



National Comprehensive
Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Bladder Cancer

Version 1.2025 — March 25, 2025

NCCN.org

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

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

Continue

National
Comprehensive
Cancer
Network®

NCCN Guidelines Version 1.2025

Bladder Cancer

[NCCN Guidelines Index](#)
[Table of Contents](#)
[Discussion](#)

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

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

Michael Abern, MD ¶
Duke Cancer Institute

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

***Rick Bangs, MBA ¥**
Patient Advocate

Jovan Begovic, MD ϕ
UT Southwestern Simmons
Comprehensive Cancer Center

Jason Brown, MD, PhD †
Case Comprehensive Cancer Center/
University Hospitals Seidman Cancer Center and
Cleveland Clinic Taussig Cancer Institute

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

Kevin Chan, MD ϖ
City of Hope National Medical Center

***Sam S. Chang, MD, MBA ¶, ϖ**
Vanderbilt-Ingram Cancer Center

Paul Chang, MD §
The UChicago Medicine
Comprehensive Cancer Center

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

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

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

Jean Hoffman-Censits, MD †
Johns Hopkins Kimmel Cancer Center

Hristos Kaimakliotis, MD ϖ
Indiana University Melvin and Bren Simon
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

Lin Mei, MD ‡
Abramson Cancer Center at the
University of Pennsylvania

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

***Mamta Parikh, MD, MS †**
UC Davis Comprehensive Cancer Center

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

Charles Peyton, MD ϖ
O'Neal Comprehensive Cancer Center at UAB

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

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

Kyle Richards, MD ϖ
University of Wisconsin Carbone Cancer Center

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

***Tyler Stewart, MD †**
UC San Diego Moores Cancer Center

***Debasish Sundi, MD ϖ**
The Ohio State University Comprehensive
Cancer Center - James Cancer Hospital
and Solove Research Institute

Matthew Tollefson, MD ϖ
Mayo Clinic Comprehensive Cancer Center

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

Jonathan L. Wright, MD, MS ϖ
Fred Hutchinson Cancer Center

NCCN

Carly J. Cassara, MSc
Lisa Gurski, PhD
Bailee Sliker, PhD

Continue

ϕ Diagnostic radiology
‡ Hematology/Hematology
oncology
‡ Internal medicine
† Medical oncology
≠ Pathology

¥ Patient advocacy
§ Radiotherapy/Radiation
oncology
¶ Surgery/Surgical oncology
ϖ Urology
* Discussion writing
committee member

[NCCN Guidelines Panel Disclosures](#)



[NCCN Bladder Cancer Panel Members](#) [Summary of the Guidelines Updates](#)

Bladder Cancer

- [Clinical Presentation and Initial Evaluation \(BL-1\)](#)
- [Non-Muscle Invasive or CIS, Primary Evaluation/Surgical Treatment \(BL-1\)](#)
 - ▶ [Risk Stratification of NMIBC \(BL-2\)](#)
 - ▶ [Management per NMIBC Risk Group \(BL-3\)](#)
 - ▶ [Management of Positive Urine Cytology \(BL-4\)](#)
- [Muscle Invasive or Metastatic, Primary Evaluation/Surgical Treatment, Additional Workup \(BL-1\)](#)
 - ▶ [Stage II \(cT2, N0\) Primary and Subsequent Treatment \(BL-5\)](#)
 - ▶ [Stage IIIA \(cT3, N0; cT4a, N0; cT1–cT4a, N1\) Primary and Subsequent Treatment \(BL-7\)](#)
 - ▶ [Stage IIIB \(cT1–cT4a, N2,3\) Primary and Subsequent Treatment \(BL-8\)](#)
 - ▶ [Stage IVA \(cT4b, Any N, M0; Any T, Any N, M1a\) Primary and Subsequent Treatment \(BL-9\)](#)
 - ▶ [Metastatic Disease, Additional Workup, Primary Treatment \(BL-10\)](#)
 - ▶ [Follow-up, Recurrent, or Persistent Disease \(BL-11\)](#)
- [Principles of Imaging for Bladder/Urothelial Cancer \(BL-A\)](#)
- [Principles of Surgical Management \(BL-B\)](#)
- [Principles of Pathology Management \(BL-C\)](#)
- [Bladder Cancer: Non-Urothelial and Urothelial with Subtype Histology \(BL-D\)](#)
- [Follow-up \(BL-E\)](#)
- [Principles of Instillation Therapy \(BL-F\)](#)
- [Principles of Systemic Therapy \(BL-G\)](#)
- [Principles of Radiation Management of Invasive Disease \(BL-H\)](#)
- [Principles of Alternative Risk Classifiers and Biomarkers \(BL-I\)](#)

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

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

See [NCCN Categories of Evidence and Consensus](#).

NCCN Categories of Preference: All recommendations are considered appropriate.

See [NCCN Categories of Preference](#).

Upper Genitourinary (GU) Tract Tumors

- [Renal Pelvis \(UTT-1\)](#)
- [Urothelial Carcinoma of the Ureter \(UTT-2\)](#)
- [Urothelial Carcinoma of the Prostate \(UCP-1\)](#)
- [Primary Carcinoma of the Urethra \(PCU-1\)](#)
- [Staging \(ST-1\)](#)
- [Abbreviations \(ABBR-1\)](#)

The NCCN Guidelines® are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representations or warranties of any kind regarding their content, use or application and disclaims any responsibility for their application or use in any way. The NCCN Guidelines are copyrighted by National Comprehensive Cancer Network®. All rights reserved. The NCCN Guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2025.



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

Global

- Language changed: ~~Tis~~ *CIS*

[BL-2](#)

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

[BL-3](#)

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

[BL-4](#)

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

[BL-5](#)

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

[BL-6](#)

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

[BL-8](#)

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

[BL-A 3 of 5](#)

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

[BL-B 2 of 4](#)

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

[BL-B 4 of 4](#)

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



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

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

[BL-D 1 of 2](#)

- Page has been extensively modified

[BL-E 1 of 6](#)

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

[BL-E 3 of 6](#)

- Blood tests, year 2-5, bullet 3 modified: B₁₂ annually *based on clinical judgment* (also for BL-E 4 of 6)
- Blood tests, year 5-10 and >10: B₁₂ annually *based on clinical judgment* (also for BL-E 4 of 6)
- Urine tests, year 1, bullet 1 modified: *Consider* urine cytology every 6–12 mo (also for BL-E 4 of 6)

[BL-E 6 of 6](#)

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

[BL-F 3 of 4](#)

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

[BL-G](#)

- Section extensively modified

[BL-I](#)

- Section new to Guidelines

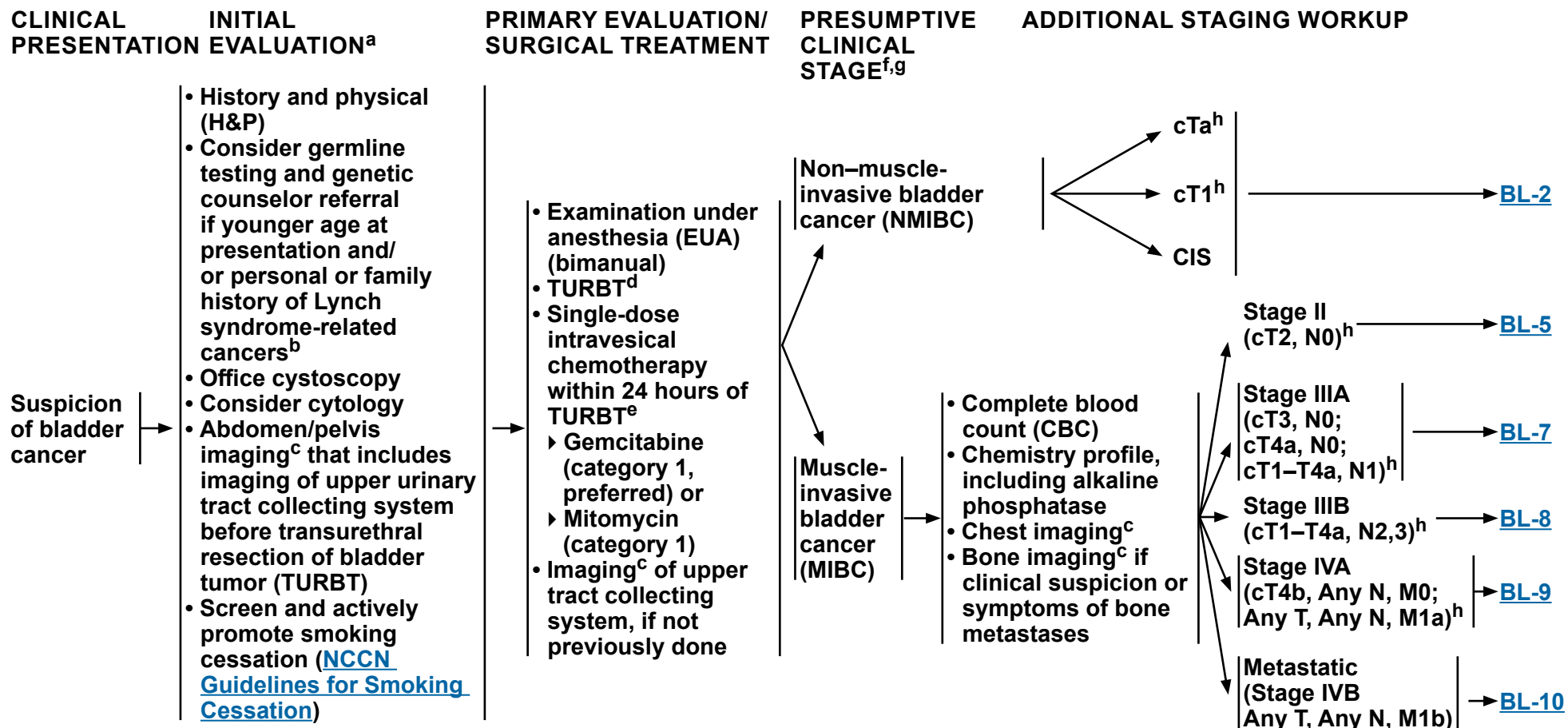
[UTT-1](#)

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



NCCN Guidelines Version 1.2025

Bladder Cancer



^aFor tools to aid optimal assessment and comprehensive care of older adults with cancer, see [NCCN Guidelines for Older Adult Oncology](#).

