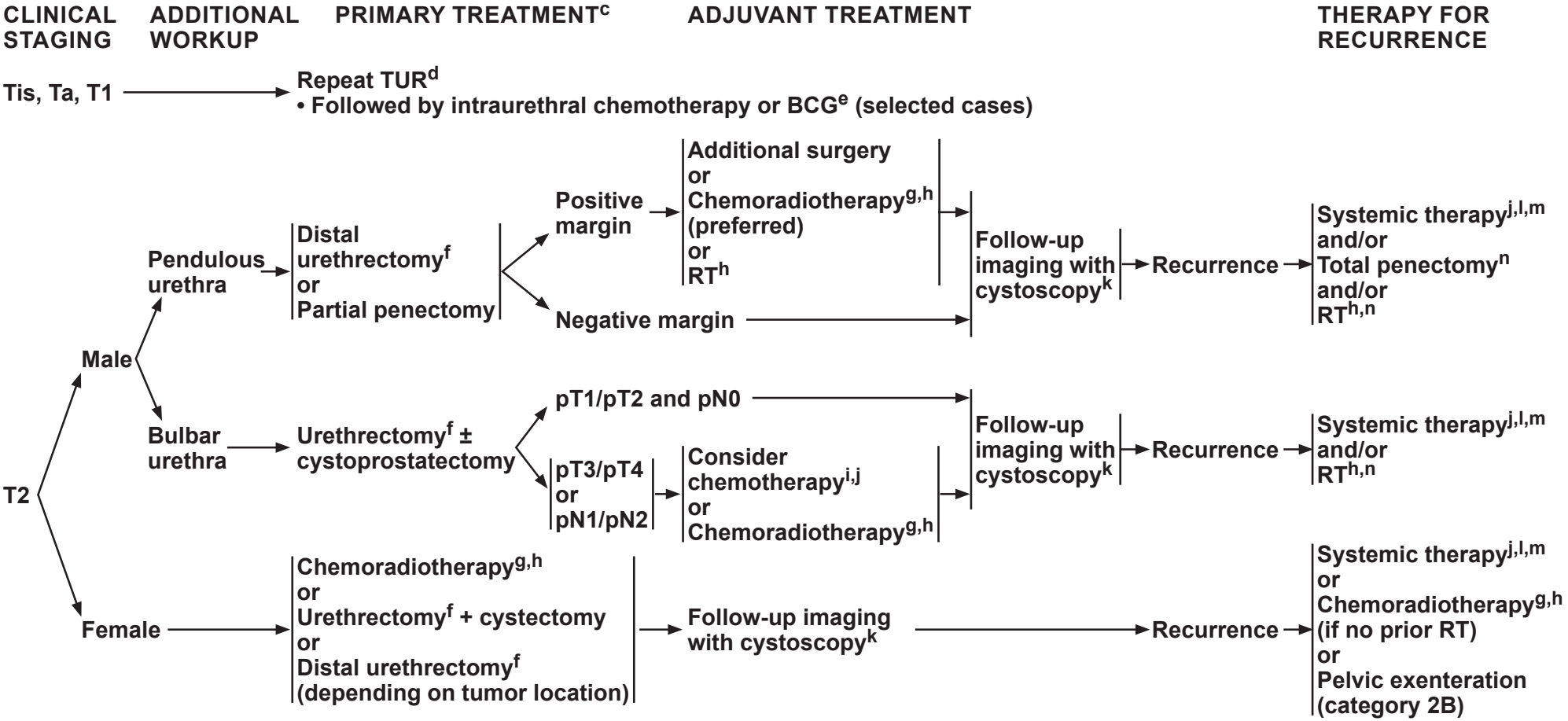
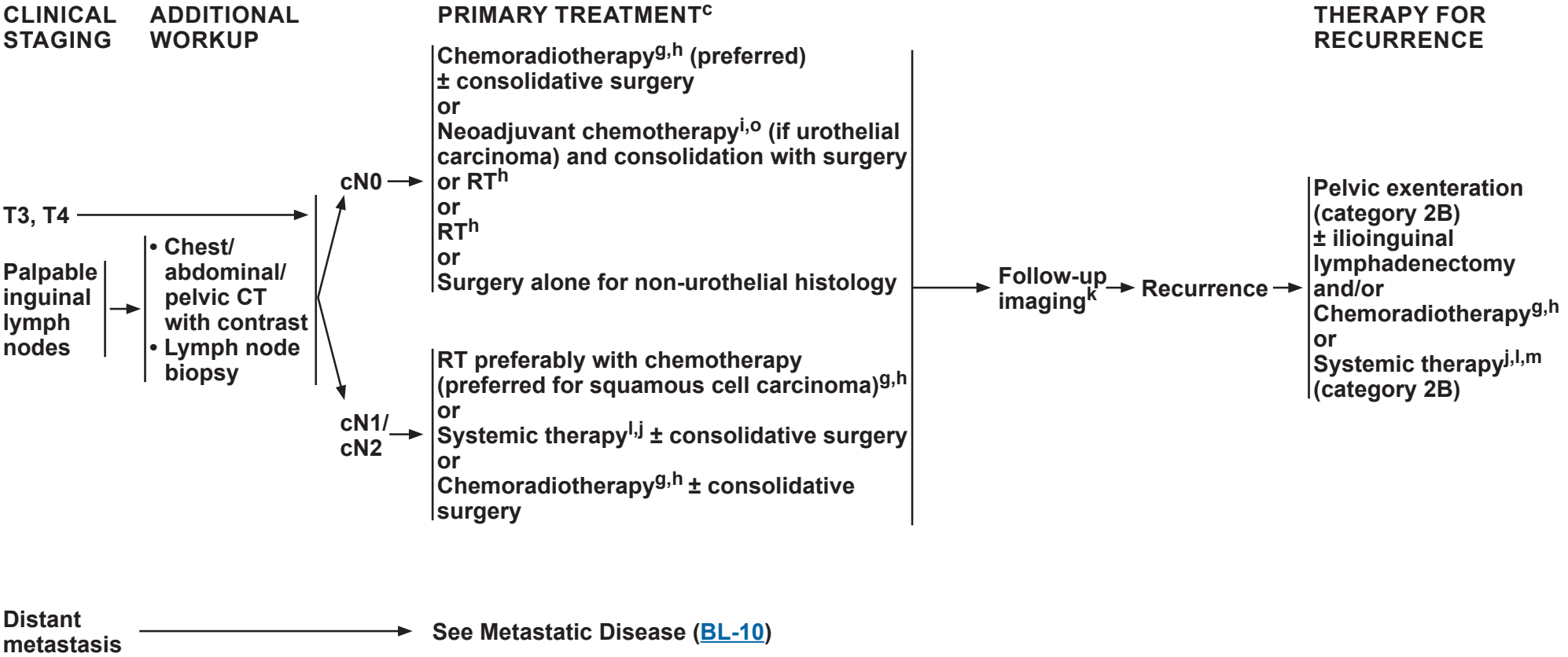
NCCN Guidelines Version 6.2021
Primary Carcinoma of the Urethra



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

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



[c] See Principles of Surgical Management (BL-B).
[g] See Principles of Systemic Therapy (BL-G 5 of 7).
[h] See Principles of Radiation Management of Invasive Disease-Carcinoma of the Urethra (BL-H 2 of 3).
[i] See Principles of Systemic Therapy (BL-G 1 of 7).
[j] Chemotherapy regimen based on histology. (Dayyani F, Pettaway C, Kamat A, et al. Retrospective analysis of survival outcomes and the role of cisplatin-based chemotherapy in patients with urethral carcinomas referred to medical oncologists. Urol Oncol 2013;31:1171-1177.) Also see Non-Urothelial Cell and Urothelial with Variant Histology (BL-D).
[k] See Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
[l] See Principles of Systemic Therapy (BL-G 2 of 7).
[m] See Principles of Systemic Therapy (BL-G 3 of 7 and 4 of 7).
[o] 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.

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

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

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

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

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

LG	Low-grade
HG	High-grade

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

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

Table 2. **AJCC Prognostic Groups**

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

Continued

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

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

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

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

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

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

LG	Low-grade
HG	High-grade

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

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

Table 4. **AJCC Prognostic Groups**

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

Continued

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

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

Male Penile Urethra and Female Urethra

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

Prostatic Urethra

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

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

M	Distant Metastasis
M0	No distant metastasis
M1	Distant metastasis

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

LG	Low grade
HG	High grade

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

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

Table 6. **AJCC Prognostic Groups**

	T	N	M
Stage 0is	Tis	N0	M0
Stage 0a	Ta	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1	N1	M0
	T2	N1	M0
	T3	N0	M0
	T3	N1	M0
Stage IV	T4	N0	M0
	T4	N1	M0
	Any T	N2	M0
	Any T	Any N	M1

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

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

All recommendations are category 2A unless otherwise indicated.

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

All recommendations are considered appropriate.

National Comprehensive Cancer Network®

NCCN Guidelines Version 6.2021
Bladder Cancer

Discussion

This discussion corresponds to the NCCN Guidelines for Bladder Cancer. Last updated December 6, 2021.

Table of Contents

Overview

An estimated 83,730 new cases of urinary bladder cancer (64,280 males and 19,450 females) will be diagnosed in the United States in 2021 with approximately 17,200 deaths (12,260 males and 4940 females) occurring during this same period.[1] Bladder cancer, the sixth most common cancer in the United States, is rarely diagnosed in individuals younger than 40 years. Given that the median age at diagnosis is 73 years,[2] medical comorbidities are a frequent consideration in patient management.

Risk factors for developing bladder cancer include male sex, white race, smoking, personal or family history of bladder cancer, pelvic radiation, environmental/occupational exposures, exposure to certain drugs, chronic infection or irritation of the urinary tract, and certain medical conditions including obesity and diabetes.[3-6] While diabetes mellitus appears to be associated with an elevated risk of developing bladder cancer,[4] treatment with metformin may be associated with improved prognosis in patients with bladder cancer and diabetes.[7] Certain genetic syndromes, most notably Lynch syndrome, may also predispose an individual to urothelial carcinoma.[8]

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

Literature Search Criteria and Guidelines Update Methodology

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

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

The data from key PubMed articles as well as articles from additional sources deemed as relevant to these Guidelines 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. NCCN recommendations have been developed to be inclusive of individuals of all sexual and gender identities to the greatest extent possible. When citing data and recommendations from other organizations, the terms *men*, *male*,

women, and *female* will be used to be consistent with the cited sources.

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

Clinical Presentation and Workup

The most common presenting symptom in patients with bladder cancer is microscopic or gross hematuria, although urinary frequency due to irritation or a reduced bladder capacity can also develop. Less commonly, the presenting symptom is a urinary tract infection. Upper tract obstruction or pain may occur in patients with a more advanced lesion. Patients presenting with these symptoms should be evaluated with office cystoscopy to determine if a lesion is present. Enhanced cystoscopy may be used if available. If a lesion is documented, the patient should be scheduled for a transurethral resection of the bladder tumor (TURBT) to confirm the diagnosis and determine the extent of disease within the bladder. Urine cytology may also be obtained around the time of cystoscopy. Because smoking is a major risk factor for bladder cancer,[10] screening for smoking and initiation of treatment for smoking cessation, if appropriate, is recommended during the initial evaluation (see NCCN Guidelines for Smoking Cessation).

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

TURBT with a bimanual examination under anesthesia (EUA) is performed to resect visible tumor and to sample muscle within the area of the tumor to assess invasion. In a case where the tumor is clearly not invasive (eg, multiple small papillary tumors), EUA would not be necessary. The goal of TURBT is to correctly identify the clinical stage and grade of disease while completely resecting all visible tumor. Therefore, an adequate sample that includes bladder muscle (ie, muscularis propria) preferentially should be obtained in the resection specimen, most notably in high-grade disease. A small fragment of tumor with few muscle fibers is inadequate for assessing the depth of invasion and guiding treatment recommendations. When a large papillary lesion is noted, more than one session may be needed to completely resect the tumor. With carcinoma in situ (CIS), biopsy of sites adjacent to the tumor and multiple random biopsies may be performed to assess for a field change. Single-dose intravesical gemcitabine or mitomycin (both category 1, although gemcitabine is preferred due to better tolerability and lower cost) within 24 hours of TURBT is recommended if non-muscle invasive disease is suspected (see *Intravesical Therapy)*. Existing data support this approach largely for low-volume, low-grade disease.[11-13]

Mapping or random biopsies of normal-appearing urothelium rarely yield positive results and lack sensitivity for CIS, especially for low-risk tumors.[14-17] In addition, these biopsies often cause additional damage to the bladder without benefit to the patient. Therefore, mapping biopsies of normal-appearing urothelium are not recommended for most patients.

Positive urinary cytology may indicate urothelial tumor anywhere in the urinary tract. In the presence of a positive cytology and a normal

cystoscopy, the upper tracts and the prostate (prostatic urethra) in men must be evaluated and ureteroscopy may be considered.

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

Pathology and Staging

The most commonly used staging system is the tumor, node, metastasis (TNM) staging system by the AJCC[18] (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 and TURBT specimens, with attention to histology, grade, and depth of invasion. These factors are used to estimate the probability of recurrence and progression to a more advanced stage. Patient bladder function, comorbidities, and life expectancy are also important considerations.

Approximately 75% of newly detected cases are non-muscle invasive disease—exophytic papillary tumors confined largely to the mucosa (Ta) (70%–75%) or, less often, to the lamina propria (T1) (20%–25%) or flat high-grade lesions (CIS, 5%–10%).[19,20] These tumors tend to be friable and have a high propensity for bleeding. Their natural history is characterized by a tendency to recur in the bladder, and these recurrences can either be at the same stage as the initial tumor or at a more advanced stage.

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.[21] These probabilities of recurrence vary as a function of the initial stage and grade, size, and multiplicity. Refining these estimates for individual patients is an area of active research.