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

^c[Principles of Imaging for Bladder/Urothelial Cancer \(BL-A\)](#).

^d[Principles of Surgical Management \(BL-B\)](#).

^eImmediate intravesical chemotherapy reduces the recurrence rate by 35% for selected patients. Most efficacious in patients with low-grade, low-volume Ta urothelial cancer. Post-TURBT intravesical chemotherapy should not be utilized if concern for bladder perforation. See [Principles of Instillation Therapy \(BL-F\)](#).

^f[Principles of Pathology Management \(BL-C\)](#).

^g[Bladder Cancer: Non-Urothelial and Urothelial with Subtype Histology \(BL-D\)](#).

^hThe modifier “c” refers to clinical staging based on bimanual EUA, endoscopic surgery (biopsy or transurethral resection [TUR]), and imaging studies. The modifier “p” refers to pathologic staging based on cystectomy and lymph node dissection.

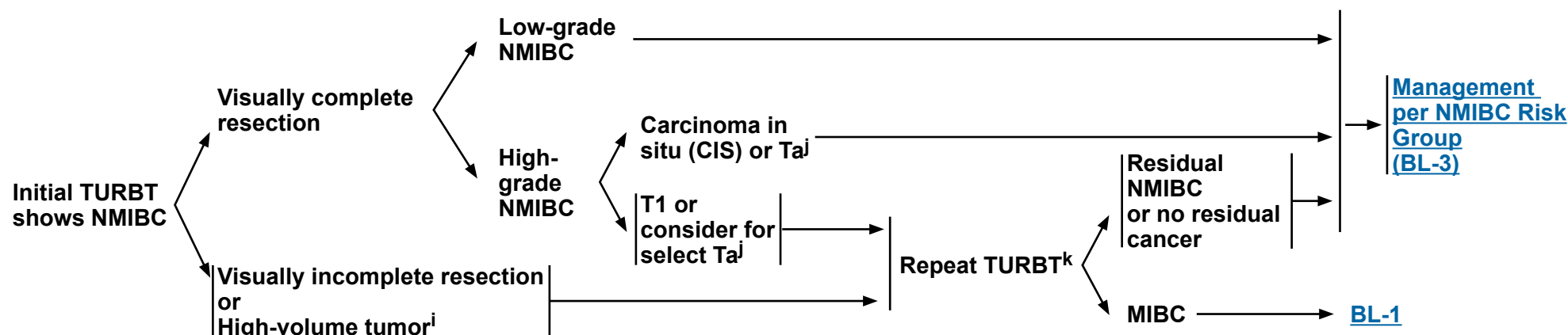
Note: All recommendations are category 2A unless otherwise indicated.



NCCN Guidelines Version 1.2025

Non–Muscle-Invasive Bladder Cancer

RISK STRATIFICATION OF NMIBC



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

Low Risk	Intermediate Risk	High Risk
<ul style="list-style-type: none"> • Papillary urothelial neoplasm of low malignant potential • Low grade urothelial carcinoma <ul style="list-style-type: none"> ▶ Ta and ▶ ≤3 cm and ▶ Solitary 	<ul style="list-style-type: none"> • Low grade urothelial carcinoma <ul style="list-style-type: none"> ▶ T1 or ▶ >3 cm or ▶ Multifocal or ▶ Recurrence within 1 year • High grade urothelial carcinoma <ul style="list-style-type: none"> ▶ Ta and ▶ ≤3 cm and ▶ Solitary 	<ul style="list-style-type: none"> • High grade urothelial carcinoma <ul style="list-style-type: none"> ▶ CIS or ▶ T1 or ▶ >3 cm or ▶ Multifocal • Very high risk features (any): <ul style="list-style-type: none"> ▶ BCG unresponsive^l ▶ Certain histopathologic subtypes^m ▶ Lymphovascular invasion ▶ Prostatic urethral invasion

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

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

ⁱ High-volume tumors (large or highly multifocal) are at high risk of residual tumor.

^j Consider repeat TURBT for high-grade Ta particularly if large, and/or no muscle in specimen.

^k Muscle should be present in repeat TURBT pathology specimen if possible.

^l Kamat AM, et al. J Clin Oncol 2016;34:1935-1944.

^m See aggressive subtype histologies listed on [Bladder Cancer: Non-Urothelial and Urothelial with Subtype Histology \(BL-D\)](#).

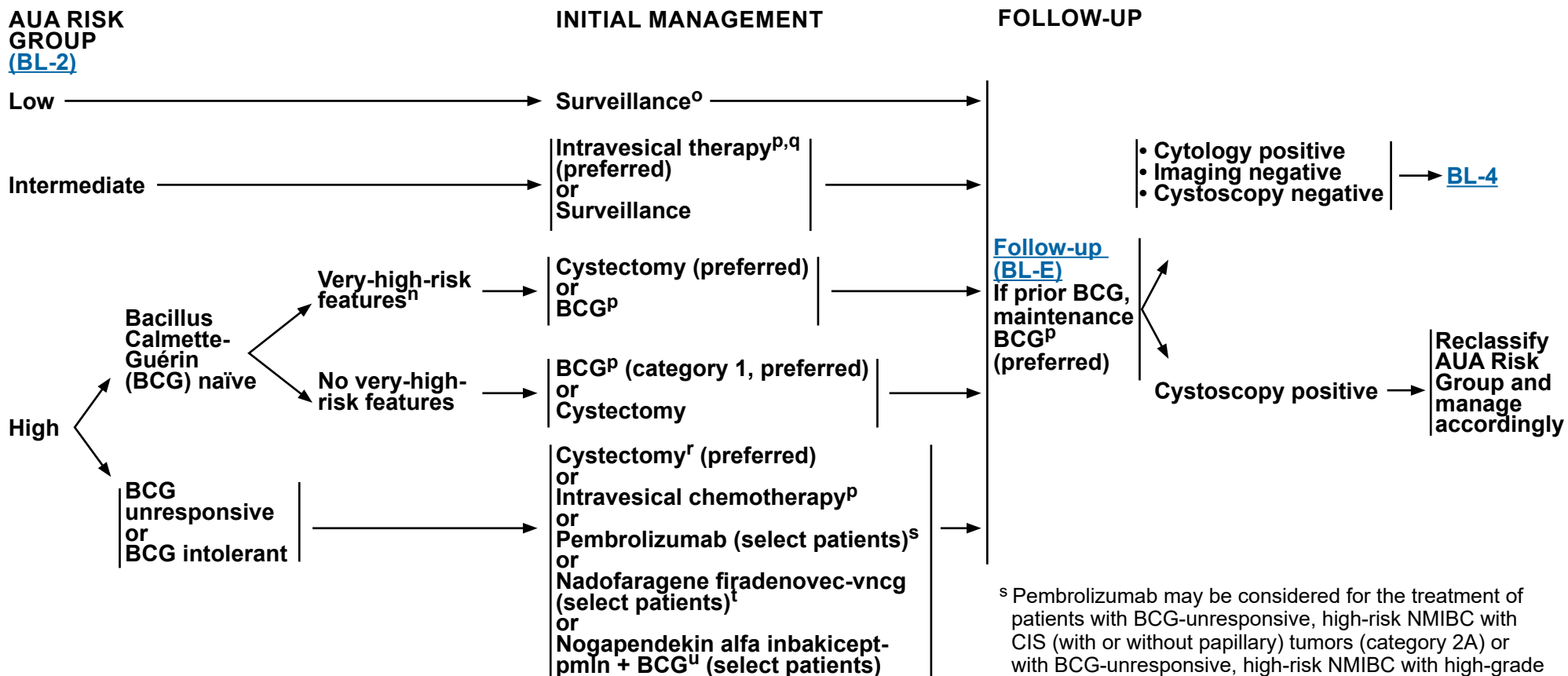
Note: All recommendations are category 2A unless otherwise indicated.



NCCN Guidelines Version 1.2025

Non–Muscle-Invasive Bladder Cancer

MANAGEMENT PER NMIBC RISK GROUP



ⁿ Lymphovascular invasion, prostatic urethral involvement of tumor, subtype histology (eg, micropapillary, plasmacytoid, sarcomatoid).

^o Should consider single perioperative instillation of intravesical chemotherapy at time of TURBT.

^p [Principles of Instillation Therapy \(BL-F\)](#).

^q Options for intravesical therapy for intermediate-risk disease include BCG and chemotherapy; should consider BCG availability in decision-making.

^r If not a cystectomy candidate, and recurrence is high-grade cTa or cT1, consider concurrent chemoradiotherapy (category 2B for cTa, category 2A for cT1) or a clinical trial. See [Principles of Systemic Therapy \(BL-G 5 of 7\)](#).

^s Pembrolizumab may be considered for the treatment of patients with BCG-unresponsive, high-risk NMIBC with CIS (with or without papillary) tumors (category 2A) or with BCG-unresponsive, high-risk NMIBC with high-grade papillary Ta/T1 only tumors without CIS (category 2B) who are ineligible for or have elected not to undergo cystectomy.

^t Nadofaragene firadenovec-vncg may be considered for the treatment of patients with BCG-unresponsive, high-risk, NMIBC with CIS (with or without papillary) (category 2A) or with BCG-unresponsive, high-risk, NMIBC with high-grade papillary Ta/T1 only tumors without CIS (category 2B).

^u Nogapendekin alfa inbakicept-pmln in combination with BCG may be considered for the treatment of patients with BCG-unresponsive, high-risk NMIBC with CIS (with or without papillary) tumors.

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



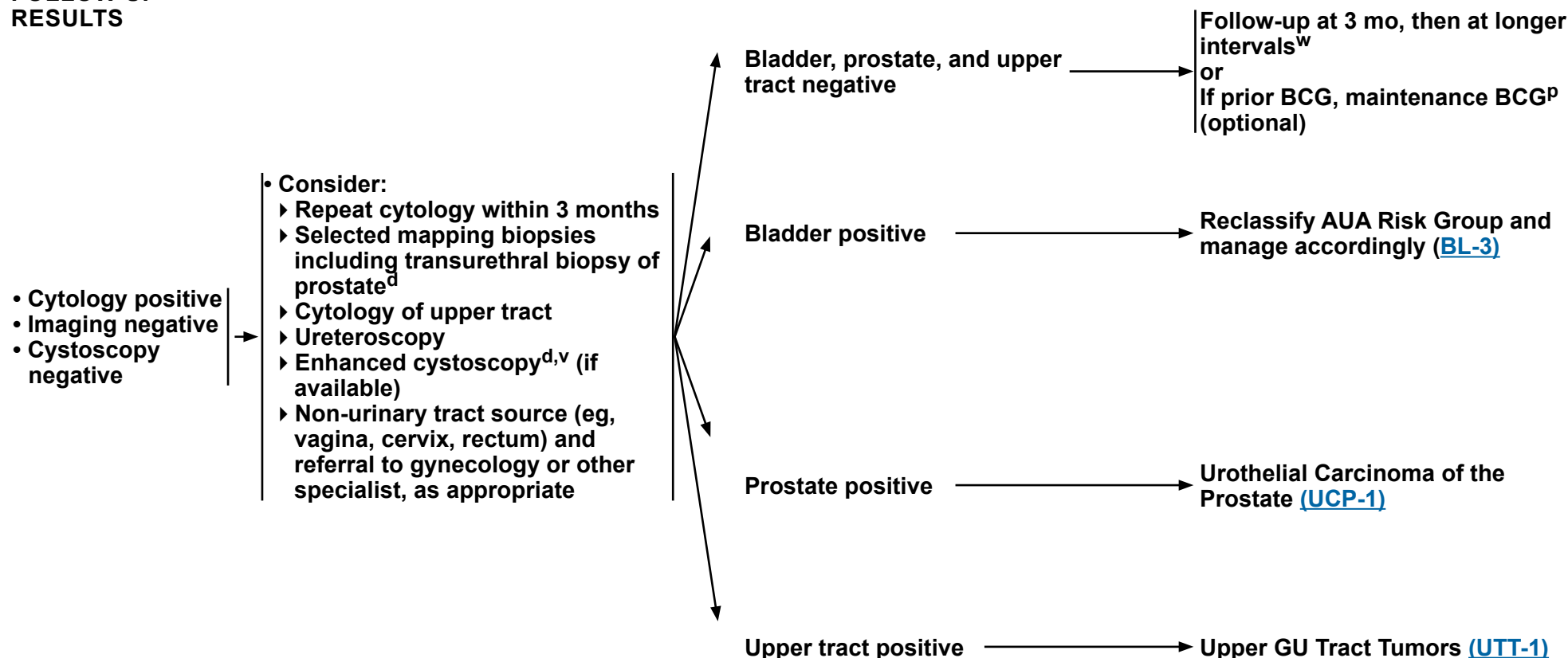
NCCN Guidelines Version 1.2025

Management of Positive Urine Cytology

RECURRENT OR PERSISTENT DISEASE FOLLOW-UP RESULTS

EVALUATION

TREATMENT

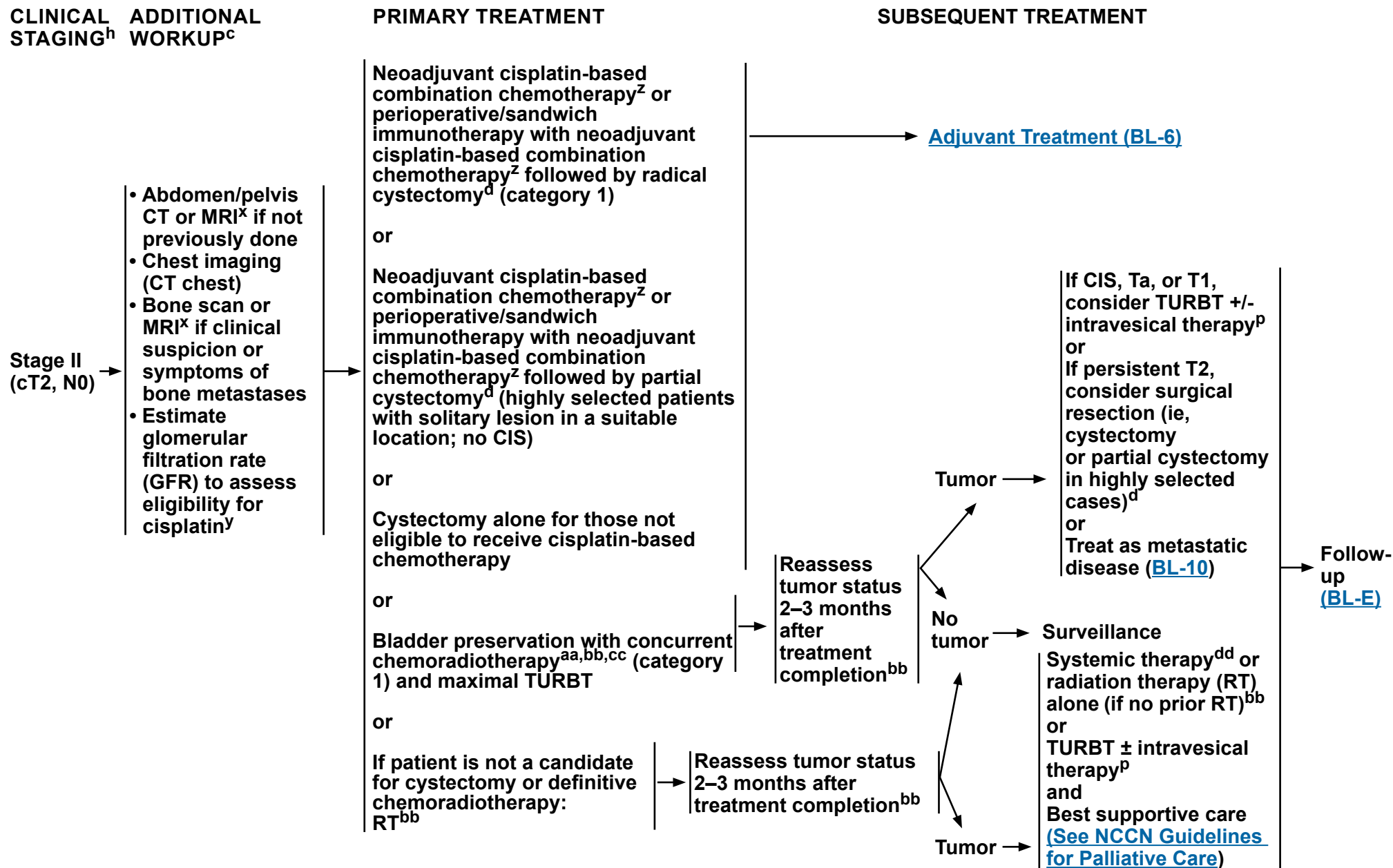
^d [Principles of Surgical Management \(BL-B\)](#).^p [Principles of Instillation Therapy \(BL-F\)](#).^v If enhanced cystoscopy is not readily available, proceed to cystoscopy with bladder biopsies with or without uroscopy.^w [Follow-up \(BL-E\)](#).