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

The 8th edition of the AJCC Staging Manual includes changes to the staging of urinary bladder carcinoma, including the subdivision of stages III and IV disease (stage III into stage IIIA and stage IIIB; stage IV into stage IVA and stage IVB).[18] Notably, the new staging system groups T1–T4a, N1 within stage IIIA and T1–T4a, N2–3 within stage IIIB; N1–3 was previously grouped within stage IV, regardless of T stage.[18,22] The NCCN Guidelines for Bladder Cancer were updated to reflect appropriate treatment options based on this new staging system (see *Treatment of Stage II and IIIA Tumors*, *Treatment of Stage IIIB Tumors*, and *Treatment of Stage IVA Tumors*).

Enhanced Cystoscopy

White light cystoscopy (WLC) is the current standard in the evaluation and staging of bladder cancer. While WLC has a high sensitivity for

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

Blue Light Cystoscopy

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

Several prospective clinical studies have evaluated BLC in conjunction with WLC and found higher detection rates of non-muscle invasive lesions with BLC.[23-28] Particularly CIS, which is often missed by WLC, was detected at a higher rate. A meta-analysis of BLC TURBT in NMIBC included 12 randomized controlled trials with a total of 2258 patients.[29] A lower recurrence rate was observed (overall response [OR], 0.5; $P < .00001$) with a delayed time to first recurrence by 7.39 weeks ($P < .0001$). Recurrence-free survival was improved at 1 year (hazard ratio [HR], 0.69; $P < .00001$) and at 2 years (HR, 0.65; $P = .0004$). However, no significant reduction in the rate of progression to muscle invasive bladder cancer was seen (OR, 0.85; $P = .39$).

In a meta-analysis from Burger et al,[30] 1345 patients with Ta, T1, or CIS disease showed improved detection of bladder tumors and a reduction in recurrence.[30] Compared to WLC, BLC detected more Ta tumors (14.7%; $P < .001$; OR, 4.898; 95% CI, 1.937–12.390) and CIS lesions (40.8%; $P < .001$; OR, 12.372; 95% CI, 6.343–0.924). Importantly, 24.9% of patients had at least one additional Ta/T1 tumor detected ($P < .001$) and improved detection was seen in both primary (20.7%; $P < .001$) and recurrent disease (27.7%; $P < .001$). Another review of the literature included 26 studies with 5-ALA, 15 studies with HAL, and two studies that used both methodologies. The results from this review also support greater detection and reduced recurrence but no reduction in disease progression.[31]

Although most studies have found no significant reduction in disease progression, a recent analysis reported a trend towards a lower rate with the use of BLC compared to WLC (12.2% vs. 17.6%, respectively; $P = .085$) with a longer time to progression ($P = .05$).[32] 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.[31] The limitations of BLC require judicious application of this additional diagnostic tool.

Narrow-Band Imaging

NBI uses two narrow bands of light at 415 nanometers and 540 nanometers that are absorbed by hemoglobin. The shorter wavelength provides analysis of the mucosa and the longer wavelength allows for evaluation of the deeper submucosal blood vessels. Studies suggest that there is an increase in bladder tumor detection compared with WLC, although the rate of false positives is higher.[33-37]

A systematic review and meta-analysis including 7 prospective studies and 1040 patients with non-muscle invasive disease evaluated the accuracy of NBI compared to WLC. In total, 1476 tumors were detected by biopsy in 611 patients. The additional detection rate for NBI was higher on the patient level (17%; 95% CI, 10%–25%) and tumor level (24%; 95% CI, 17%–31%). In total, 107 patients were further identified as having non-muscle invasive disease by NBI compared to the 16 patients by WLC. Similarly, 276 additional tumors were reported in 5 studies using NBI versus 13 additional tumors by WLC. Although individual studies demonstrated an increase in the rate of false positives, the meta-analysis reported no statistical significance. However, it was acknowledged that data are limited due to the relatively new application of this technique and interpretation is impeded by the degree of heterogeneity among the studies. Finally, the meta-analysis was unable to determine if there was a long-term advantage of NBI, as measured by a reduction in recurrence or progression.

A randomized prospective trial followed patients for 1 year after NBI- or WLC-guided transurethral resection (TUR) to evaluate recurrence. NBI had a reduced 1-year recurrence rate (32.9%; 25 of 76 patients) compared to WLC (32.9% vs. 51.4%, respectively; OR, 0.62).[38] However, the small number of patients in this study is limiting. A larger international, multicenter, randomized controlled trial compared 1-year recurrence rates in 965 patients who received either NBI- or WLC-guided TUR for treatment of NMIBC. This study found that while recurrence rates were similar between the two groups in the study population overall, NBI-guided TUR significantly reduced the likelihood of disease recurrence at 1 year in low-risk patients (5.6% for NBI vs. 27.3% for WLC; P = .002).[39] These results are supported by the systemic reviews and meta-analyses that have also shown reduced recurrence rates following NBI-guided TUR compared to WLC-guided TUR.[40,41]

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.[39-42]

Histology

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

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

Urothelial (transitional cell) carcinomas are the most common histologic subtype in the United States and Europe and may develop anywhere transitional epithelium is present, from the renal pelvis to the ureter,

bladder, and proximal two thirds of the urethra. Variant histology is common with higher grades. The fourth edition of the World Health Organization (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.[43,44] The presence of histologic variants in urothelial carcinoma should be documented as data suggest that the subtype may represent an increased risk of progression, reflect different genetic etiology, and subsequently determine whether a more aggressive treatment approach should be considered (see *Bladder Cancer: Non-Urothelial and Urothelial with Variant Histology* in the algorithm).[45-47] 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.[48] Squamous cell carcinoma of the bladder is morphologically indistinguishable from squamous cell carcinoma of other sites and generally presents at an advanced stage. The three variants within this subtype are pure squamous cell carcinoma, verrucous carcinoma, and squamous cell papilloma.

Other histologic subtypes derived from cells of urothelial origin include glandular neoplasms, epithelial tumors of the upper urinary tract, and tumors arising in a bladder diverticulum. Glandular neoplasms include adenocarcinoma and villous adenoma. Urachal tumors are non-urothelial tumors, most commonly adenocarcinomas, which arise from the urachal ligament and secondarily involve the midline/dome of the bladder.[49] Tumors arising within the genitourinary tract but that are not of urothelial origin (eg, tumors of Müllerian type, melanocytic tumors, mesenchymal tumors) are beyond the scope of these guidelines.

Non-Muscle Invasive Urothelial Bladder Cancer

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

Intravesical Therapy

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

Immediate Intravesical Therapy Post TURBT

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

European Organization for Research and Treatment of Cancer (EORTC) recurrence score greater than or equal to 5.

Phase III trials have reported a reduced risk of recurrence for patients with suspected non-muscle invasive disease who are treated with immediate postoperative gemcitabine or mitomycin. A randomized, double-blind, phase III trial of 406 patients with suspected low-grade NMIBC based on cystoscopic appearance showed that immediate post-TURBT instillation of gemcitabine reduced the rate of recurrence compared to saline instillation (placebo).[11] In the intention to treat (ITT) analysis, 35% of patients treated with gemcitabine and 47% of those who received placebo had disease recurrence within 4 years (HR, 0.66; 95% CI, 0.48–0.90; $P < .001$).[11] Intravesical therapy for a previous NMIBC was allowed in the study if received at least 6 months prior to enrollment. Another phase III, prospective, multicenter, randomized study of 2844 patients with NMIBC showed that an immediate instillation of mitomycin C after TURBT reduces recurrence regardless of the number of adjuvant instillations. Recurrence risk was 27% for immediate instillation versus 36% for delayed instillation ($P < .001$) for all patients in the study, with the benefit of immediate instillation present across risk groups.[12] Previous intravesical chemotherapy was permitted in study participants as long as it was received at least 3 years prior to participation. For both studies, the rate of adverse events (AEs) did not significantly differ between the treatment and control groups, indicating that immediate intravesical instillation of gemcitabine or mitomycin was well tolerated.[11,12] Gemcitabine is preferred over mitomycin based on toxicity profiles and lower cost.[50] For tumors with an intermediate or high risk of progression, subsequent treatment with intravesical induction (adjuvant) therapy may be given. Perioperative intravesical treatment should not be given if there is extensive TURBT or suspected bladder perforation.

Induction (Adjuvant) Intravesical Chemotherapy or BCG

Although only intravesical chemotherapy is recommended in the immediate postoperative setting, both intravesical chemotherapy and BCG have been given as induction therapy in patients with NMIBC.[51] The most commonly used chemotherapy agents are mitomycin C and gemcitabine, although gemcitabine is preferred over mitomycin due to better tolerability and cost. In addition, in systematic reviews and meta-analyses, gemcitabine has shown superior efficacy compared to mitomycin, in that it demonstrated reduced rates of recurrence and progression.[52,53]

Induction BCG has been shown to decrease the risk of bladder cancer recurrence following TURBT. BCG therapy is commonly given once a week for 6 weeks, followed by a rest period of 4 to 6 weeks, with a full re-evaluation at week 12 (ie, 3 months) after the start of therapy.[54] There are several meta-analyses demonstrating that BCG after TURBT is superior to TURBT alone, or TURBT and chemotherapy in preventing recurrences of high-grade Ta and T1 tumors.[55-58] A meta-analysis including 9 trials of 2820 patients with NMIBC reported that mitomycin C was superior to BCG without maintenance in preventing recurrence, but inferior to BCG in trials using BCG maintenance.[59] Using the SEER database, a reduction in mortality of 23% was reported in patients receiving BCG therapy.[60] Other studies have also reported that BCG was better at reducing recurrence in intermediate- and high-risk NMIBC when compared to mitomycin C.[61,62]

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.[63] There were more frequent local and systemic side effects in the BCG arm; however, they were mild to moderate and the treatment was well tolerated in both groups.

The benefit of BCG with or without isoniazid compared to epirubicin alone in a long-term study of 957 patients with intermediate- or high-risk Ta or T1 disease was measured by a reduced recurrence, greater time to distant metastases, and greater overall survival (OS) and disease-specific survival (DSS); progression was similar.[64] Long-term data comparing BCG to epirubicin in combination with interferon[64,65] in patients with T1 disease showed a better reduction in recurrence with BCG; however, no differences in progression or AEs were seen.[65] Patients in both studies received 2 to 3 years of maintenance therapy.

Maintenance Therapy

Maintenance intravesical therapy may be considered following induction with chemotherapy or BCG. The role of maintenance chemotherapy is controversial. When given, maintenance chemotherapy is generally monthly. The role of maintenance BCG in those patients with intermediate- to high-risk NMIBC is more established, although the exact regimens have varied across studies. Some of the previous controversy over the effectiveness of BCG maintenance reflects the wide array of schedules and conflicting reports of efficacy. Quarterly and monthly installations as well as 3- and 6-week schedules have been evaluated. To date, the strongest data support the 3-week BCG regimen used in the SWOG trial that demonstrated reduced disease progression and metastasis.[66] The 3-week timing of BCG has shown improved outcomes compared with epirubicin[65] or isoniazid.[64] 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.[67] 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.[68] 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.[51,55,56,66,69,70]

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.[71] Installation of BCG into the bladder also mimics a urinary tract infection and may produce intense local discomfort. The side effects of treatment have translated to patient refusal of BCG therapy. Dysuria has been reported in 60% of patients in clinical trials.[71] However, the side effects are treatable in almost all cases[72] and no increase in toxicity has been reported with cumulative doses. Symptom management with single-dose, short-term quinolones and/or anticholinergics have been reported to reduce AEs.[73,74]

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.[75] Among all four groups, the percentage of patients with greater than or equal to one side effect was similar (P = .41). Although the one-third dose of BCG was effective, side effects were not reduced. Conversely, other publications suggest that

the one-third dose may reduce side effects.[76-78] Full-dose BCG is recommended by the panel until more data are available to evaluate the low-dose BCG regimen. However, dose reduction may be used if there are substantial local symptoms during maintenance.

A reduction in the frequency of BCG instillations with the goal of reducing treatment-related AEs was tested in the phase III NIMBUS trial.[79] In this trial, 345 patients with NMIBC were randomized to standard-dose BCG for 6 weeks of induction, followed by 3 weeks of maintenance at 3, 6, and 12 months (15 total instillations) or standard-dose BCG for 3 weeks of induction, followed by 2 weeks of maintenance at 3, 6, and 12 months (9 total instillations). After 12 months of follow-up the ITT population showed a higher number of recurrences in the reduced frequency treatment group (46/170) compared to the standard treatment group (21/175) and a safety analysis HR of 0.40, with the upper part of the one-sided 95% CI of 0.68, meeting the predefined criteria for immediately stopping the trial due to inferiority of the reduced frequency arm.

BCG Shortage

An ongoing shortage of BCG has existed in the United States, necessitating development of strategies to prioritize use of intravesical BCG and identify alternative treatment approaches for some patients with NMIBC.[80] Several organizations, including the American Urological Association (AUA), American Association of Clinical Urologists (AACU), Bladder Cancer Advocacy Network (BCAN), Society of Urologic Oncology (SUO), the Large Urology Group Practice Association (LUGPA), and the Urology Care Foundation (UCF), issued a notice outlining strategies to maximize care for patients with NMIBC in the context of this shortage.[81] NCCN Panel Members recommend several strategies to help alleviate problems associated with this shortage.

In the event of a BCG shortage, priority for treatment should be to provide patients with high-risk NMIBC (cT1 high grade or CIS) with induction BCG. For patients who do not receive BCG, intravesical chemotherapy may be used as an alternative. The intravesical chemotherapies most commonly used for this purpose are gemcitabine[50,82] and mitomycin.[83] Two separate meta-analyses of randomized trials reported that there were no differences in risk of recurrence between BCG and mitomycin,[51,84] although BCG may show more favorable outcomes from maintenance regimens.[51] Other options include epirubicin,[64,85] valrubicin,[86] docetaxel,[87] sequential gemcitabine/docetaxel,[88] or gemcitabine/mitomycin.[89] Another alternative to intravesical BCG for patients with NMIBC at high risk of recurrence and, particularly, at high risk of progression, is initial radical cystectomy.[90]

Another option during a shortage is splitting the dose of BCG so that multiple patients may be treated using a single vial. While several randomized trials have reported that one-third dose BCG showed similar outcomes when compared to full-dose BCG,[77,91,92] a phase 3 trial of 1355 patients with intermediate- or high-risk NMIBC reported that patients receiving the full dose of BCG show a longer disease-free interval, compared with those receiving the one-third dose.[68] In this study, the 5-year disease-free rate was 58.5% for the one-third dose compared to 61.7% for the full dose; therefore, the null hypothesis of inferiority for duration of the disease-free interval of one-third dose BCG could not be rejected (HR, 1.15; 95% CI, 0.98–1.35; P = .045), although there were no differences in progression or survival rates.[68] Based on these data, the panel recommends that one-half or one-third dose may be considered for BCG induction during a shortage and should be used for BCG maintenance, if supply allows. Maintenance BCG should be prioritized for patients with high-risk NMIBC (cT1 high grade or CIS) in the early maintenance period (eg, 3 and 6 months post-induction),

although in cases of shortage, BCG induction therapy should be prioritized over maintenance BCG.

Pembrolizumab for NMIBC

Pembrolizumab is a programmed death (PD)-1 inhibitor that has been evaluated as treatment for BCG-unresponsive, NMIBC with CIS in the single-arm, phase II KEYNOTE-057 study (pembrolizumab is also indicated for treatment of metastatic urothelial carcinoma; for the metastatic setting see the *Immune Checkpoint Inhibitors and Targeted Therapies* section below). In the KEYNOTE-057 study, 101 patients with high-risk CIS, with or without papillary tumor, who received previous BCG therapy and were either unable or unwilling to undergo cystectomy were treated with pembrolizumab.[93] Ninety-six patients were eligible for inclusion in the efficacy analysis. The 3-month complete response rate was 41% (95% CI, 30.7%–51.1%), and the median duration of response (DOR) from time of onset was 16.2 months (95% CI, 6.7–36.2). Forty-six percent of complete responses were maintained for at least 1 year. Grade ≥3 treatment-related AEs were reported in 13% of patients, with arthralgia and hyponatremia being the most common. Serious treatment-related AEs occurred in 8% of patients.

NCCN Recommendations for Treatment of NMIBC

The NCCN Panel recommends management of NMIBC based on AUA/SUO risk stratification,[19] with the caveat that an individual patient within each of the risk strata may have more or less concerning features that can influence care decisions (see *AUA Risk Stratification for Non-Muscle Invasive Bladder Cancer* in the algorithm). Retrospective reviews have shown that the AUA/SUO risk classification accurately stratifies patients with NMIBC by the likelihood of recurrence and progression.[94]

After the initial TURBT shows NMIBC, a repeat TURBT is recommended for visually incomplete or high-volume tumors and for high-grade NMIBC, which is found to be T1 on the initial TURBT.[95] 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.[96] All patients received adjuvant intravesical therapy. Although OS was similar, the 3-year recurrence-free survival was significantly higher in the repeat TURBT arm versus the control arm (69% vs. 37%, respectively), especially among patients with high-grade tumors. Similarly, a randomized 10-year extension trial of 210 patients with pT1 NMIBC found that patients who underwent repeat TURBT had a significantly higher 5-, 7-, and 10-year relapse-free survival (RFS) and progression-free survival (PFS) and, in addition, the 10-year OS rate was significantly higher in patients with repeat TURBT (59.1% vs. 40.8%; P = .004).[97] Repeat TURBT was found to be an independent determinant of prolonged OS on multivariate analysis.

Repeat TURBT may also be considered for select patients with high-grade Ta on initial TURBT, particularly if the tumor is large and/or there was no muscle present in the initial TURBT specimen. Restaging TURBT detected residual disease in 27% of Ta patients when muscle was present in the original TURBT.[98] In the absence of muscularis propria in the initial TURBT specimen, 49% of patients with non-muscle invasive disease will be understaged versus 14% if muscle is present.[99]

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

Treatment of Low-Risk NMIBC

By the AUA/SUO risk stratification, low-risk NMIBC includes papillary urothelial neoplasm of low malignant potential and low-grade urothelial carcinoma that is a solitary Ta and less than or equal to 3 centimeters

(cm).[19] For these tumors, risk of recurrence or progression is low following TURBT and no further treatment is necessary, although a single instillation of intravesical chemotherapy immediately post-TURBT can be helpful in reducing the risk of recurrence.[13] An appropriate surveillance schedule is recommended for early detection of disease recurrence.

Treatment of Intermediate-Risk NMIBC

Intermediate-risk NMIBC includes low-grade urothelial carcinoma that has any of the following characteristics: T1, size greater than 3 cm, multifocal, or recurrence within 1 year. In addition, high-grade urothelial carcinoma that is solitary, Ta, and less than or equal to 3 cm is also considered intermediate risk.[19] Although a complete TURBT alone can eradicate intermediate-risk NMIBC, there is a relatively high risk for recurrence. Therefore, after TURBT and immediate intravesical chemotherapy, the panel recommends a 6-week induction course of intravesical therapy. Options for intravesical therapy for intermediate-risk NMIBC include BCG or chemotherapy. The availability of BCG should be considered in decision-making as it may be prioritized for treatment of higher risk disease. While an induction course of intravesical therapy is preferred, surveillance is also an option for intermediate-risk disease.

The value of an induction course of intravesical therapy depends on the patient's prognosis and likelihood of disease recurrence. Factors to consider include the size, number, T category, and grade of the tumor(s), as well as concomitant CIS and prior recurrence.[21] Meta-analyses have confirmed the efficacy of adjuvant (induction) intravesical chemotherapy in reducing the risk of recurrence.[100,101] In the literature, there are four meta-analyses confirming that BCG after TURBT is superior to TURBT alone, or TURBT and chemotherapy in preventing recurrences of Ta and T1 tumors.[55-58] Close follow-up of all patients is needed, although the risk for progression to a more advanced stage is low (see *Surveillance* in the discussion and algorithm).

Treatment of High-Risk NMIBC

High-risk NMIBC has a relatively high risk for recurrence and progression towards more invasiveness. According to the AUA/SUO risk stratification, high-risk NMIBC includes high-grade urothelial carcinoma that has any of the following characteristics: CIS, T1, size greater than 3 cm, or multifocal. In addition, a subgroup of very-high-risk features includes BCG unresponsiveness, variant histologies, lymphovascular invasion, and prostatic urethral invasion.[19] 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. The presence of CIS is associated with an increased risk of invasive disease, including increased cancer progression rates and worse cancer-specific outcomes.[18] If untreated, 50% of CIS progresses to muscle invasive disease within 5 years and, even with treatment, 30% to 40% progresses within 10 years.[102]

Treatment options for high-risk NMIBC depend on whether the tumor has previously been shown to be unresponsive or intolerant to BCG. For BCG-naïve NMIBC, the options are cystectomy or BCG. When very high-risk features are present, cystectomy is preferred because of the high risk for progression to a more advanced stage,[103,104] while BCG is preferred when these are not present. BCG is also a category 1 recommendation for BCG-naïve, high-risk NMIBC without very-high-risk features. For some patients, BCG is not an option due to side effects or a tumor that is BCG-resistant. For these patients, cystectomy is preferred although other intravesical chemotherapy or pembrolizumab

are other options (see *Pembrolizumab for NMIBC* for patient and disease characteristics for which this treatment option would be appropriate). When high-risk NMIBC has been shown to be BCG unresponsive or intolerant, cystectomy is the preferred option, with intravesical chemotherapy or pembrolizumab as other options for select patients.

Surveillance

For intermediate and high-risk NMIBC, follow-up is recommended with a urinary cytology and cystoscopy at 3- to 6-month intervals for the first 2 years, and at longer intervals as appropriate thereafter. Imaging of the upper tract should be considered every 1 to 2 years for high-risk tumors (see *Follow-up* in the algorithm). Urine molecular tests for urothelial tumor markers are now available.[105] Many of these tests have a better sensitivity for detecting bladder cancer than urinary cytology, but specificity is lower. Considering this, evaluation of urinary urothelial tumor markers may be considered during surveillance of high-risk NMIBC. However, it remains unclear whether these tests offer additional useful information for detection and management of non-muscle invasive bladder tumors. Therefore, the panel considers this to be a category 2B recommendation.

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

Posttreatment of Recurrent or Persistent Disease

Treatment of Patients with Positive Cystoscopy

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

Treatment of Patients With Positive Cytology

In patients without a documented recurrence but with initial positive cytology and negative cystoscopy and imaging, it may be appropriate to repeat the cytology test within 3 months. If subsequent cytology tests are positive, selected mapping biopsies including transurethral resection of the prostate (TURP) may be considered. In addition, the upper tract must be evaluated and ureteroscopy may be considered for detecting tumors of the upper tract. If available, enhanced cystoscopy should be considered (see *Enhanced Cystoscopy*, above). If the bladder, prostate, and upper tract continue to show negative results on further evaluation, additional follow-up is indicated after 3 months, then at longer intervals. If BCG was given previously, maintenance BCG may be considered.

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

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 are unresponsive to BCG or for persistent or recurrent disease post-BCG treatment, the subsequent management options

include cystectomy, changing the intravesical agent, or participation in a clinical trial. Pembrolizumab is also an option for patients with BCG-unresponsive, high-risk, NMIBC with Tis, with or without papillary tumors, who are ineligible for or have elected not to undergo cystectomy, although the data are currently not mature enough to determine if pembrolizumab can be considered curative in this setting. (see *Pembrolizumab for NMIBC*, above). Non-cystectomy candidates with recurrent or persistent cTa or cT1 disease may also consider concurrent chemoradiotherapy as an option (category 2A for cT1, category 2B for cTa). Valrubicin is approved for CIS that is refractory to BCG, although panelists disagree on its value.[86] For patients with disease that does not respond or shows an incomplete response to treatment following a change in intravesical agent, subsequent management is cystectomy.

In a phase II multicenter study of NMIBC that recurred following 2 courses of BCG, intravesical gemcitabine demonstrated activity that was relegated to high-risk NMIBC.[106] In the 47 patients with evaluable response, 47% had disease-free survival (DFS) at 3 months. The 1-year RFS was 28% with all cases except for two attributed to the high-risk group. The 2-year RFS was 21%. Intravesical gemcitabine had some activity in the high-risk group, and may be an option if a candidate is not eligible for a cystectomy; however, the study results indicate that cystectomy is preferred when possible. Similarly, for patients with recurrence of high-grade cT1 disease after TURBT and induction BCG, cystectomy is the recommended option with the best data for cure.[107] Observation may be reasonable in highly select cases where low-grade, small-volume tumors had limited lamina propria invasion and no CIS.[108,109] Further investigation and validation of results is warranted for establishing the efficacy of alternative agents for BCG-unresponsive or -refractory disease.[110] Recurrences that are found to be muscle invasive or metastatic disease should be treated as described in the appropriate section below.

Muscle Invasive Urothelial Bladder Cancer

Additional Workup

Several workup procedures are recommended to accurately determine clinical staging of muscle invasive disease. Laboratory studies, such as a complete blood cell count (CBC) and chemistry profile, including alkaline phosphatase, must be performed. Since cisplatin-based chemotherapy is a preferred approach both for neoadjuvant therapy prior to cystectomy and as part of trimodal therapy for bladder preservation, an estimated glomerular filtration rate (GFR) should be obtained to assess patient eligibility for cisplatin. For patients with borderline GFR results, a timed or measured urine collection may be considered to more accurately determine cisplatin eligibility.[111]

Patients should also be assessed for regional or distant metastases. This evaluation should include chest imaging (CT [preferred], x-ray, or fluorodeoxyglucose [FDG]-PET/CT [category 2B]) and evaluation for suspected bone metastasis in patients with symptoms or clinical suspicion of bone metastasis (eg, elevated alkaline phosphatase, focal bone pain). Chest imaging with CT is preferred over chest x-ray based on studies showing better sensitivity of CT for detection of metastatic disease.[112,113] Bone imaging may include a bone scan, MRI, or FDG-PET/CT (category 2B). Imaging studies help assess the extent of tumor spread to lymph nodes or distant organs.[114,115] An abdominal/pelvic CT or MRI is used to assess the local and regional extent of disease.[116,117] Unfortunately, CT scans, ultrasound, and MRI cannot accurately predict the true depth of invasion.

The overwhelming majority of muscle invasive tumors are high-grade urothelial carcinomas. Further treatment following initial TURBT is often

required for muscle invasive tumors, although select patients may be treated with TURBT alone.[118,119] Different treatment modalities are discussed below. These include radical cystectomy, partial cystectomy, neoadjuvant or adjuvant therapy, bladder-preserving approaches, and systemic therapy for advanced disease.

Radical Cystectomy

Radical surgical treatment of bladder cancer involves a cystoprostatectomy or a cystectomy and commonly a hysterectomy for those with a uterus, followed by the formation of a urinary diversion, although in appropriately selected patients, approaches that preserve the uterus, vagina, fallopian tubes, and/or ovaries may be used.[120,121] This surgery can be performed in an open or robotic manner.[122-125] Prostatectomy includes removal of the prostate, seminal vesicles, proximal vas deferens, and proximal urethra. Hysterectomy should include removal of the uterus, ovaries, fallopian tubes, urethra, and part of the vagina. Forms of urinary diversion include an ileal conduit or directing urine to an internal urinary reservoir (such as a continent pouch), with drainage to the abdominal wall or the urethra (orthotopic neobladder). Relative contraindications to urethral drainage include Tis in the prostatic ducts or positive urethral margin. Orthotopic diversion or a neobladder provides the closest bladder function to that of a native bladder albeit with an increased risk for nighttime incontinence as well as urinary retention requiring intermittent self-catheterization.

Unfortunately, the accuracy of the staging cystoscopy, EUA, and TURBT is modest, even when combined with cross-sectional imaging and when understaging is frequently encountered. A retrospective study of 778 patients with bladder cancer found that 42% of patients were upstaged following cystectomy.[126] A pelvic lymph node dissection (PLND) is considered an integral part of the surgical management of bladder cancer. A more extensive PLND, which may include the common iliac or even lower para-aortic or para-caval nodes, yields more nodes to be examined, increases yield of positive nodes, and may be associated with better survival and a lower pelvic recurrence rate.[127-131] Conversely, a 2019 prospective, randomized trial concluded that an extended LND did not show a significant advantage over limited LND for RFS, cancer-specific survival, or OS.[132] However, differing definitions of “extended” versus “limited” LND between studies and specifics on how the study was powered complicate these results. Therefore, additional information will be needed to determine whether extended LND leads to improved outcomes. Results from the SWOG-1011 trial, which is fully accrued but not yet reported, may help to further inform this question.[133] Patient factors that may preclude a PLND include severe scarring secondary to previous treatments or surgery, advanced age, or severe comorbidities.