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



NCCN Guidelines Version 1.2025

Muscle-Invasive Bladder Cancer



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

[Footnotes on BL-6](#)



ADJUVANT TREATMENT

Following
cystectomy



- If gemcitabine + cisplatin + durvalumab given preoperatively, then durvalumab should be used postoperatively.
- Based on pathologic risk,
 - If no cisplatin neoadjuvant treatment given and pT3, pT4a, or pN+
 - ◊ Adjuvant cisplatin-based chemotherapy should be discussed (preferred)^z
 - or
 - ◊ Consider adjuvant nivolumab^{ee} or pembrolizumab^{z,ee}
 - or
 - If cisplatin neoadjuvant chemotherapy given and ypT2–ypT4a or ypN+, consider nivolumab^{ee} or pembrolizumab^{z,ee}
 - or
 - Consider adjuvant RT in selected patients (pT3–4, positive nodes/margins at the time of surgery)^{bb} (category 2B)



[Follow-up
\(BL-E\)](#)

^c [Principles of Imaging for Bladder/Urothelial Cancer \(BL-A\)](#).

^d [Principles of Surgical Management \(BL-B\)](#).

^h The modifier “c” refers to clinical staging based on bimanual EUA, endoscopic surgery (biopsy or TUR), and imaging studies. The modifier “p” refers to pathologic staging based on cystectomy and lymph node dissection.

^p [Principles of Instillation Therapy \(BL-F\)](#).

^x Consider FDG-PET/CT scan (skull base to mid-thigh) (category 2B).

^y For patients with borderline GFR, consider timed urine collection, which may more accurately determine eligibility for cisplatin.

^z [Principles of Systemic Therapy \(BL-G 1 of 7\)](#).

^{aa} [Principles of Systemic Therapy \(BL-G 5 of 7\)](#).

^{bb} [Principles of Radiation Management of Invasive Disease \(BL-H\)](#).

^{cc} Optimal candidates for bladder preservation with chemoradiotherapy include patients with tumors that present without moderate/severe hydronephrosis, are without concurrent extensive or multifocal CIS, and are <6 cm. Ideally, tumors should allow for a visually complete or maximally debulking TURBT. See [Principles of Radiation Management of Invasive Disease \(BL-H\)](#).

^{dd} [Principles of Systemic Therapy \(BL-G 2 of 7\)](#).

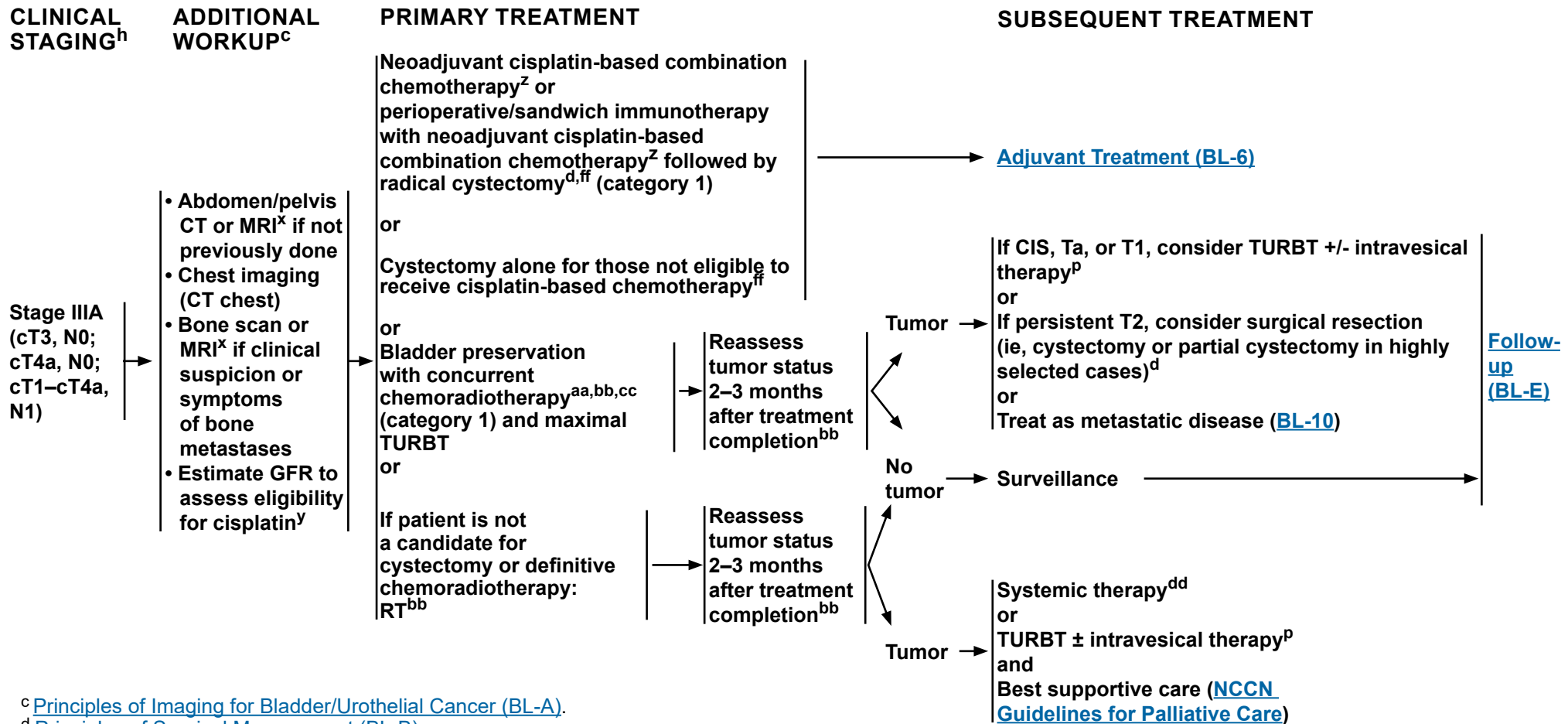
^{ee} Most appropriate for patients who value an opportunity to delay recurrence even if the chance of cure was not improved, and for whom the risk of side effects was acceptable.

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



NCCN Guidelines Version 1.2025

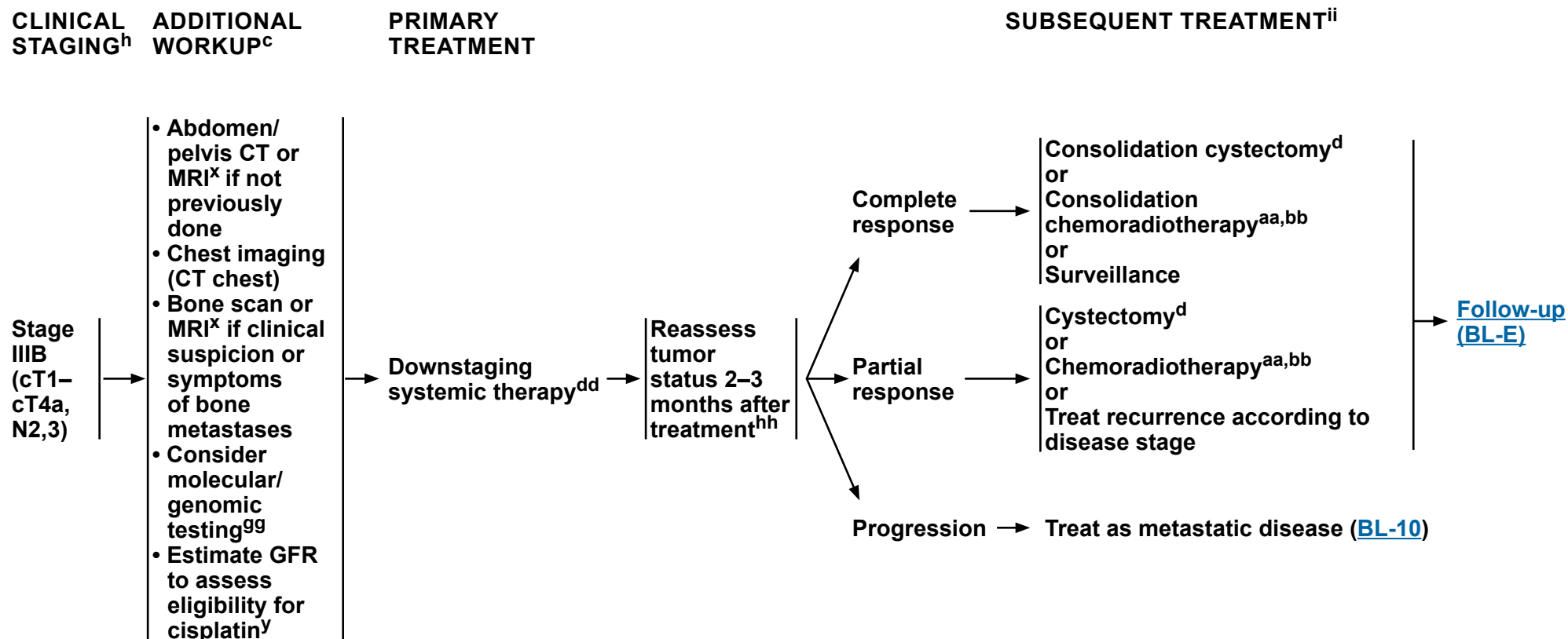
Muscle-Invasive Bladder Cancer

^c [Principles of Imaging for Bladder/Urothelial Cancer \(BL-A\)](#).^d [Principles of Surgical Management \(BL-B\)](#).^h The modifier "c" refers to clinical staging based on bimanual EUA, endoscopic surgery (biopsy or TUR), and imaging studies. The modifier "p" refers to pathologic staging based on cystectomy and lymph node dissection.^p [Principles of Instillation Therapy \(BL-F\)](#).^x Consider FDG-PET/CT scan (skull base to mid-thigh) (category 2B).^y For patients with borderline GFR, consider timed urine collection, which may more accurately determine eligibility for cisplatin.^z [Principles of Systemic Therapy \(BL-G 1 of 7\)](#).^{aa} [Principles of Systemic Therapy \(BL-G 5 of 7\)](#).^{bb} [Principles of Radiation Management of Invasive Disease \(BL-H\)](#).^{cc} Optimal candidates for bladder preservation with chemoradiotherapy include patients with tumors that present without moderate/severe hydronephrosis, are without concurrent extensive or multifocal CIS, and are <6 cm. Ideally, tumors should allow a visually complete or maximally debulking TURBT. See [Principles of Radiation Management of Invasive Disease \(BL-H\)](#).^{dd} [Principles of Systemic Therapy \(BL-G 2 of 7\)](#).^{ff} Patients with cN1 disease have better outcomes if they are given neoadjuvant chemotherapy and have a response.
[Recurrent or Persistent Disease \(BL-11\)](#)
Note: All recommendations are category 2A unless otherwise indicated.