Partial Cystectomy

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

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

Neoadjuvant Chemotherapy

One of the most noteworthy issues in the treatment of bladder cancer is the optimal use of perioperative chemotherapy for muscle invasive disease. Data support the role of neoadjuvant chemotherapy before cystectomy for stage II and IIIA lesions.[134-139] In a SWOG randomized trial of 307 patients with muscle invasive disease, radical cystectomy alone versus 3 (28-day) cycles of neoadjuvant methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) followed by radical cystectomy were compared. Neoadjuvant chemotherapy increased median survival (77 vs. 46 months; $P = .06$) and lowered the rate of residual disease (15% vs. 38%; $P < .001$) with no apparent increase in treatment-related morbidity or mortality.[134] In a meta-analysis of 11 trials involving 3005 patients, cisplatin-based multiagent neoadjuvant chemotherapy was associated with improved 5-year OS and DFS (5% and 9% absolute improvement, respectively).[138] The randomized, phase III JCOG0209 study comparing neoadjuvant MVAC to no neoadjuvant chemotherapy also found no difference in health-related quality of life after cystectomy, further supporting the use of neoadjuvant chemotherapy in all patients who are eligible to receive it.[140] A review of the National Cancer Database (NCDB) supports initiation of neoadjuvant chemotherapy as soon as possible, but not more than 8 weeks after diagnosis to prevent upstaging after radical cystectomy.[141]

Since the neoadjuvant trial with MVAC, the use of dose-dense MVAC (ddMVAC) with growth factor support in the metastatic setting has been shown to have good comparable tolerance with an increased complete response rate compared to standard (28-day) dosing of MVAC (11% vs. 25%; 2-sided $P = .006$).[142] 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.[143] ddMVAC was anticipated to have a safer profile, a shorter time to surgery, and a similar pathologic complete response rate compared to historical control data for neoadjuvant MVAC chemotherapy given in previous studies. Patients receiving ddMVAC had no grade 3 or 4 renal toxicities and no toxicity-related deaths. Grade 1 or 2 treatment-related toxicities were seen in 82% of patients. The median time to cystectomy was 9.7 weeks from the start of chemotherapy.[143] A separate single-arm phase II study also reported pathologic downstaging in 49% of patients receiving neoadjuvant ddMVAC with a similar safety profile.[144] An additional neoadjuvant clinical trial of ddMVAC with bevacizumab reported 5-year survival outcomes of 63% and 64% (OS and DSS, respectively; median follow-up, 49 months), with pT0N0 and less than or equal to pT1N0 downstaging rates of 38% and 53%, respectively.[145] Bevacizumab had no definitive impact on overall outcomes.

Gemcitabine and cisplatin (GC) has also been evaluated for neoadjuvant therapy of muscle invasive bladder cancer, albeit mainly in smaller phase II or retrospective studies. Overall, these studies showed that GC is effective and well-tolerated when used as neoadjuvant therapy for muscle invasive bladder cancer,[146-150] although some of the studies report lower pathologic response compared to MVAC[149] and lack of a demonstrated OS benefit due to short follow-up or small study

size.[147,148] More recently, the phase II COXEN trial has evaluated ddMVAC and GC as neoadjuvant therapy for muscle invasive bladder cancer with the aim of validating scoring from a coexpression extrapolation algorithm-generated gene expression model.[151] In the ITT population of 227 patients, pT0 rates for ddMVAC and GC were 28% and 30% (*P* = .75) and downstaging was 47% and 40% (*P* = .27), respectively. OS data have not yet been reported. Dose-dense GC has been evaluated as neoadjuvant therapy in a prospective, phase II trial including 46 evaluable patients.[152] The primary endpoint of this trial was met as 57% of patients had their disease downstaged to NMIBC (less than pT2, N0). Pathologic response also correlated with improved RFS and OS. Thirty-nine percent of patients experienced dose modifications due to treatment toxicity, but no patients were unable to undergo cystectomy due to treatment-related AEs. The most frequent treatment-related AE was anemia (12% grade 3).

The randomized phase III GETUG/AFU V05 VESPER trial compared the efficacy and of ddMVAC to GC in the perioperative setting for 500 patients with muscle invasive bladder cancer.[153,154] Of the 437 patients who received neoadjuvant chemotherapy, organ-confined response (less than ypT3, N0) was observed more frequently with ddMVAC than GC (77% vs. 63%; *P* = .001).[153] PFS at 3 years was also significantly higher among those who received neoadjuvant ddMVAC compared to neoadjuvant GC (66% vs. 56%; HR, 0.70; 95% CI, 0.51–0.96; *P* = .025). An analysis comparing secondary endpoints of the VESPER trial also reported a higher complete pathologic response rate for neoadjuvant ddMVAC compared to GC (42% vs. 36%).[154] Reported toxicity was similar between the therapies, with 52% of patients experiencing grade 3 or higher AEs with ddMVAC compared to 55% with GC. Grade 3 or higher AEs that were more frequently observed with ddMVAC included gastrointestinal disorders (*P* = .003) and asthenia (*P* = .001).

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.[139] However, based on NCCN Panel consensus that this regimen is not used in their practices, CMV is no longer recommended as an option for neoadjuvant or adjuvant therapy.

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

Adjuvant Systemic Therapy

Data are less clear regarding the role of adjuvant systemic therapy in invasive bladder cancer. Studies have shown that adjuvant chemotherapy may delay recurrences and improve OS[155-157]; however, no randomized comparisons of adequate sample size have definitively

shown a survival benefit, in large part due to poor accrual.[158] 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.[159-161] However, methodologic issues question the applicability of these studies to all patients with urothelial tumors. In the MVEC trial, patients who experienced relapse in the control arm did not receive chemotherapy, which is not typical of more contemporary treatment approaches. Many of these trials were not randomized, raising the question of selection bias in the analysis of outcomes.

A meta-analysis of 6 trials found a 25% mortality reduction with adjuvant chemotherapy, but the authors pointed out several limitations of the data and concluded that evidence is insufficient for treatment decisions.[162] Interestingly, the follow-up analysis included 3 more studies for a total of 9 trials (N = 945 patients).[157] 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.[157] An observational study evaluated 5653 patients of which 23% received adjuvant chemotherapy post-cystectomy.[156] Patients who received adjuvant chemotherapy had an improved OS (HR, 0.70; 95% CI, 0.06–0.76).[156] Other studies have reported similar results.[163] Although evidence for adjuvant therapy is not as strong as for neoadjuvant therapy, the growing body of data support the administration of adjuvant therapy for certain patients with a high risk for relapse.

The VESPER trial, described in detail above, included a subgroup of 55 patients who were treated with either ddMVAC or GC as adjuvant therapy.[153,154] While results were not conclusive due to small sample size for the adjuvant group, 3-year PFS was improved in the ddMVAC group than in the GC group for all patients who received perioperative therapy (64% vs. 56%; HR, 0.77; 95% CI, 0.57–1.02; *P* = .066) as was time to progression (3-year rate 69% vs. 58%; HR, 0.68; 95% CI, 0.50–0.93; *P* = .014). Based on these results, ddMVAC is preferred over GC for adjuvant chemotherapy.

Checkpoint inhibitors have also been investigated in the adjuvant setting, with the phase 3 CheckMate 274 trial of adjuvant nivolumab reporting positive results for its primary endpoints across the entire study population, although the authors note the possibility of a larger effect size for bladder compared to UTUC (see *Adjuvant Treatment and Follow-up* under *UTUC*, below for more discussion on these data).[164] In the ITT population of 709 patients with muscle invasive urothelial carcinoma treated with radical surgery on CheckMate 274, DFS was 20.8 months with nivolumab compared to 10.8 months with placebo (HR, 0.70; 98.22% CI, 0.55–0.90; *P* < .001). For patients with a programmed death-ligand 1 (PD-L1) expression level of 1% or more, DFS was 74.5% with nivolumab and 55.7% with placebo (HR, 0.55; 98.72% CI, 0.35–0.85; *P* < .001). Importantly, adjuvant nivolumab was tested both in patients who had received neoadjuvant therapy as well as those who did not; 43.4% of the trial participants had received previous cisplatin-based neoadjuvant therapy. Treatment-related AEs of grade 3 or higher occurred in 17.9% of those treated with nivolumab and 7.2% of placebo. Further follow-up is ongoing to assess OS outcomes. While atezolizumab has also been tested in the adjuvant setting for patients with high-risk muscle invasive urothelial carcinoma in the phase 3 IMvigor010 study, this study failed to meet its primary endpoint of improved DFS with adjuvant atezolizumab compared to observation.[165] Median DFS was 19.4 months with atezolizumab compared to 16.6 months with observation (HR, 0.89; 95% CI, 0.74–1.08; *P* = .24).

The NCCN Guidelines suggest that adjuvant systemic therapy should be discussed with patients with high-risk pathology after cystectomy. If cisplatin-based neoadjuvant therapy was not given and the tumor is found to be pT3, pT4, or pN+ following resection, adjuvant cisplatin-based chemotherapy is the preferred approach, although adjuvant nivolumab may also be considered. If cisplatin-based neoadjuvant therapy was given and the tumor is ypT2–ypT4a or ypN+, nivolumab may be considered, although consideration of this approach should balance its effect at delaying progression of disease with the risk of side effects. A minimum of 3 cycles of a cisplatin-based combination, such as ddMVAC (preferred) or GC, may be used in patients undergoing perioperative chemotherapy. Chemotherapy regimen and dosing recommendations are mainly based on studies in advanced disease.[134,146,166,167] Carboplatin has not demonstrated a survival benefit and should not be substituted for cisplatin in the perioperative setting. It should be noted that patients with tumors that are pT2 or less and have no nodal involvement or lymphovascular invasion after cystectomy are considered to have lower risk and are not recommended to receive adjuvant therapy.

Adjuvant Radiation

Patients with locally advanced disease (pT3–4) have high rates of pelvic recurrence and poor OS after radical cystectomy, PLND, and perioperative chemotherapy (pelvic failure 20%–45% and survival 10%–50% at 5 years, depending on risk factors).[168-171] There is an interest in using adjuvant radiation to improve these outcomes, but data are limited and further prospective studies are needed to confirm its benefits. One older randomized study of 236 patients with pT3a to pT4a bladder cancer demonstrated improvement in 5-year DFS and local control compared to surgery alone.[172] A more recent randomized phase II trial compared adjuvant sequential chemotherapy and radiation versus adjuvant chemotherapy alone in 120 patients with locally advanced disease with 1 or more risk factors (≥pT3b, grade 3, or node-positive), in a study population with a high proportion of squamous cell carcinoma. This study demonstrated a significant improvement in local control for chemoradiation (3-year local control of 96% vs. 69%; $P < .01$) and marginal improvements in DFS and OS. Late-grade ≥3 gastrointestinal toxicity on the chemoradiation arm was low (7% of patients).[173] A 2019 systematic review evaluating the oncologic efficacy of adjuvant radiation for bladder cancer or UTUC concluded that there was no clear benefit of adjuvant radiation following radical surgery (eg, cystectomy), although the combination of adjuvant radiation with chemotherapy may be beneficial in locally advanced disease.[174]

While there are no conclusive data demonstrating improvements in OS, it is reasonable to consider adjuvant radiation in patients with pT3/pT4 pN0–2 urothelial bladder cancer following radical cystectomy, although this approach has been evaluated in only a limited number of studies, reflected by the category 2B designation. Patients meeting these characteristics with positive surgical margins and/or lymph nodes identified in the pelvic dissection have especially high pelvic recurrence rates (40%–45% by 5 years), and adjuvant radiation is reasonably well tolerated and improves local control. Radiation with a dose range of 45 to 50.4 Gy without concurrent chemotherapy may be used. In patients who have not had prior neoadjuvant chemotherapy, it may be reasonable to sandwich adjuvant radiation between cycles of adjuvant chemotherapy.[173] The safety and efficacy of concurrent sensitizing chemotherapy and radiation in the adjuvant setting needs to be further studied.

Bladder Preservation

All bladder-sparing approaches are based on the principle that not all cases require an immediate cystectomy, and the decision to remove the bladder can be deferred until the response to organ-sparing therapy is

assessed. Bladder-preserving approaches are reasonable alternatives to cystectomy for patients who are medically unfit for surgery and those seeking an alternative to radical cystectomy.[175,176] Combined modality chemoradiation therapy as an alternative to immediate cystectomy for muscle invasive bladder cancer is endorsed by multiple international organizations that have developed evidence-based consensus guidelines and recommendations, including the International Consultation on Urologic Diseases-European Association of Urology (ICUD-EAU), UK National Institute for Health and Care Excellence (NICE), and the AUA/ASCO/ASTRO/SUO.[177-179] There is an apparent underutilization of aggressive bladder-preserving therapies for non-cystectomy candidates, especially the elderly and racial minorities.[180,181] Between 23% and 50% of patients with muscle invasive bladder cancer who are 65 years and older receive no treatment or non-aggressive therapy, despite prospective, phase II data showing that bladder preservation with trimodality therapy has positive outcomes and an acceptable toxicity profile for patients 65 years and older, with a 2-year OS of 94.4% and 2-year DFS of 72.6%.[182] For tools to aid in the optimal assessment and management of older adults with cancer, see the NCCN Guidelines for Older Adult Oncology.

With any of the alternatives to cystectomy, there is concern that bladders that appear to be endoscopically free of tumor based on a clinical assessment (cT0) that includes a repeat TURBT may not be pathologically free of tumor (pT0). Reports have suggested that up to 45% of bladders may be clinically understaged after TURBT.[181,183,184] 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.[185] Although studies report differing frequencies of residual disease after cytotoxic agents (either radiation or chemotherapy), there is consensus that the rate is lower for patients who present with T2 disease than with T3 disease, which should be considered when proposing a bladder-sparing approach.