NCCN Guidelines Version 1.2025

Muscle-Invasive Bladder Cancer

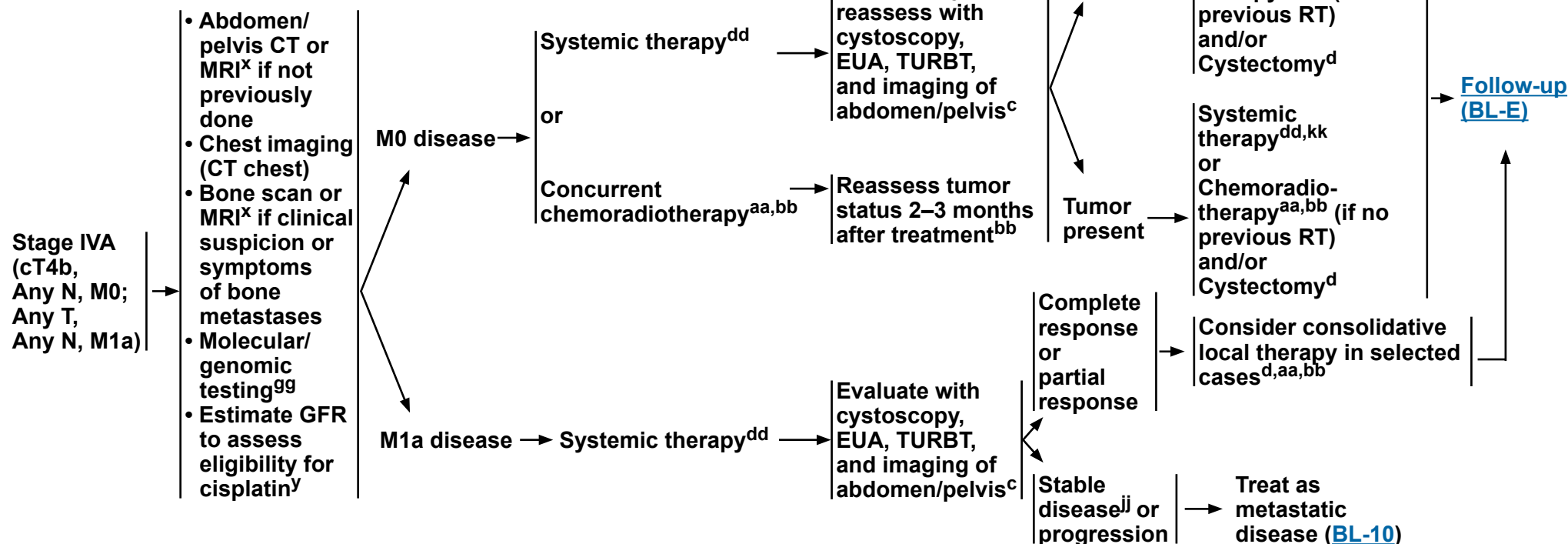
^c [Principles of Imaging for Bladder/Urothelial Cancer \(BL-A\).](#)^d [Principles of Surgical Management \(BL-B\).](#)^h The modifier “c” refers to clinical staging based on bimanual EUA, endoscopic surgery (biopsy or TUR), and imaging studies. The modifier “p” refers to pathologic staging based on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

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



NCCN Guidelines Version 1.2025

Muscle-Invasive Bladder Cancer

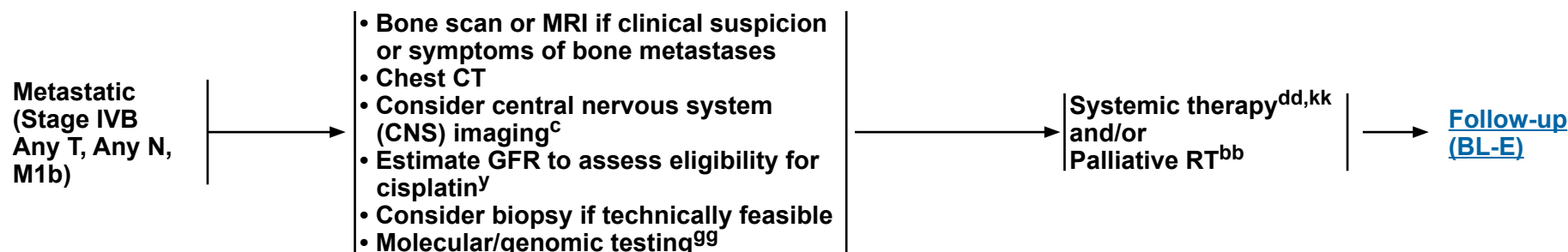
**CLINICAL
STAGING^h****ADDITIONAL WORKUP^c****PRIMARY TREATMENT****SUBSEQUENT TREATMENT**^c [Principles of Imaging for Bladder/Urothelial Cancer \(BL-A\)](#).^d [Principles of Surgical Management \(BL-B\)](#).^h The modifier “c” refers to clinical staging based on bimanual EUA, endoscopic surgery (biopsy or TUR), and imaging studies. The modifier “p” refers to pathologic staging based on cystectomy and lymph node dissection.^x Consider FDG-PET/CT scan (skull base to mid-thigh) (category 2B).^y For patients with borderline GFR, consider timed urine collection, which may more accurately determine eligibility for cisplatin.^{aa} [Principles of Systemic Therapy \(BL-G 5 of 7\)](#).^{bb} [Principles of Radiation Management of Invasive Disease \(BL-H\)](#).^{dd} [Principles of Systemic Therapy \(BL-G 2 of 7\)](#).^{gg} See [Principles of Alternative Risk Classifiers and Biomarkers \(BL-I\)](#).^{jj} Non-bulky disease and no significant clinical progression.^{kk} See Principles of Systemic Therapy ([BL-G 3 of 7](#) and [4 of 7](#)).**[Recurrent or Persistent Disease \(BL-11\)](#)****Note: All recommendations are category 2A unless otherwise indicated.**



CLINICAL STAGING^h

ADDITIONAL WORKUP^c

PRIMARY TREATMENT



^c [Principles of Imaging for Bladder/Urothelial Cancer \(BL-A\)](#).

^h The modifier “c” refers to clinical staging based on bimanual EUA, endoscopic surgery (biopsy or TUR), and imaging studies. The modifier “p” refers to pathologic staging based on cystectomy and lymph node dissection.

^y For patients with borderline GFR, consider timed urine collection, which may more accurately determine eligibility for cisplatin.

^{bb} [Principles of Radiation Management of Invasive Disease \(BL-H\)](#).

^{dd} [Principles of Systemic Therapy \(BL-G 2 of 7\)](#).

^{gg} See [Principles of Alternative Risk Classifiers and Biomarkers \(BL-I\)](#).

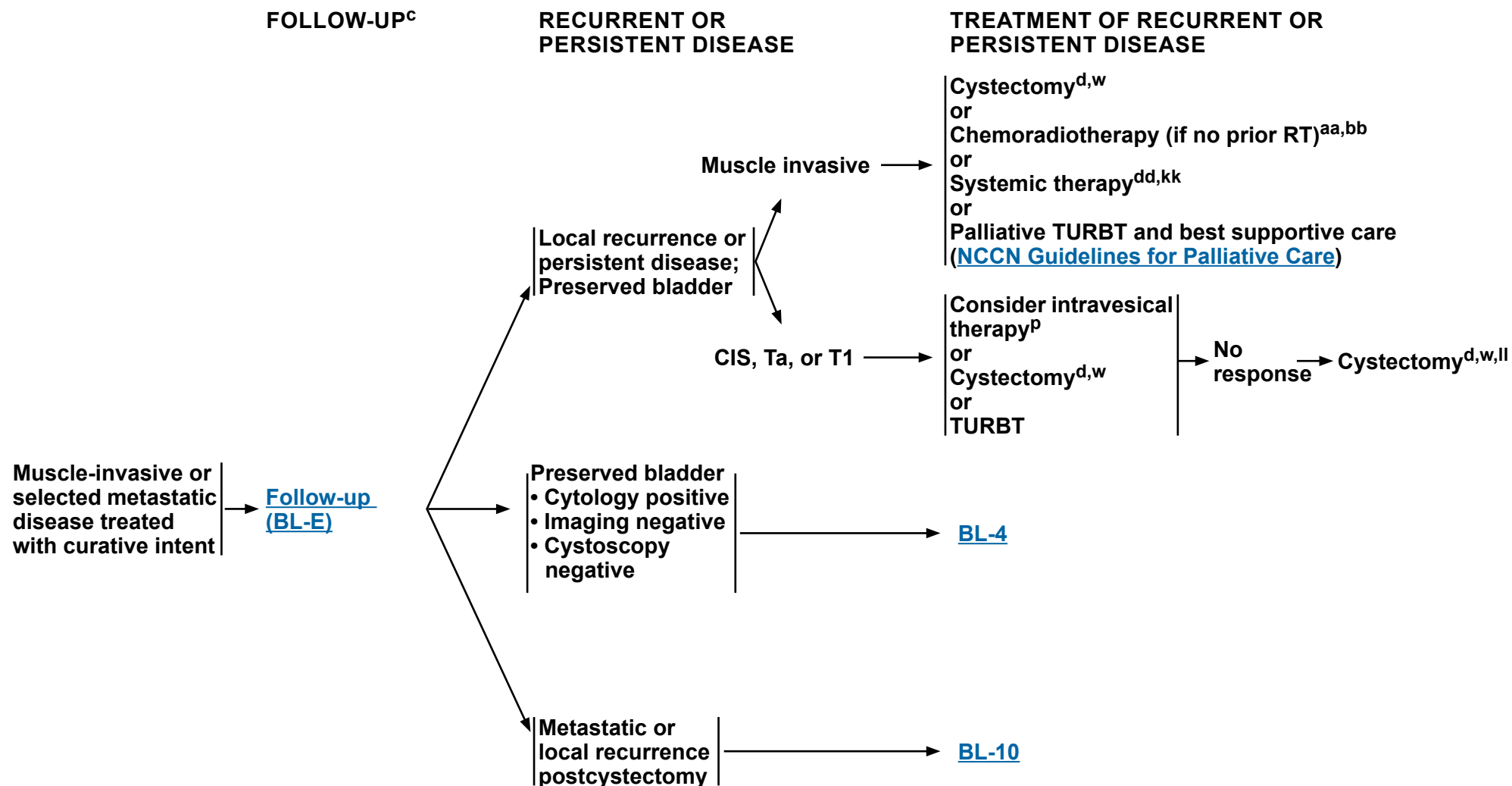
^{kk} See Principles of Systemic Therapy ([BL-G 3 of 7](#) and [4 of 7](#)).

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



NCCN Guidelines Version 1.2025

Muscle-Invasive Bladder Cancer

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

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

**PRINCIPLES OF IMAGING FOR BLADDER/UROTHELIAL CANCER**

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

Non–Muscle-Invasive Bladder Cancer (NMIBC)**Chest Imaging**

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

Abdomen and Pelvis Imaging

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

Evaluation for Suspected Bone Metastasis

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

Neurologic/Brain Imaging^{4,5}

- Staging:
 - Brain MRI not generally recommended.

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

[Continued](#)
[References](#)**BL-A**
1 OF 5

**PRINCIPLES OF IMAGING FOR BLADDER/UROTHELIAL CANCER**

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

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

- **Staging⁴:**
 - ▶ **CT of the chest with or without contrast (preferred)⁶**
 - ▶ **Posteroanterior (PA) and lateral chest x-ray**
 - ▶ **FDG-PET/CT (category 2B) may be beneficial in selected patients with T2 (muscle-invasive disease) and in patients with \geq cT3 disease. This will also include abdomen and pelvis if performed.⁷⁻¹⁰ FDG-PET/CT should not be used to delineate the anatomy of the upper urinary tract.**
- **Follow-up with or without cystectomy: [\(BL-E\)](#)**
 - ▶ **Chest CT with or without IV contrast (preferred)**
 - ◊ **May be performed without contrast if IV contrast cannot be given.**
 - ◊ **Consider performing with the abdomen and pelvis for a single exam in patients who also need imaging of the abdomen and pelvis.**
 - ▶ **PA and lateral chest x-ray**
 - ▶ **FDG-PET/CT (category 2B) may be performed if not previously done or if metastasis is suspected in selected patients. This examination will also include the abdomen and pelvis. FDG-PET/CT should not be used to delineate the anatomy of the upper urinary tract.**
- **Follow-up of cT4b [\(BL-E\)](#) and metastatic disease:**
 - ▶ **Chest CT with or without IV contrast (preferred)**
 - ◊ **May be performed without contrast if IV contrast cannot be given.**
 - ◊ **Consider performing with the abdomen and pelvis for a single exam in patients who also need imaging of the abdomen and pelvis.**
 - ▶ **PA and lateral chest x-ray**
 - ▶ **FDG-PET/CT (category 2B) may be performed if not previously done or in patients with high-risk MIBC in whom metastatic disease is suspected. This could also be used to guide biopsy in certain patients. FDG-PET/CT should not be used to delineate the anatomy of the upper urinary tract.**

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

[Continued](#)
[References](#)

BL-A
2 OF 5

**PRINCIPLES OF IMAGING FOR BLADDER/UROTHELIAL CANCER****Muscle-Invasive Bladder Cancer** (continued)**Abdomen and Pelvis Imaging**

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

Evaluation for Suspected Bone Metastasis

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

Metastatic Disease - Patients Being Observed

- See Follow-Up ([BL-E 6 of 6](#))

Neurologic/Brain Imaging^{4,5}

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

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

[Continued](#)
[References](#)**BL-A**
3 OF 5



PRINCIPLES OF IMAGING FOR BLADDER/UROTHELIAL CANCER

Upper Tract (renal pelvis and urothelial carcinoma of the ureter)¹²

- Staging and follow-up of $\leq T1$ disease (see recommendations for NMIBC bladder cancer).
- Staging and follow-up of $\geq T2$ disease (see recommendations for MIBC bladder cancer).

Urothelial Carcinoma of the Prostate/Primary Carcinoma of the Urethra

- Staging:
 - ▶ Chest CT (preferred) or PA and lateral chest x-ray.
 - ▶ Consider abdomen CT or MRI in high-risk T1 disease or patients with $\geq T2$ disease.¹³
 - ▶ MRI of the pelvis without and with IV contrast for local staging.
- Additional staging if urothelial carcinoma of prostate:
 - ▶ Imaging of upper tracts and collecting system.
 - ▶ CTU (CT of the abdomen and pelvis without and with IV contrast with excretory imaging).
 - ▶ MRU may be appropriate in patients with poor renal function or iodinated contrast allergy but with GFR >30 and no acute renal failure.
 - ▶ Ureteroscopy
 - ▶ Renal US or CT without contrast may be utilized in conjunction with retrograde evaluation in patients who cannot receive either iodinated or gadolinium-based contrast material.
- Additional staging if primary carcinoma of the urethra:
 - ▶ In the setting of palpable inguinal lymph nodes:
 - ◊ Biopsy of palpable nodes.
 - ◊ CT of the chest, abdomen, and pelvis for additional staging, if not yet performed.
- Follow-up:
 - ▶ Low-risk T1 or $<T1$ disease:
 - ◊ MRI or CT of pelvis with and without IV contrast.
 - ▶ High-risk T1 or $\geq T2$:
 - ◊ May consider more extensive follow-up based on risk factors; 3–6 months for 2 years and then yearly.
 - Chest imaging with x-ray and/or CT as previously discussed.
 - Imaging of abdomen and pelvis with MRI or CT with and without contrast.

[References](#)

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



PRINCIPLES OF IMAGING FOR BLADDER/UROTHELIAL CANCER REFERENCES

- ¹Leyendecker JR, Clingan MJ, Eberhardt SC, et al; Expert Panel on Urologic Imaging. ACR Appropriateness Criteria post-treatment surveillance of bladder cancer [online publication]. Reston, VA: American College of Radiology (ACR); 2014.
- ²Tekes A, Kamel I, Imam K, et al. Dynamic MRI of bladder cancer: evaluation of staging accuracy. *AJR Am J Roentgenol* 2005;184:121-127.
- ³Wu LM, Chen XX, Xu JR, et al. Clinical value of T2-weighted imaging combined with diffusion-weighted imaging in preoperative T staging of urinary bladder cancer: a large-scale, multiobserver prospective study on 3.0-T MRI. *Acad Radiol* 2013;20:939-946.
- ⁴Shinagare AB, Ramaiya RH, Jagannathan JP, et al. Metastatic pattern of bladder cancer: correlation with the characteristics of the primary tumor. *AJR Am J Roentgenol* 2011;196:117-122.
- ⁵Anderson TS, Regine WF, Kryscio R, et al. Neurologic complications of bladder carcinoma: A review of 359 cases. *Cancer* 2003;97:2267-2272.
- ⁶Witjes JA, Compérat E, Cowan NC, et al. EAU guidelines on muscle-invasive and metastatic bladder cancer: summary of the 2013 guidelines. *Eur Urol* 2014;65:778-792.
- ⁷Kollberg P, Almquist H, Bläckberg M, et al. [18F]Fluorodeoxyglucose – positron emission tomography/computed tomography improves staging in patients with high-risk muscle-invasive bladder cancer scheduled for radical cystectomy. *Scand J Urol* 2015;49:1-6.
- ⁸Goodfellow 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.
- ⁹Lu YY, Chen JH, Liang JA, et al. Clinical value of FDG-PET or PET/CT in urinary bladder cancer: A systematic review and meta-analysis. *Eur J of Radiol* 2012;81:2411-2416.
- ¹⁰Kibel AS, Dehdashti F, Katz MD, et al. Prospective study of [18F]fluorodeoxyglucose positron emission tomography/computed tomography for staging of muscle-invasive bladder carcinoma. *J Clin Oncol* 2009;27:4314-4320.
- ¹¹Zhang J, Gerst S, Lefkowitz RA, et al. Imaging of bladder cancer. *Radiol Clin North Am* 2007;45:183-205.
- ¹²Rouprêt M, Babjuk M, Compérat E, et al. European guidelines on upper tract urothelial carcinomas: 2013 update. *Eur Urol* 2013;63:1059-1071.
- ¹³Gakis G, Witjes JA, Compérat E, et al. EAU guidelines on primary urethral carcinoma. *Eur Urol* 2013;64:823-830.