The decision to use a bladder-preserving approach is partially based on the location of the lesion, depth of invasion, size of the tumor, status of the "uninvolved" urothelium, and status of the patient (eg, bladder capacity, bladder function, comorbidities). Bladder preservation as an alternative to cystectomy is generally reserved for patients with smaller solitary tumors, negative nodes, no extensive or multifocal CIS, no tumor-related moderate or severe hydronephrosis, and good pre-treatment bladder function. Patients who are medically fit for radical cystectomy but who have hydronephrosis are poor candidates for bladder-sparing procedures.[186,187] Maximal TURBT with concurrent chemoradiotherapy should be given as primary treatment for these patients, with radiotherapy alone or TURBT alone reserved for select patients (see *TURBT Alone as Primary Treatment for Muscle Invasive Bladder Cancer* below for more information). When possible, bladder-sparing options should be chosen in the context of clinical trials.

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

Several groups have investigated the combination of concurrent or sequential chemotherapy and radiotherapy after TURBT. First, an endoscopic resection that is as complete as possible is performed. Incomplete resection is an unfavorable prognostic factor for the ability to preserve the bladder.[188-190]

Radiation Therapy Oncology Group (RTOG) protocol 89-03 compared concurrent cisplatin and radiotherapy with or without 2 cycles of induction MCV (methotrexate, cisplatin, and vinblastine) chemotherapy.[187] No difference in complete clinical response or 5-year OS was observed between the treatment arms. Other studies also reported no significant survival benefit for neoadjuvant chemotherapy

before bladder-preserving chemotherapy with radiation therapy (RT).[189,191]

Conversely, results from several prospective trials have demonstrated the effectiveness of this approach. In the phase 3 RTOG 89-03 trial in which 123 patients with clinical stage T2–T4a were treated with radiotherapy plus concurrent cisplatin, with or without induction MCV chemotherapy, 5-year OS was approximately 49% in both arms.[187] The subsequent RTOG 95-06 trial treated 34 patients with twice-daily irradiation and concurrent cisplatin and fluorouracil (5-FU) and reported a 3-year OS of 83%.[192] The RTOG 97-06 trial treated 47 patients with twice-daily irradiation and concurrent cisplatin; patients also received adjuvant chemotherapy with CMV.[193] 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%.[194] In RTOG 0233, 97 patients received twice-daily radiation with concurrent paclitaxel plus cisplatin or 5-FU plus cisplatin. Five-year OS was 73%.[195] RTOG 0712 investigated 5-FU plus cisplatin with twice-daily radiation or gemcitabine with once daily radiation, with 33 patients eligible for analysis on each arm. Three-year distant metastasis-free survival rates were 78% and 84%, respectively.[196] Taken together, the complete response rates ranged from 59% to 88%.

Up to approximately 80% of long-term survivors maintain an intact bladder, while other patients ultimately require radical cystectomy.[186-194] A combined analysis of survivors from 4 of these trials, with a median follow-up of 5.4 years, showed that combined-modality therapy was associated with low rates of late grade 3 toxicity (5.7% genitourinary and 1.9% gastrointestinal).[197] No late grade 4 toxicities or treatment-related deaths were recorded.

Based on the trials described above, as well as the phase 3 BC2001 trial that demonstrated a locoregional DFS benefit for those treated with 5-FU and mitomycin concurrently with radiotherapy compared to radiotherapy alone, with no significant increase in AEs,[198] bladder preservation with concurrent chemoradiotherapy was given a category 1 designation for primary treatment of stage II or IIIA bladder cancer.

A meta-analysis of individual patient data from two randomized, phase III studies (BC2001 and BCON) compared two radiotherapy fractionation schedules that are commonly used in treatment of locally advanced bladder cancer, a standard schedule of 64 Gy in 32 fractions over 6.5 weeks and a hyperfractionated schedule of 55 Gy in 20 fractions over 4 weeks.[199] This analysis found that the hypofractionated schedule is noninferior to the standard fractionation schedule for both invasive local control and toxicity and that the hypofractionated schedule is superior regarding invasive local control.

Chemotherapy Following TURBT as Primary Treatment for Muscle Invasive Bladder Cancer

Chemotherapy alone is considered to be inadequate without additional treatment to the bladder and it remains investigational. Studies showed that the proportions of complete pathologic response in the bladder using neoadjuvant chemotherapy alone were only up to 38%.[134] A higher proportion of bladders can be rendered tumor-free and therefore preserved when chemotherapy is combined with concurrent radiotherapy.

Radiotherapy Following TURBT as Primary Treatment for Muscle Invasive Bladder Cancer

Radiotherapy alone is inferior to radiotherapy combined with chemotherapy for patients with an invasive bladder tumor, and is not considered standard for patients who can tolerate combined therapy.[198,200] 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.[198] Hence, radiotherapy alone is only indicated for those who cannot tolerate a cystectomy or chemotherapy because of medical comorbidities.

TURBT Alone as Primary Treatment for Muscle Invasive Bladder Cancer

TURBT alone may be an option for patients with stage II disease who are not candidates for cystectomy. TURBT alone may be curative in selected cases that include solitary lesions less than 2 cm in size that have minimally invaded the muscle. These cases should also have no associated in situ component, palpable mass, or associated hydronephrosis.[201]

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

NCCN Recommendations for Treatment of Muscle Invasive Bladder Cancer

Treatment of Stage II and IIIA Tumors

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

Primary surgical treatment for stage II and IIIA disease is a radical cystectomy and pelvic lymphadenectomy. Neoadjuvant chemotherapy is recommended (category 1). Partial cystectomy along with neoadjuvant cisplatin-based chemotherapy can be considered for stage II (cT2, N0) disease with a single tumor in a suitable location and no presence of Tis. Partial cystectomy is not an option for stage III patients. If cisplatin-based neoadjuvant therapy was not given and the tumor is found to be pT3, pT4, or pN+ following resection, adjuvant cisplatin-based chemotherapy is the preferred approach, although adjuvant nivolumab may also be considered. If cisplatin-based neoadjuvant therapy was given and the tumor is ypT2–ypT4a or ypN+, nivolumab may be considered. Adjuvant RT is another option for patients with tumors that are T3–4, or with positive nodes or margins, following surgery (category 2B).

Bladder preservation with maximal TURBT followed by concurrent chemoradiotherapy is another category 1 primary treatment option for these patients. Candidates for this bladder-sparing approach include patients with tumors that present without hydronephrosis or with tumors that allow a visibly complete or a maximally debulking TURBT. Radiotherapy with concurrent cisplatin-based chemotherapy or 5-FU plus mitomycin as a radiosensitizer is the most common and well-studied chemoradiation method used to treat muscle invasive bladder cancer.[185-189,198,200,202] The following radiosensitizing regimens are recommended: cisplatin plus 5-FU; cisplatin plus paclitaxel; 5-FU plus mitomycin C; and cisplatin alone. Doublet chemotherapy is generally preferred. Low-dose gemcitabine (category 2B) may be considered as an alternative regimen.

After a complete TURBT, 60 to 66 Gy of external beam RT (EBRT) is administered. Two doses of concurrent radiosensitizing chemotherapy may be given on weeks 1 and 4 (although weekly schedules are

possible as well). Alternatively, an induction dose of 40 to 45 Gy radiotherapy may be given following complete TURBT. The overall tumor status should be reassessed 2 to 3 months after treatment. If no residual tumor is detected, observation is appropriate. If residual disease is present, surgical consolidation of bladder-only residual disease or treatment as metastatic disease are appropriate. If residual disease is Tis, Ta, or T1, intravesical BCG may be considered.

In patients with extensive comorbid disease or poor performance status who are non-cystectomy candidates, treatment options include concurrent chemoradiation (preferred, category 1) or radiotherapy alone. TURBT is another option for patients with stage II disease who are non-cystectomy candidates. Based on high-level evidence showing superiority to radiotherapy alone, the NCCN Panel recommends chemoradiotherapy as the preferred option for these patients.[198,200] 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, systemic therapy, concurrent chemoradiotherapy or radiotherapy alone (if no prior radiotherapy), TURBT with or without intravesical therapy, or best supportive care may be given.

Treatment of Stage IIIB Tumors

Primary treatment for stage IIIB (cT1–T4a, N2–3) disease can include either downstaging systemic therapy or concurrent chemoradiotherapy.[203,204] A population-based study of 659 patients with cT1–T4a, node-positive urothelial bladder cancer tested the effectiveness of induction chemotherapy for pathologic downstaging.[204] For cN1 disease, complete pathologic downstaging was achieved in 39% of patients who received induction chemotherapy compared to 5% of patients who did not receive induction chemotherapy. For cN2–3, the rate of pathologic downstaging was 27% versus 3% for these two groups. OS was also improved in patients who received induction chemotherapy ($P < .001$), although the nature of the study limits interpretation of the OS results.[204] Another study used the National Cancer Database to analyze outcomes of 1783 patients with clinically node-positive bladder cancer who were treated with chemotherapy alone (n = 1388) or chemoradiotherapy (n = 395).[203] This study found that patients treated with chemoradiotherapy had a higher median OS than those treated with chemotherapy (19.0 vs. 13.8 months; $P < .001$). The improvement in outcome with chemoradiotherapy persisted upon evaluation of propensity-matched populations ($P < .001$).[203] Cystectomy as primary treatment or for surgical palliation may be appropriate in very select situations, such as in patients with limiting local symptoms and/or those with comorbidities that prevent administration of chemotherapy.

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

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

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

Treatment of Stage IVA Tumors

Stage IVA includes patients with cT4b, any N, M0 or any T, any N, M1a disease.[18] For patients with stage IVA disease, treatment options differ depending on the presence of distant metastasis (M0 vs. M1a).

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

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

Follow-up

Results from a meta-analysis of 13,185 patients who have undergone cystectomy reported a 0.75% to 6.4% prevalence of upper tract recurrence.[205] Surveillance by urine cytology or upper tract imaging detected recurrences in 7% and 30% of cases, respectively.

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

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

For patients who have a preserved bladder, there is a risk for recurrence in the bladder or elsewhere in the urothelial tract and distantly. Imaging studies and laboratory testing should be performed as outlined under post-cystectomy follow-up. Additionally, continued monitoring of the urothelium with cystoscopy and urinary cytologies with

or without mapping biopsy is a routine part of the management of all cases in which the bladder is preserved.

Recurrent or Persistent Disease

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

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

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

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

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

Metastatic (Stage IVB) Urothelial Bladder Cancer

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

Evaluation of Metastatic Disease

If metastasis is suspected, additional workup to evaluate the extent of the disease is necessary. This includes a chest CT and a bone scan if enzyme levels are abnormal or the patient shows signs or symptoms of skeletal involvement. Central nervous system (CNS) imaging should be considered. An estimated GFR should be obtained to assess patient eligibility for cisplatin. For patients with borderline GFR results, a timed or measured urine collection may be considered to more accurately determine cisplatin eligibility.[111] If the evidence of spread is limited to nodes and biopsy is technically feasible, nodal biopsy should be considered and patients should be managed as previously outlined for positive nodal disease (stage IIIA, stage IIIB, or stage IVA). Molecular testing should also be performed for patients with metastatic disease (see *Molecular/Genomic Testing*, below).

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

Metastasectomy for Oligometastatic Disease

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

A phase II trial of 11 patients with bladder primary urothelial carcinoma metastatic to the retroperitoneal lymph nodes who underwent complete bilateral retroperitoneal lymph node dissection reported 4-year DSS and RFS rates of 36% and 27%. Patients with viable tumor in no more than 2 lymph nodes and/or excellent response to presurgical systemic chemotherapy showed the best survival rates indicating that a low burden of disease or good response to presurgical chemotherapy may be important in achieving benefit from metastastectomy.[206] Another phase II trial of 70 patients who underwent complete surgical resection of bladder cancer metastases investigated survival, performance status, and quality of life following surgery. This study reported no survival advantage from surgery, although the quality of life and performance status were improved for symptomatic patients.[207]

Beyond these prospective data, several retrospective studies have demonstrated a survival advantage following metastasectomy.[208-211] A retrospective series of 55 patients with bladder primary urothelial carcinoma metastatic to the pelvic or retroperitoneal lymph nodes, who underwent post-chemotherapy lymph node dissection, reported 5-year DSS and RFS rates of 40% and 39%. The best outcomes were associated with radiologic nodal complete response to preoperative chemotherapy and pN0 versus pN+, but similar for cN1–3 versus cM1.[212] A systematic review and meta-analysis of available studies, including a total of 412 patients with metastatic urothelial carcinoma, reported an improved OS for patients who underwent metastasectomy compared to non-surgical treatment of metastatic lesions. Five-year survival in these studies ranged from 28% to 72%.[213] Another population-based analysis of 497 patients 65 years and older who had at least one metastasectomy for treatment of urothelial carcinoma found that with careful patient selection, metastasectomy is safe and can be associated with long-term survival in this patient population.[214] Conversely, a study that queried the NCDB database from 2004 to 2016 reported no difference in OS between propensity score-matched patients with urothelial carcinoma who had undergone metastasectomy compared with those who had not (HR, 0.94; 95% CI, 0.83–1.07; *P* = .38).[215] This study found that 7% of metastatic urothelial carcinoma patients were treated with metastasectomy and, on average, patients treated with metastasectomy were younger, had greater than cT3 disease, had radical surgery on the primary tumor, and received systemic therapy.

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

Molecular/Genomic Testing

The panel recommends that molecular/genomic testing be performed for stages IVA and IVB bladder cancer and may be considered for stage IIIB. This testing should be performed only in laboratories that are certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA-88) as qualified to perform highly complex molecular pathology testing.[216] The NCCN Bladder Cancer Panel recommends that molecular/genomic testing be conducted early, ideally at diagnosis of advanced bladder cancer, to facilitate treatment decision-making and to prevent delays in administering later lines of therapy. In addition to determining eligibility for FDA-approved therapies, molecular/genomic testing may be used to screen for clinical trial eligibility.

Based on the FDA approval of erdafitinib (see *Immune Checkpoint Inhibitors and Targeted Therapies*, below), molecular testing should include analysis for *FGFR3* or *FGFR2* genetic alterations. The therascreen FGFR RGQ RT-PCR Kit has been approved as a companion diagnostic for erdafitinib.[217,218] For certain patients who are ineligible to receive cisplatin, the checkpoint inhibitor atezolizumab may be considered for first-line therapy based on PD-L1 testing results (see *Immune Checkpoint Inhibitors and Targeted Therapies*, below). Companion diagnostics have been approved in this setting.[219]

Genetic alterations are known to be common in bladder cancer, with data from the Cancer Genome Atlas ranking bladder cancer as the third highest mutated cancer.[220,221] Supporting this, a study that looked at comprehensive genomic profiling of 295 cases of advanced urothelial carcinoma found that 93% of cases had at least one clinically relevant genetic alteration, with a mean of 2.6 clinically relevant genetic alterations per case. The most commonly identified clinically relevant genetic alterations were cyclin-dependent kinase inhibitor 2A (*CDKN2A*, 34%), *FGFR3* (21%), phosphatidylinositol 3-kinase catalytic subunit alpha (*PIK3CA*, 20%), and *ERBB2* (17%).[222]

Chemotherapy for Metastatic Disease

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

GC[223,224] and ddMVAC[142,166] are commonly used combination chemotherapy regimens that have shown clinical benefit. A large, international, phase III study randomized 405 patients with locally advanced or metastatic disease to GC or standard (28-day) MVAC.[167] At a median follow-up of 19 months, OS and time to progression were similar in the two arms. Fewer toxic deaths were recorded among patients receiving GC compared to MVAC (1% vs. 3%), although this did not reach statistical significance. A 5-year update analysis confirmed that GC was not superior to MVAC in terms of survival (OS, 13.0% vs. 15.3%; PFS, 9.8% vs. 11.3%, respectively).[224] Another large, randomized, phase III trial compared ddMVAC to standard (28-day) MVAC.[142,166] At a median follow-up of 7.3 years, 24.6% of patients were alive in the ddMVAC cohort compared with 13.2% in the standard MVAC cohort. There was one toxic death in each arm, but less overall toxicity was seen in the dose-dense group. From these data, ddMVAC had improved toxicity and efficacy as compared to standard MVAC;

therefore, standard (28-day) MVAC is no longer used. Both GC and ddMVAC with growth factor support are category 1 recommendations for metastatic disease. Alternative first-line regimens also include carboplatin or taxane-based regimens (category 2B) or single-agent chemotherapy (category 2B).

The performance status of the patient is a major determinant in the selection of a regimen. Regimens with lower toxicity profiles are recommended in patients with compromised liver or renal status or serious comorbid conditions. In patients who are not cisplatin-eligible and whose tumors express PD-L1 or in patients who are not eligible for any platinum-containing chemotherapy, atezolizumab or pembrolizumab are appropriate first-line options (see *Targeted Therapies* in the discussion). Alternatively, carboplatin may be substituted for cisplatin in the metastatic setting for cisplatin-ineligible patients such as those with a GFR less than 60 mL/min. A phase II/III study assessed two carboplatin-containing regimens in medically unfit patients (performance status 2).[225] The overall response rate (ORR) was 42% for gemcitabine plus carboplatin and 30% for methotrexate, carboplatin, and vinblastine. However, the response rates dropped to 26% and 20%, respectively, with increased toxicity among patients who were both unfit and had renal impairment (GFR <60 mL/min).

Taxanes have been shown to be active as treatment options for urothelial bladder cancer.[226-229] Based on these results, several groups are exploring two- and three-drug combinations using these agents, with and without cisplatin. A randomized phase III trial was conducted to compare GC and GC plus paclitaxel in 626 patients with locally advanced or metastatic urothelial cancer.[230] The addition of paclitaxel to GC resulted in higher response rates and a borderline OS advantage, which was not statistically significant in the ITT analysis. Analysis of eligible patients only (92%) resulted in a small (3.2 months) but statistically significant survival advantage in favor of the three-drug regimen (P = .03). There was no difference in PFS. The incidence of neutropenic fever was substantially higher with the three-drug combination (13.2% vs. 4.3%; P < .001). Panelists feel that the risk of adding paclitaxel outweighs the limited benefit reported from the trial. The alternative regimens, including cisplatin/paclitaxel,[231] gemcitabine/paclitaxel,[232] cisplatin/gemcitabine/paclitaxel,[233] carboplatin/gemcitabine/paclitaxel,[234] and cisplatin/gemcitabine/docetaxel,[235] have shown modest activity in patients with bladder cancer in phase I–II trials. Category 1 level evidence now supports the use of checkpoint inhibitors in patients with advanced disease previously treated with a platinum-containing regimen (see *Targeted Therapies* in the discussion).

Although current data are insufficient to recommend the above alternative regimens as routine first-line options, non–cisplatin-containing regimens may be considered in patients who cannot tolerate cisplatin because of renal impairment or other comorbidities (see *Principles of Systemic Therapy* in the algorithm). Additionally, two checkpoint inhibitors, atezolizumab and pembrolizumab, have been FDA approved for use as a first-line therapy in certain patients. Consideration of checkpoint inhibitors must be integrated into the therapeutic planning for all patients with locally advanced and metastatic disease (see *Targeted Therapies* in the discussion). The NCCN Panel recommends enrollment in clinical trials of potentially fewer toxic therapies.

Independent of the specific regimen used, patients with metastatic disease are re-evaluated after two to three cycles of chemotherapy, and treatment is continued for two more cycles in patients whose disease responds or remains stable. Chemotherapy may be continued for a maximum of six cycles, depending on response. If no response is noted

after two cycles or if significant morbidities are encountered, a change in therapy is advised, considering the patient's current performance status, extent of disease, and specific prior therapy. A change in therapy is also advised for patients who experience systemic relapse after adjuvant chemotherapy.

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

Avelumab Maintenance Therapy

For patients who show either response or stable disease through their full course of platinum-based first-line chemotherapy, maintenance therapy with the PD-L1 inhibitor, avelumab, is recommended. The randomized, phase III JAVELIN Bladder 100 trial showed that avelumab significantly prolonged OS in all 700 randomized patients compared to best supportive care alone (median OS of 21.4 vs. 14.3 months; HR, 0.69; 95% CI, 0.56–0.86; *P* = .001).[236] The OS benefit was observed in all prespecified subgroups, including patients with PD-L1–positive tumors. Grade ≥3 AEs were reported in 47.4% of patients treated with avelumab compared to 25.2% of those with best supportive care alone. Based on these positive OS data in a phase III trial, the NCCN Panel has assigned avelumab maintenance therapy a category 1 recommendation.

Immune Checkpoint Inhibitors and Targeted Therapies

Platinum-based chemotherapy is recommended as first-line treatment for most patients with metastatic disease with an OS of 9 to 15 months.[224,237] However, in patients with disease that relapses after this type of chemotherapy, the median survival is reduced to 5 to 7 months.[238] Several new agents, notably checkpoint inhibitors, have data supporting improved outcomes compared to standard therapies for metastatic urothelial carcinoma. Additionally, the FGFR inhibitor, erdafitinib, and the antibody-drug conjugates, enfortumab vedotin and sacituzumab govitecan, have demonstrated effectiveness for the treatment of previously treated urothelial carcinoma.

The FDA has approved the PD-L1 inhibitors atezolizumab and avelumab as well as the PD-1 inhibitors nivolumab and pembrolizumab for patients with urothelial carcinoma. Pembrolizumab, nivolumab, and avelumab are approved for the treatment of locally advanced or metastatic urothelial cell carcinoma that has progressed during or after platinum-based chemotherapy or that has progressed within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy, regardless of PD-L1 expression levels. Avelumab has also been approved as maintenance treatment for patients with locally advanced or metastatic urothelial carcinoma that has not progressed with first-line platinum-containing chemotherapy (see *Chemotherapy for Metastatic Disease*, above). Additionally, atezolizumab and pembrolizumab are approved as a first-line treatment option for patients with locally advanced or metastatic urothelial cell carcinoma who are not eligible for any platinum-containing chemotherapy. Atezolizumab is also approved for first-line therapy in patients who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1. Many of these approvals have been based on category 2 level evidence, although pembrolizumab as second-line therapy post-platinum, enfortumab vedotin as subsequent treatment post-platinum and checkpoint inhibitor, and avelumab as maintenance therapy after first-line platinum have category 1 level evidence supporting their approvals.[236,239,240]

Pembrolizumab

Pembrolizumab is a PD-1 inhibitor that has been evaluated as second-line therapy for patients with bladder cancer who previously received platinum-based therapy and subsequently progressed or metastasized.[241] An open-label, randomized, phase III trial compared pembrolizumab to chemotherapy (paclitaxel, docetaxel, or vinflunine) in 542 patients with advanced urothelial carcinoma that recurred or progressed after platinum-based chemotherapy. Data from this trial showed a longer median OS for patients treated with pembrolizumab compared to chemotherapy (10.3 vs. 7.4 months; *P* = .002). In addition, fewer grade 3, 4, or 5 treatment-related AEs occurred in the pembrolizumab-treated patients compared to those treated with chemotherapy (15.0% vs. 49.4%).[242] Long-term results (>2 years' follow-up) from this same phase III trial were consistent with earlier reports, with longer 1- and 2- year OS and PFS results for pembrolizumab compared to chemotherapy.[243] The median DOR was not reached for pembrolizumab compared to 4.4 months for chemotherapy. Pembrolizumab also showed lower rates of any grade (62% vs. 90.6%) and grade ≥3 AEs (16.5% vs. 50.2%) compared to chemotherapy. Results from this phase 3 trial have led the NCCN Panel to assign pembrolizumab a category 1 recommendation as a second-line therapy.

The single-arm, phase II KEYNOTE-052 trial evaluated pembrolizumab as a first-line therapy in 370 patients with advanced urothelial carcinoma who were ineligible for cisplatin-based therapy. Data from this study showed an ORR of 24%, with 5% of patients achieving a complete response. Grade 3 or higher treatment-related AEs occurred in 16% of patients treated with pembrolizumab at the time of data cutoff.[244] Long-term outcomes of KEYNOTE-052 were similar to the initial analysis with an ORR of 28.6% and a median OS of 11.3 months.[245] In May 2018, the FDA issued a safety alert for the use of first-line pembrolizumab and atezolizumab, which warned that early reviews of data from two clinical trials (KEYNOTE-361 and IMvigor130) showed decreased survival for patients receiving pembrolizumab or atezolizumab as first-line monotherapy compared to those receiving cisplatin- or carboplatin-based therapy.[219] Based on these data, the pembrolizumab prescribing information was initially amended to restrict first-line use to patients who either 1) are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 as measured by a combined positive score (CPS) of at least 10; or 2) are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.[246] Subsequently, the first-line indication was further restricted to only patients who were not eligible for any platinum-containing chemotherapy, removing eligibility for first-line pembrolizumab from the PD-L1–high, platinum-eligible population.[247] This amended indication was granted a full (regular) approval by the FDA.

The final approval for pembrolizumab as a first-line therapy for patients who were not eligible for any platinum-containing chemotherapy was based on results of the phase III KEYNOTE-361 trial, which randomized 1010 patients with previously untreated advanced, unresectable, or metastatic urothelial carcinoma to treatment with pembrolizumab plus platinum-based chemotherapy, pembrolizumab alone, or platinum-based chemotherapy alone.[248] After a median follow-up of 31.7 months, the addition of pembrolizumab to chemotherapy did not significantly prolong median PFS or OS compared to chemotherapy alone (8.3 vs. 7.1 months for PFS; *P* = .0033 and 17.0 vs. 14.3 months for OS; *P* = .0407). Additionally, analyses for first-line pembrolizumab versus chemotherapy alone found that OS was similar both for the total population (14.3 vs. 15.6 months) as well as those with high PD-L1 expression as measured by a CPS of at least 10 (16.1 vs. 15.2 months).

Atezolizumab

Data from the two-cohort, multicenter, phase II IMvigor210 trial evaluated atezolizumab in patients with metastatic disease. In cohort 1, atezolizumab was evaluated as a first-line therapy in 119 patients with locally advanced or metastatic urothelial carcinoma who were ineligible for cisplatin. Data from this study showed an ORR of 23% with 9% of patients showing a complete response. Median OS was 15.9 months. Grade 3 or 4 treatment-related AEs occurred in 16% of patients.[249] In May 2018, the FDA issued a safety alert for the use of first-line pembrolizumab and atezolizumab, which warned that early reviews of data from two ongoing clinical trials (KEYNOTE-361 and IMvigor130) showed decreased survival for patients receiving pembrolizumab or atezolizumab as first-line monotherapy compared to those receiving cisplatin- or carboplatin-based therapy.[219] Based on these data, the atezolizumab prescribing information was subsequently amended to restrict first-line use to patients who either 1) are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 as measured by PD-L1–stained tumor-infiltrating immune cells covering at least 5% of the tumor area; or 2) are not eligible for any platinum-containing chemotherapy regardless of the level of tumor PD-L1 expression.[250]

Atezolizumab has also been investigated for patients with metastatic urothelial carcinoma post-platinum treatment, although it is no longer FDA-approved or recommended by NCCN in that setting. Cohort 2 of the IMvigor210 trial enrolled 310 patients with metastatic urothelial carcinoma post-platinum treatment and showed a significantly improved ORR compared to historical controls (15% vs. 10%; *P* = .0058).[251] Follow-up to date suggests these responses may be durable with ongoing responses recorded in 38 (84%) of 45 responders with a median follow-up of 11.7 months. At the investigator's discretion, patients in this trial could continue atezolizumab beyond Response Evaluation Criteria in Solid Tumors (RECIST) progression.[252] An analysis of post-progression outcomes showed that those who continued atezolizumab had longer post-progression OS (8.6 months) compared to those who received a different treatment (6.8 months) and those who received no further treatment (1.2 months).