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



PRINCIPLES OF SURGICAL MANAGEMENT

TURBT for Staging

- Adequate resection with muscle in specimen
 - ▶ Muscle may be omitted in cases of documented low-grade Ta disease
 - ▶ In cases of suspected or known CIS:
 - ◊ Biopsy adjacent to papillary tumor
 - ◊ Consider prostate urethral biopsy
 - ▶ Papillary appearing tumor (likely non-muscle invasive)
 - ◊ Early repeat TURBT (within 6 weeks) if:
 - Incomplete initial resection
 - No muscle in original specimen for high-grade disease
 - Large (≥3 cm) or multifocal lesions
 - Any T1 lesion
 - ▶ Transurethral resection (TUR) for sessile or invasive appearing tumor (likely muscle invasive)
 - ◊ Repeat TURBT if:
 - Prior resection did not include muscle in the setting of high-grade disease
 - Any T1 lesion
 - First resection does not allow adequate staging/attribution of risk for treatment selection
 - Incomplete resection and considering tri-modality bladder preservation therapy
- Enhanced (blue light and narrow-band imaging) cystoscopy may be helpful in identifying lesions not visible using white light cystoscopy.

TURBT/Maximal TURBT for Treatment

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

[Continued](#)

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



PRINCIPLES OF SURGICAL MANAGEMENT

Transurethral Resection of the Prostate (TURP)

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

TUR of the Urethral Tumor

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

Partial Cystectomy

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

Radical Cystectomy/Cystoprostatectomy

- In non–muscle-invasive disease, radical cystectomy is generally reserved for residual high-grade cT1, aggressive histopathologic subtypes, lymphovascular invasion, concomitant CIS, and BCG-unresponsive disease ([Bladder Cancer: Non-Urothelial and Urothelial with Subtype Histology \[BL-D\]](#)).
- Cystectomy should be done within 3 months of diagnosis if no therapy is given.
- Primary treatment option for cT2, cT3, and cT4a disease. Highly select patients with cT4b disease that responds to primary treatment may be eligible for cystectomy.
- Bilateral pelvic lymphadenectomy should be performed.
- In appropriately selected patients, approaches that preserve the uterus, vagina, and/or ovaries should be employed when feasible.

Radical Nephroureterectomy with Cuff of Bladder

- Primary treatment option for non-metastatic high-grade upper GU tract tumors.

[Continued](#)

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



PRINCIPLES OF SURGICAL MANAGEMENT

Regional Lymphadenectomy

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

Urethrectomy

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

Pelvic Exenteration (category 2B)

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

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

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

[Continued](#)

BL-B
3 OF 4



PRINCIPLES OF SURGICAL MANAGEMENT

Endoscopic Management of Upper Tract Urothelial Cancer (UTUC)

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

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

**PRINCIPLES OF PATHOLOGY MANAGEMENT**
2022 WHO Classification of Tumors of the Urothelial Tract^{1,2}**Urothelial Tumors**

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

Squamous Cell Neoplasms

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

Glandular Neoplasms

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

Urachal Carcinoma**Tumors of Müllerian Type**

- Clear cell carcinoma
- Endometrioid carcinoma

Neuroendocrine Tumors

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

Mesenchymal Tumors

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

Urothelial Tract Hematopoietic and Lymphoid Tumors**Miscellaneous Tumors**

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

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

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

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

² Netto GJ, Amin MB, Berney DM, et al. The 2022 World Health Organization Classification of Tumors of the Urinary System and Male Genital Organs - Part B: Prostate and Urinary Tract Tumours. Eur Urol 2022;82:469-486.

Continued

**PRINCIPLES OF PATHOLOGY MANAGEMENT**

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

³ CAP Cancer Protocol Templates (<https://www.cap.org/protocols-and-guidelines/cancer-reporting-tools/cancer-protocol-templates>).

⁴ Cheng L, et al. Non-invasive papillary urothelial carcinoma, high-grade. In: WHO Classification of Tumors. 5th: Urinary and Male Genital Tumors. WHO Classification of Tumors Editorial Board; International Agency for Research on Cancer; 2022:143-146.

⁵ Bochner BH, et al. Urinary Bladder. In: Amin MB, ed. AJCC Cancer Staging Manual. 8th Springer; 2017:757-765.

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

**BLADDER CANCER: NON-UROTHELIAL AND UROTHELIAL WITH SUBTYPE HISTOLOGY****Mixed Histology:**

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

Aggressive Subtype Histologies:

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

Pure Small Cell Carcinoma or Mixed Histology with Any Small Cell Component (or neuroendocrine features):

- Neurologic/brain imaging is recommended ([BL-A 3 of 5](#)).
- Concurrent chemoradiotherapy or neoadjuvant systemic therapy followed by local treatment (cystectomy or RT) is recommended for any patient with small cell component histology with localized disease regardless of stage (including non-muscle-invasive disease).
- Neoadjuvant systemic therapy
 - Regimens recommended in the [NCCN Guidelines for Small Cell Lung Cancer - Principles of Systemic Therapy](#)
 - or
 - Alternating ifosfamide + doxorubicin with etoposide + cisplatin⁴⁻⁶
- Metastatic systemic therapy
 - Regimens recommended in the [NCCN Guidelines for Small Cell Lung Cancer - Principles of Systemic Therapy](#) or
 - Alternating ifosfamide + doxorubicin with etoposide + cisplatin⁴⁻⁶

Pure Squamous Carcinoma:

- There is no proven role for neoadjuvant/adjuvant chemotherapy for pure squamous cell carcinoma of the bladder.
- Local control with surgery or chemoradiotherapy and best supportive care ([NCCN Guidelines for Palliative Care](#)) are recommended.
- For advanced disease, clinical trial is preferred. For selected patients,

combination chemotherapy with paclitaxel, ifosfamide, and cisplatin may be considered.⁷

- Consider postoperative RT in selected cases (positive margins).⁸

Pure Adenocarcinoma Including Urachal Carcinoma:

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

Primary Bladder Sarcoma:

- Treatment as per [NCCN Guidelines for Soft Tissue Sarcoma](#).

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

References



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

- ¹ Meeks JJ, Taylor JM, Matsushita K, et al. Pathological response to neoadjuvant chemotherapy for muscle-invasive micropapillary bladder cancer. *BJU Int* 2013;111:E325-E330.
- ² Siefker-Radtke AO, Dinney CP, Shen Y, et al. A phase 2 clinical trial of sequential neoadjuvant chemotherapy with ifosfamide, doxorubicin, and gemcitabine followed by cisplatin, gemcitabine, and ifosfamide in locally advanced urothelial cancer: Final results. *Cancer* 2013;119:540-547.
- ³ Dayyani F, Czerniak BA, Sircar K, et al. Plasmacytoid urothelial carcinoma, a chemosensitive cancer with poor prognosis, and peritoneal carcinomatosis. *J Urol* 2013;189:1656-1661.
- ⁴⁷ Galsky M, Iasonos A, Mironov S, et al. Prospective trial of ifosfamide, paclitaxel, and cisplatin in patients with advanced non-transitional cell carcinoma of the urothelial tract. *Urology* 2007;69:255-259.
- ⁵⁸ Zaghloul MS, Awwad HK, Akoush HH, et al. Postoperative radiotherapy of carcinoma in bilharzial bladder: improved disease free survival through improving local control. *Int J Radiat Oncol Biol Phys* 1992;23:511-517.
- ⁶ Siefker-Radtke A, Gee J, Shen Y, et al. Multimodality management of urachal carcinoma: The M. D. Anderson Cancer Center experience. *J Urol* 2003;169:1295-1298.
- ⁷⁴ Siefker-Radtke AO, Kamat AM, Grossman HB, et al. Phase II clinical trial of neoadjuvant alternating doublet chemotherapy with ifosfamide/doxorubicin and etoposide/cisplatin in small-cell urothelial cancer. *J Clin Oncol* 2009; 27:2592-2597.
- ⁸⁵ Lynch SP, Shen Y, Kamat A, et al. Neoadjuvant chemotherapy in small cell urothelial cancer improves pathologic downstaging and long-term outcomes: Results from a retrospective study at the MD Anderson Cancer Center. *Eur Urol* 2013;64:307-313.
- ⁹⁶ Siefker-Radtke AO, Dinney CP, Abrahams NA, et al. Evidence supporting preoperative chemotherapy for small cell carcinoma of the bladder: A retrospective review of the M. D. Anderson cancer experience. *J Urol* 2004;172:481-484.