The multicenter, randomized phase III IMvigor211 study compared atezolizumab to chemotherapy (vinflunine, paclitaxel, or docetaxel) in 931 patients with locally advanced or metastatic urothelial carcinoma following progression with platinum-based chemotherapy.[253] The primary endpoint of this study, median OS in patients with IC2/3 PD-L1 expression levels (n = 234), showed no significant difference between atezolizumab and chemotherapy (11.1 vs. 10.6 months; *P* = .41). Likewise, confirmed ORR was similar between atezolizumab and chemotherapy treatments in this group of patients (23% vs. 22%). While atezolizumab was not associated with significantly longer OS compared to chemotherapy, the safety profile of atezolizumab was favorable, with 20% of patients experiencing grade 3 or 4 adverse effects compared to 43% with chemotherapy.

The phase IIIb SAUL study and another expanded access study of atezolizumab evaluated the safety and efficacy of atezolizumab in patients who more closely resembled the real-world population, including those ineligible for IMvigor211.[254,255] These studies reported similar efficacy and safety results compared to the pivotal clinical trial.

In March 2021, the makers of atezolizumab voluntarily withdrew their indication for patients with locally advanced or metastatic urothelial carcinoma that was previously treated with a platinum-based chemotherapy.[256] This withdrawal was based on the IMvigor211 trial failing to meet its primary endpoint of improved OS. Therefore, the NCCN Panel does not recommend atezolizumab as a second-line

option following platinum-based therapy, although it is still recommended in its first-line indication.

Nivolumab

Data from a phase II trial in patients with locally advanced or metastatic urothelial carcinoma who progressed after at least one platinum-containing regimen reported an ORR in 52 of 265 patients (19.6%; 95% CI, 15.0–24.9) following treatment with nivolumab that was unaffected by PD-1 tumor status.[257] Out of the 270 patients enrolled in the study, grade 3 or 4 treatment-related AEs were reported in 18% of patients. Three patient deaths were the result of treatment.[257] The median OS was 8.74 months (95% CI, 6.05–not yet reached). Based on PD-L1 expression of less than 1% and 1% or greater, OS was 5.95 to 11.3 months, respectively. These data are comparable to the phase I/II data that reported an ORR of 24.4% (95% CI, 15.3%–35.4%) that was unaffected by PD-1 tumor status. Of the 78 patients enrolled in this study, 2 experienced grade 5 treatment-related AEs, and grade 3 or 4 treatment-related AEs were reported in 22% of patients.[258] An extended follow-up of this same phase I/II study (minimum follow-up of 37.7 months) reported a similar ORR of 25.6% (95% CI, 16.4%–36.8%) for nivolumab monotherapy, with a median DOR of 30.5 months.[259]

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

Avelumab

Avelumab is another PD-L1 inhibitor currently in clinical trials to evaluate its activity in the treatment of bladder cancer. Results from the phase 1b trial for 44 patients with platinum-refractory disease demonstrated an ORR of 18.2% that consisted of five complete responses and three partial responses following treatment with avelumab. The median PFS was 11.6 weeks and the median OS was 13.7 months with a 54.3% OS rate at 12 months. Grade 3 or 4 treatment-related AEs occurred in 6.8% of patients treated with avelumab.[260] A pooled analysis of two expansion cohorts of the same trial reported results for 249 patients with platinum-refractory metastatic urothelial carcinoma or who were ineligible for cisplatin-based chemotherapy. Of the 161 post-platinum patients with at least 6 months of follow-up, the ORR as determined by independent review was 17%, with 6% reporting complete responses and 11% reporting partial responses. Grade 3 or 4 treatment-related AEs occurred in 8% of patients and, likewise, 8% of patients had a serious AE related to treatment with avelumab.[261]

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

Erdafitinib

Erdafitinib is a pan-FGFR inhibitor that has been evaluated in a global, open-label phase II trial of 99 patients with a prespecified *FGFR* alteration who had either previously received chemotherapy or who were cisplatin ineligible, chemotherapy naïve. Of these patients, 12% were chemotherapy naïve and 43% had received two or more prior lines of therapy. The confirmed ORR was 40% (95% CI, 31%–50%), consisting of 3% complete responses and 37% partial responses. Among patients who had previously received immunotherapy, the confirmed ORR was 59%. Median PFS was 5.5 months and the median OS was 13.8 months. Grade ≥3 treatment-related AEs were reported in 46% of patients and 13% of patients discontinued treatment due to AEs.[262] Based on these data, the FDA has approved erdafitinib for patients with locally advanced or metastatic urothelial carcinoma that has progressed during or after platinum-based chemotherapy and

whose tumors have susceptible *FGFR3* or *FGFR2* genetic alterations.[263]

Enfortumab Vedotin-ejfv

Enfortumab vedotin is a Nectin-4-directed antibody–drug conjugate that was evaluated in a global, phase II, single-arm EV-201 study of 125 patients with metastatic urothelial carcinoma who had previously received both a platinum-containing chemotherapy regimen and a PD-1/PD-L1 checkpoint inhibitor. The confirmed ORR was 44% (95% CI, 35.1%–53.2%), including 12% complete responses. Similar response rates were seen in subgroups of patients with liver metastases and in those with no response to prior checkpoint inhibitor therapy. The median DOR was 7.6 months. Grade ≥3 treatment-related AEs were reported in 54% of patients and treatment-related AEs lead to dose reductions or discontinuation of therapy in 32% and 12% of patients, respectively.[264] Subsequently, an open-label, phase III trial of enfortumab vedotin (EV-301) evaluated the therapy in 608 patients with advanced urothelial carcinoma who had previously received both a platinum-containing regimen as well as a checkpoint inhibitor.[240] Patients were randomized 1:1 to either enfortumab vedotin or the investigator's choice of chemotherapy (docetaxel, paclitaxel, or vinflunine). After a median follow-up of 11.1 months, OS was longer with enfortumab vedotin than with chemotherapy (12.88 vs. 8.97 months; HR, 0.70; 95% CI, 0.56–0.89; *P* = .001). Median PFS was also longer for enfortumab vedotin (5.55 vs. 3.71 months; HR, 0.62; 95% CI, 0.51–0.75; *P* <.001). The incidence of grade 3 or greater AEs was similar in both groups, 51.4% with enfortumab vedotin compared to 49.8% with chemotherapy.

Enfortumab vedotin has also been evaluated as a second-line treatment option. Cohort 2 of the phase II EV-201 study enrolled 91 patients who had previously been treated with a PD-1 or PD-L1 checkpoint inhibitor therapy and were ineligible for a cisplatin-containing regimen.[265] Of the 89 patients who received treatment with enfortumab vedotin, the confirmed ORR was 52% (95% CI, 41%–62%) with 20% of patients having a complete response. Fifty-five percent of patients had grade 3 or higher AEs, with neutropenia, maculopapular rash, and fatigue being the most common. Four deaths were considered to be related to treatment, caused by acute kidney injury, metabolic acidosis, multiple organ dysfunction, and pneumonitis. Data supporting second-line use of enfortumab vedotin post-platinum or other non-platinum chemotherapy is more limited than post-checkpoint inhibitor, although the phase I EV-101 dose escalation/expansion study did include patients with pre-treated metastatic urothelial carcinoma who had not previously received a checkpoint inhibitor.[266] Of the 23 patients in this category, 43.5% showed a clinical response to enfortumab vedotin treatment. Furthermore, the FDA indication for second-line enfortumab vedotin specifies that the therapy is "indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer who are ineligible for cisplatin-containing chemotherapy and have previously received one or more prior lines of therapy."[267]

Sacituzumab Govitecan-hziy

Sacituzumab govitecan is another antibody–drug conjugate composed of an anti-Trop-2 humanized monoclonal antibody coupled to SN-38, the active metabolite of the topoisomerase 1 inhibitor, irinotecan. Sacituzumab govitecan has been evaluated in cohort 1 of TROPHY-U-01, a phase II open-label study with 113 patients in cohort 1.[268] Patients within this cohort had locally advanced, unresectable, or metastatic urothelial carcinoma that had progressed following prior platinum-based and PD-1/PD-L1 checkpoint inhibitor therapy and were treated with sacituzumab govitecan. At a median follow-up of 9.1 months, ORR was 27% (95% CI, 19.5%–36.6%) and 77% of participants showed a decrease in measurable disease. The median DOR was 7.2 months

(95% CI, 4.7–8.6 months), median PFS was 5.4 months (95% CI, 3.5–7.2 months), and median OS was 10.9 months (95% CI, 9.0–13.8 months). Key grade greater than or equal to three treatment-related AEs were neutropenia (35%), leukopenia (18%), anemia (14%), diarrhea (10%), and febrile neutropenia (10%). Six percent of patients in the study discontinued treatment as a result of treatment-related AEs.

NCCN Recommendations for Systemic Therapy of Metastatic Disease

Based on the available data, the NCCN Panel recommends that patients with metastatic urothelial carcinoma who are eligible for a cisplatin-containing regimen receive either GC or ddMVAC with growth factor support as first-line therapy. Both of these regimens are supported by category 1 data. A patient who is ineligible for cisplatin, but eligible for carboplatin, should preferentially receive gemcitabine in combination with carboplatin first-line. If there is no progression on a first-line platinum-containing chemotherapy, avelumab maintenance therapy is preferred (category 1).

For patients with metastatic urothelial carcinoma who are ineligible for a cisplatin-containing chemotherapy, atezolizumab and pembrolizumab are also preferred first-line treatment options. Atezolizumab is a first-line treatment option for patients who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression. Pembrolizumab is a first-line option only for patients who are not eligible for any platinum-containing chemotherapy or who have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. Several chemotherapy regimens, including gemcitabine, alone or in combination with paclitaxel, or the combination of ifosfamide, doxorubicin, and gemcitabine may also be appropriate first-line treatment options for some patients.

Clinical trial enrollment is recommended by the NCCN Panel for all patients when appropriate, but is strongly recommended for second-line and subsequent therapies since data for locally advanced or metastatic disease treated with subsequent-line therapy are highly variable. The available second-line options depend on what was given as first-line. If a platinum-based chemotherapy was given first-line, pembrolizumab, nivolumab, avelumab, erdafitinib (if eligible on the basis of *FGFR3* or *FGFR2* genetic alterations), or enfortumab vedotin are preferred second-line treatment options. Pembrolizumab is supported by category 1 level data in this setting. These recommendations also pertain to patients who receive a non-platinum chemotherapy first-line. If PFS was more than 1 year following treatment with a platinum-containing regimen, retreatment with platinum may be considered.[269] If a checkpoint inhibitor was given first-line, preferred second-line options include enfortumab vedotin or gemcitabine in combination with carboplatin for those who are cisplatin-ineligible or GC or ddMVAC with growth factor support for those who are cisplatin-eligible. Other regimens may also be appropriate in the second-line setting (see *Principles of Systemic Therapy* within the algorithm).

For subsequent therapy, after treatment with a platinum-based therapy and a checkpoint inhibitor, if the patient is eligible for these, the preferred regimens are enfortumab vedotin or erdafitinib, if eligible based on *FGFR3/FGFR2* testing results. Enfortumab vedotin is supported by category 1 level data in this setting. A number of chemotherapy regimens and the antibody-drug conjugate, sacituzumab govitecan, are also recommended options in this setting.

Targeted Therapies Not Recommended

Early results from a phase I/II multicenter study of durvalumab for 61 patients with PD-L1–positive inoperable or metastatic urothelial bladder cancer that progressed following a platinum-based regimen showed that 46.4% of patients who were PD-L1 positive had disease that responded to treatment; no response was seen in patients who were PD-L1 negative.[270] A 2017 update on this study (N = 191) showed an ORR of 17.8% and a median OS of 18.2 months, with 55% of patients surviving at 1 year.[271] In May 2017, the FDA granted accelerated approval to durvalumab based on these initial results.[272] Subsequently, in February 2021, the makers of durvalumab voluntarily withdrew this indication based on negative results from the phase III DANUBE trial.[273] DANUBE evaluated the use of durvalumab, with or without tremelimumab, compared to chemotherapy for first-line treatment of advanced urothelial carcinoma.[274] The trial did not meet its primary endpoints as both durvalumab alone and in combination with tremelimumab failed to improve OS compared to chemotherapy.

Likewise, in March 2021, the makers of atezolizumab voluntarily withdrew their indication for patients with locally advanced or metastatic urothelial carcinoma that was previously treated with a platinum-based chemotherapy.[256] This withdrawal was based on the IMvigor211 trial failing to meet its primary endpoint of improved OS. More information and the data from this trial are described above in the *Atezolizumab* section.

In response to these voluntary withdrawals, the NCCN Panel voted to remove atezolizumab and durvalumab as treatment options for patients with metastatic urothelial carcinoma in the post-platinum setting.

While several ongoing studies are investigating the addition of a targeted therapy agent to chemotherapy for treatment of bladder cancer, there are no sufficient data to support this approach. The phase III KEYNOTE-361 trial of pembrolizumab alone or in combination with chemotherapy for first-line treatment of advanced urothelial carcinoma showed no improved efficacy compared to chemotherapy and, therefore, this combination is not recommended for treatment of metastatic bladder cancer.[248]

Non-Urothelial Carcinomas of the Bladder

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

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

Data are limited to support perioperative chemotherapy for non-urothelial carcinomas; however, neoadjuvant chemotherapy may benefit patients with small cell carcinoma of the bladder and is

recommended by the panel for any patient with small-cell component histology with localized disease regardless of stage.[275-279] In addition, a retrospective analysis has shown that neoadjuvant chemotherapy may have a modest benefit for other variant histologies.[280] In patients with non-urothelial carcinomas of any stage, no data support the use of adjuvant chemotherapy, although the risk for relapse may be high. Some of the general principles of management applicable to urothelial carcinomas are appropriate with minor variations.

Patients with small cell carcinoma of the bladder are best treated with initial systemic therapy (see NCCN Guidelines for Small Cell Lung Cancer) followed by either RT or cystectomy as consolidation, if there is no metastatic disease. In addition to the regimens recommended for small cell lung cancer, a regimen alternating ifosfamide plus doxorubicin with etoposide plus cisplatin has also been tested specifically for small cell bladder cancer and found to be effective both as neoadjuvant and metastatic therapy.[277] Concurrent chemoradiotherapy is also an option for these patients.[281] Primary bladder sarcomas are treated as per the NCCN Guidelines for Soft Tissue Sarcoma.

Upper Tract Urothelial Carcinoma

Upper tract tumors, including those that originate in the renal pelvis or in the ureter, are relatively uncommon.[282] The treatment recommendations discussed in this section are based on the most common histology of upper tract tumors, urothelial carcinoma.

Renal Pelvis Tumors

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

Workup

The evaluation of a patient with a suspected renal pelvic tumor should include cystoscopy and imaging of the upper tract collecting system with CT or MR urography; renal ultrasound or CT without contrast with retrograde ureteropyelography; or ureteroscopy with biopsy and/or selective washings. A chest radiograph or CT can help evaluate for possible metastasis and assess for any comorbid diseases. Urine cytology obtained from a urine sample or during a cystoscopy may help identify carcinoma cells. Hematologic, renal, and hepatic function should also be evaluated. Additional imaging studies, such as a renal scan or bone scan, may be needed if indicated by the test results or by the presence of specific symptoms. Recent evidence has suggested a high prevalence of Lynch syndrome in patients with UTUC.[8,283] Therefore, it is recommended to take a thorough family history for all patients with UTUC and consider evaluation for Lynch syndrome for those who are at high risk (see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal for more information).

Primary Treatment

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

Well-differentiated tumors of low grade may be managed with a nephroureterectomy with a bladder cuff with or without perioperative intravesical chemotherapy. Several prospective, randomized, clinical trials have shown a reduction of risk of bladder recurrence following nephroureterectomy when a single postoperative intravesical instillation of chemotherapy was administered.[284-286] While the studies have generally looked at early instillation (within 24–48 hours of surgery),[285,286] some centers are delaying intravesical instillation of

chemotherapy by up to 1 week to administer a cystogram confirming there is no perforation. While mitomycin is most commonly used, gemcitabine is an option for select patients. As an alternate to nephroureterectomy, a nephron-sparing procedure through a transureteroscopic approach or a percutaneous approach may be used, with or without postsurgical intrapelvic chemotherapy or BCG (see *Endoscopic Management of UTUC*).

High-grade tumors or those that are large and/or invade the renal parenchyma are managed through nephroureterectomy with a bladder cuff and regional lymphadenectomy with or without perioperative intravesical chemotherapy. Decline in renal function following surgery may preclude adjuvant therapy. Hence, in selected patients, neoadjuvant chemotherapy may be considered. The data supporting the use of neoadjuvant chemotherapy for UTUC are more limited than for urothelial bladder cancer, although a growing body of evidence suggests that this approach may be beneficial to certain patients. A phase II trial demonstrated the safety and activity of accelerated MVAC as neoadjuvant therapy for high-grade UTUC with a pathologic complete response rate of 14% and a final pathologic stage of ypT1 or less in more than 60% of patients.[287] Systematic reviews and meta-analyses have also reported that neoadjuvant chemotherapy may also improve outcomes compared to no perioperative treatment, although more prospective data are needed.[288-291]

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

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

Endoscopic Management of UTUC

Nephron-sparing endoscopic treatment is a treatment option for certain patients with UTUC, depending on clinical and pathologic criteria and/or comorbid conditions that may contraindicate nephroureterectomy. Favorable clinical and pathologic criteria for nephron preservation include a papillary, unifocal, low-grade tumor, and size less than 1.5 cm, where cross-sectional imaging shows no concern for invasive disease.[282,292] Although there are no randomized controlled trials, systematic reviews of retrospective studies have shown that nephron-sparing approaches show similar outcomes compared to nephroureterectomy for these patients.[293,294] In addition, patients with bilateral disease, solitary functional or anatomic kidney, chronic kidney disease, or renal insufficiency are contraindicated from nephroureterectomy and should receive nephron-sparing treatment.[282,295] Long-term surveillance (>5 years), including urine cytology and cross-sectional urography or endoscopic visualization, is required following nephron-sparing treatment due to a high risk of disease recurrence.[282]

Mitomycin for pyelocalyceal solution (also called UGN-101 or mitomycin gel) has been FDA-approved for treatment of adult patients with low-grade UTUC.[296] This approval was based on OLYMPUS, a single-arm, multicenter, phase 3 trial of patients with treatment-naïve or recurrent low-grade noninvasive UTUC with at least one measurable papillary tumor above the ureteropelvic junction who were scheduled to receive 6 weekly instillations of mitomycin ureteral gel via retrograde catheter to the renal pelvis and calyces.[297] Of the 71 patients who received at least one dose of mitomycin gel, 59% showed a complete response at the primary disease evaluation visit (95% CI, 47%–71%; $P < .0001$).

Durability of response was estimated at 84.2% 12 months after the primary disease evaluation, with a median time to recurrence of 13 months. The most common all-cause AEs in this study were ureteric stenosis, urinary tract infections, hematuria, flank pain, and nausea. Based on these data, the NCCN Panel recommends mitomycin gel be considered for use in this setting, with the caveat that complete or near complete endoscopic resection or ablation is recommended prior to gel application. Treatment with mitomycin gel is most appropriate for patients with a solitary residual, low-grade, UTUC tumor that is low volume (eg, 5–15 mm) and who are not candidates for or are not seeking nephroureterectomy as a definitive treatment.

Adjuvant Treatment and Follow-up

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

While a previous retrospective study of 1544 patients with pT2–4 or node-positive UTUC showed no difference in OS between adjuvant chemotherapy and observation following radical nephroureterectomy,[298] the more recent phase III POUT trial has demonstrated benefit of adjuvant therapy for these patients.[299] POUT randomized 261 patients with pT2–4 or pN1–3, M0 UTUC after nephroureterectomy to either surveillance or adjuvant chemotherapy. Chemotherapy consisted of gemcitabine, in combination with either cisplatin or carboplatin. Adjuvant therapy significantly improved DFS (HR, 0.45; 95% CI, 0.30–0.68; *P* = .0001) after a median follow-up of 30.3 months. Three-year event-free estimates were 71% for those who received adjuvant chemotherapy and 46% for surveillance. Forty-four percent of those who started chemotherapy had grade 3 or higher treatment-emergent AEs compared to 4% with surveillance. Nivolumab has also been investigated for adjuvant treatment of UTUC as the above-mentioned CheckMate 274 trial included 21% of patients with UTUC (96 renal pelvis and 53 ureter).[164] Results from the full trial population are detailed in the section on *Adjuvant Systemic Therapy* under *Muscle Invasive Bladder Cancer*, above. While the authors note that the analysis shows the possibility of a larger effect size for bladder compared to UTUC, they caution that the trial was designed to measure the entire trial population and that further analyses are planned to test the effects on these subgroups.

There have also been some data on the use of adjuvant RT or chemoradiotherapy following nephroureterectomy for UTUC. One study reported on local recurrence patterns and risk factors in 389 patients with UTUC who were treated with radical nephroureterectomy.[300] This study found that adjuvant RT reduced local recurrence rates (HR, 0.177; 95% CI, 0.064–0.493; *P* = .001). However, another retrospective study of 198 patients with pT3, N0, M0 UTUC found no significant differences in 2-year OS, DSS, or RFS for those who received adjuvant RT compared to those who did not.[301] In addition, a retrospective review of 31 patients with UTUC who were treated with RT, with or without concurrent chemotherapy, following attempted curative resection found that 5-year actuarial OS and DSS were longer in the patients who received adjuvant cisplatin-based chemoradiotherapy compared to those who received RT alone.[302] In this study, 5-year actuarial OS was 27% for RT alone compared to 67% for chemoradiotherapy (*P* = .01) and DSS was 41% for RT compared to 76% for chemotherapy (*P* = .06).

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

Urothelial Carcinoma of the Ureter

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

Workup

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

Primary Treatment

For resectable ureteral tumors, the primary management is surgery (see *Endoscopic Management of UTUC* within the *Renal Pelvis Tumors* section of this Discussion for more discussion of nephron-sparing approaches). The specific procedure required varies depending on the location of the tumor (upper, mid, or distal location) and disease extent. Neoadjuvant chemotherapy may be considered in selected patients, such as when the degree of invasiveness is established before definitive surgery.[288,303]

Tumors that originate in the upper ureter occasionally can be managed endoscopically but more commonly are treated with nephroureterectomy with a bladder cuff plus regional lymphadenectomy for high-grade tumors. Neoadjuvant chemotherapy should be considered in select patients, including patients with retroperitoneal lymphadenopathy; bulky (>3 cm) high-grade tumor; sessile histology; or suspected parenchymal invasion. A portion of the bladder is removed to ensure complete removal of the entire intramural ureter.

Tumors that originate in the mid portion can be divided by grade and size. Small, low-grade tumors can be managed with excision followed by ureteroureterostomy, segmental or complete ureterectomy, or ileal ureter interposition in highly selected patients. Alternatively, endoscopic resection or nephroureterectomy with a bladder cuff can be performed. Larger, high-grade lesions are managed with nephroureterectomy with a bladder cuff and regional lymphadenectomy. Neoadjuvant chemotherapy can be considered in select patients.

Distal ureteral tumors may be managed with a distal ureterectomy and regional lymphadenectomy if high grade followed by reimplantation of the ureter (preferred if clinically feasible). Other primary treatment options include endoscopic resection, or, in some cases, a nephroureterectomy with a bladder cuff, and regional lymphadenectomy if high grade. Neoadjuvant chemotherapy can be considered for select patients with distal ureteral tumors following distal ureterectomy or the nephroureterectomy with bladder cuff.

Follow-up

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

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

Urothelial Carcinomas of the Prostate

Urothelial (transitional cell) carcinomas of the prostate represent a distinct entity with a unique staging system. In this respect, they must be distinguished from urothelial carcinomas of bladder origin that invade into the prostate through the bladder wall. Urothelial carcinomas of the prostate may occur de novo or, more typically, concurrently or after treatment of bladder cancer. Similar to tumors originating in other sites of the urothelium, management of prostate urothelial carcinomas is based on the extent of disease with particular reference to the urethra, duct, acini, and stroma.

Workup

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

Primary Treatment

Pending histologic confirmation, tumors that are limited to the mucosal prostatic urethra with no acinar or stromal invasion can be managed with TURP and intravesical BCG, with follow-up similar to that for superficial disease of the bladder. A systematic review and meta-analysis of intravesical BCG for treatment of noninvasive urothelial carcinoma of the prostate found that the complete response rate for prostatic disease was 88% (95% CI, 0.81–0.96).[304] If local recurrence is seen, cystoprostatectomy with or without urethrectomy is recommended. Patients with tumors that invade the ducts, acini, or stroma should undergo an additional workup with chest radiograph or CT, and abdominal/pelvic CT if necessary, to exclude metastatic disease, and then a cystoprostatectomy with or without urethrectomy should be performed. Based on data extrapolated from bladder cancer therapy, neoadjuvant chemotherapy may be considered in patients with stromal invasion.[134-136] Adjuvant chemotherapy may be advised for stromal invasion after primary treatment if neoadjuvant therapy was not given. Alternatively, TURP and intravesical BCG may be offered to patients with only ductal and acini invasion. Local recurrences in patients undergoing TURP and BCG therapy are treated with cystoprostatectomy with or without urethrectomy.

Primary Carcinoma of the Urethra

Primary carcinoma that arises in the urethra is rare. Unlike for bladder cancer, squamous cell carcinoma is the most common histologic subtype for urethral cancer.[305] The 5-year OS is 42%.[306,307] Stage and disease location are the most important prognostic factors for male patients, while tumor size and histology are prognostically significant for female patients.[305,307] Unfortunately, there is a lack of robust,

prospective data to support treatment decisions due to disease rarity. Treatment recommendations typically encompass all of the respective histologies (ie, squamous, transitional, adenocarcinomas) with the treatment approach based on location (ie, proximal vs. distal urethral tumors).

Workup

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

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

Treatment

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

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

Initial treatment options for patients assigned female at birth with T2 tumors include chemoradiation or urethrectomy with cystectomy, with organ-sparing approaches used when feasible in appropriately selected cases.[120,121] Partial urethrectomy is possible in a minority of cases, depending on tumor location, and has been associated with a high local recurrence rate.[308] At recurrence, the patient may receive systemic therapy or chemoradiotherapy (both category 2A) or pelvic exenteration (category 2B). Pelvic exenteration for T2 urethral cancer consists of *en bloc* removal of the urethra, bladder, and anterior vagina.

A multimodal treatment approach (ie, surgery, systemic therapy, radiation) is common for advanced disease. A cohort study reported a 72% response rate with the following treatment scheme before surgery: cisplatin, gemcitabine, and ifosfamide for squamous cell carcinoma; 5-FU, gemcitabine, and cisplatin-based regimens for adenocarcinoma; and MVAC for urothelial tumors.[309] Combined chemoradiation with 5-FU and mitomycin C has shown efficacy in a series of male patients with squamous cell carcinoma of the urethra.[310] Patients undergoing surgery after chemoradiation had a higher 5-year DFS rate (72%) than those receiving chemoradiation alone (54%). If systemic therapy is used, the choice of regimen should be based on histology.

Patients with T3 or T4 disease but no clinical nodes should receive neoadjuvant chemotherapy (if urothelial carcinoma) followed by consolidative surgery or, if ineligible for standard systemic chemotherapy, radiation or chemoradiation with or without consolidative surgery. Surgery alone is an option for non-urothelial histologies. If node-positive, chemoradiation is the preferred treatment for squamous cell carcinoma. Systemic therapy or chemoradiotherapy with or without consolidative surgery are also treatment options. At recurrence, the

patient may undergo pelvic exenteration (category 2B) with or without ilioinguinal lymphadenectomy and/or chemoradiotherapy. Pelvic exenteration for T3 urethral cancer consists of urethrectomy, cystectomy, and either a prostatectomy or anterior vaginectomy with hysterectomy, as applicable. For highly local advanced T4 tumors, the posterior vagina and rectum may also need to be removed en bloc with the specimen. Systemic therapy is a category 2B option.

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

Summary

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

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

Finally, within the category of metastatic disease, several new agents have been identified that seem superior to those currently considered standard therapies, at least for subsequent lines of therapy. Checkpoint inhibitors and targeted therapies have emerged as new options 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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