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



FOLLOW-UP

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

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

Low Risk	Intermediate Risk	High Risk
<ul style="list-style-type: none"> • Papillary urothelial neoplasm of low malignant potential • Low-grade urothelial carcinoma <ul style="list-style-type: none"> ▶ Ta and ▶ ≤3 cm and ▶ Solitary 	<ul style="list-style-type: none"> • Low-grade urothelial carcinoma <ul style="list-style-type: none"> ▶ T1 or ▶ >3 cm or ▶ Multifocal or ▶ Recurrence within 1 year • High-grade urothelial carcinoma <ul style="list-style-type: none"> ▶ Ta and ▶ ≤3 cm and ▶ Solitary 	<ul style="list-style-type: none"> • High-grade urothelial carcinoma <ul style="list-style-type: none"> ▶ CIS or ▶ T1 or ▶ >3 cm or ▶ Multifocal • Very-high-risk features (any): <ul style="list-style-type: none"> ▶ BCG unresponsive^a ▶ Certain histopathologic subtypes^b ▶ Lymphovascular invasion ▶ Prostatic urethral invasion

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

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

Table 2: Low-Risk,^c Non–Muscle-Invasive Bladder Cancer

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

[Intermediate Risk, Non–Muscle Invasive \(BL-E 2 of 6\)](#)

[High-Risk, Non–Muscle Invasive \(BL-E 2 of 6\)](#)

[Post-Cystectomy Non–Muscle-Invasive Bladder Cancer \(BL-E 3 of 6\)](#)

[Post-Cystectomy Muscle-Invasive Bladder Cancer \(BL-E 4 of 6\)](#)

[Post-Bladder Sparing \(BL-E 5 of 6\)](#)

[Metastatic Disease: Surveillance \(BL-E 6 of 6\)](#)

[Recurrent or Persistent Disease \(BL-11\)](#)

^a Kamat AM, et al. J Clin Oncol 2016;34:1935-1944.

^b See aggressive subtype histologies listed on [Bladder Cancer: Non-Urothelial and Urothelial with Subtype Histology \(BL-D\)](#).

^c See AUA Risk Stratification for Non–Muscle-Invasive Bladder Cancer definitions on [BL-2](#).

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

See [NCCN Guidelines for Survivorship](#)

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



FOLLOW-UP

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

Table 3: Intermediate Risk,^c Non–Muscle-Invasive Bladder Cancer

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

Table 4: High-Risk,^c Non–Muscle-Invasive Bladder Cancer

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

^c See AUA Risk Stratification for Non–Muscle-Invasive Bladder Cancer definitions on [BL-2](#).

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

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

See [NCCN Guidelines for Survivorship](#)

BL-E
2 OF 6



FOLLOW-UP

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

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

Test	Year						
	1	2	3	4	5	5–10	>10
Cystoscopy	N/A						
Imaging ^d	• 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 ^e	As clinically indicated
Blood tests	• Renal function testing (electrolytes and creatinine) every 3–6 mo • LFT ^f every 3–6 mo • CBC, CMP every 3–6 mo if received chemotherapy	• Renal function testing (electrolytes and creatinine) annually • LFT ^f annually • B ₁₂ annually based on clinical judgment				B ₁₂ annually based on clinical judgment	
Urine tests	• Consider urine cytology every 6–12 mo • Consider urethral wash cytology every 6–12 mo ^g		Urine cytology as clinically indicated Urethral wash cytology as clinically indicated				

[Post-Cystectomy MIBC \(BL-E 4 of 6\)](#)

[Post-Bladder Sparing \(BL-E 5 of 6\)](#)

[Recurrent or Persistent Disease \(BL-11\)](#)

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

^e Renal US to look for hydronephrosis.

^f Liver function testing (LFT) includes aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, and alkaline phosphatase.

^g Urethral wash cytology is reserved for patients with high-risk disease. High-risk disease includes: positive urethral margin, multifocal CIS, and prostatic urethral invasion.

See [NCCN Guidelines for Survivorship](#)

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



FOLLOW-UP

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

Table 6: Post-Cystectomy Muscle-Invasive Bladder Cancer

Test	Year						
	1	2	3	4	5	5–10	>10
Cystoscopy	N/A						
Imaging ^d	<ul style="list-style-type: none">• CTU or MRU (image upper tracts + axial imaging of abdomen/pelvis) every 3–6 mo• CT chest (preferred) or chest x-ray every 3–6 mo or• FDG-PET/CT (category 2B) only if metastatic disease suspected		<ul style="list-style-type: none">• Abdomen/pelvis CT or MRI annually• CT chest (preferred) or chest x-ray annually or• FDG-PET/CT (category 2B) only if metastatic disease suspected			Renal US annually ^e	As clinically indicated
Blood tests	<ul style="list-style-type: none">• Renal function testing (electrolytes and creatinine) every 3–6 mo• LFT^f every 3–6 mo• CBC, CMP every 3–6 mo if received chemotherapy	<ul style="list-style-type: none">• Renal function testing (electrolytes and creatinine) annually<ul style="list-style-type: none">• LFT^f annually• B₁₂ annually based on clinical judgment				B ₁₂ annually based on clinical judgment	
Urine tests	<ul style="list-style-type: none">• Consider urine cytology every 6–12 mo• Consider urethral wash cytology every 6–12 mo^g		Urine cytology as clinically indicated Urethral wash cytology as clinically indicated				

[Post-Bladder Sparing \(BL-E 5 of 6\)](#)

[Recurrent or Persistent Disease \(BL-11\)](#)

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

^e Renal US to look for hydronephrosis.

^f LFT includes AST, ALT, bilirubin, and alkaline phosphatase.

^g Urethral wash cytology is reserved for patients with high-risk disease. High-risk disease includes: positive urethral margin, multifocal CIS, and prostatic urethral invasion.

See [NCCN Guidelines for Survivorship](#)

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



FOLLOW-UP

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

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

Test	Year						
	1	2	3	4	5	5–10	>10
Cystoscopy	Every 3 mo		Every 6 mo		Annually		As clinically indicated
Imaging ^d	<ul style="list-style-type: none">• CTU or MRU (image upper tracts + axial imaging of abdomen/pelvis) every 3–6 mo for MIBC• CT chest (preferred) or chest x-ray every 3–6 mo for MIBCor• FDG-PET/CT (category 2B) only if metastatic disease suspected		<ul style="list-style-type: none">• Abdomen/pelvis CT or MRI annually• CT chest (preferred) or chest x-ray annually or• FDG-PET/CT (category 2B) only if metastatic disease suspectedⁱ			As clinically indicated	
Blood tests	<ul style="list-style-type: none">• Renal function testing (electrolytes and creatinine) every 3–6 mo• LFT^f every 3–6 mo• CBC, CMP every 3–6 mo if received chemotherapy	<ul style="list-style-type: none">• Renal function testing (electrolytes and creatinine) as clinically indicated• LFT^f as clinically indicated					
Urine tests	Urine cytology every 6–12 mo		Urine cytology as clinically indicated				

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

^f LFT includes AST, ALT, bilirubin, and alkaline phosphatase.

^h For patients who are not eligible for aggressive therapy, less frequent surveillance may be warranted (eg, cystoscopy every 6 months, extended to annually over time).

ⁱ PET/CT not recommended for NMIBC.

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



FOLLOW-UP

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

Table 8: Metastatic Disease: Surveillance

Test	Year						
	1	2	3	4	5	5–10	>10
Cystoscopy	• As clinically indicated						
Imaging ^d	• CTU or MRU (image upper tracts + axial imaging of abdomen/pelvis) every 3–6 mo if clinically indicated and with any clinical change or new symptoms • CT chest/abdomen/pelvis 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 based on clinical judgment						
Urine tests	• Urine cytology as clinically indicated						

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

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



PRINCIPLES OF INSTILLATION THERAPY

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

Intravesical Therapy for Bladder Cancer

Immediate Postoperative Intravesical Chemotherapy

• [Clinical Presentation and Initial Evaluation \(BL-1\)](#)

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

Induction (Adjuvant) Intravesical Chemotherapy or BCG

- Treatment option for NMIBC.
- The most commonly used agents are BCG, mitomycin, and gemcitabine.
- Initiated 3–4 weeks after TURBT with or without maintenance.
- Weekly instillations during induction are given for approximately 6 weeks.
- Maximum of 2 consecutive cycle inductions without complete response.
- Withhold if traumatic catheterization, bacteriuria, persistent gross hematuria, persistent severe local symptoms, or systemic symptoms.

Maintenance Intravesical BCG

- Although there is no standard regimen for maintenance BCG, many NCCN Member Institutions follow the SWOG regimen consisting of a 6-week induction course of BCG followed by maintenance with 3 weekly instillations at months 3, 6, 12, 18, 24, 30, and 36.⁴
- Ideally maintenance should be given for 1 year for intermediate-risk and 3 years for high-risk NMIBC.
- BCG would be withheld if traumatic catheterization, bacteriuria, persistent gross hematuria, persistent severe local symptoms, or systemic symptoms.
- Dose reduction is encouraged if there are substantial local symptoms during maintenance therapy.
- Data suggest the benefit of maintenance BCG therapy through a decreased rate of recurrence for NMIBC.⁴

[Continued](#)
[References](#)

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



PRINCIPLES OF INSTILLATION THERAPY

Intravesical BCG Principles During Time of BCG Shortage:

- BCG induction and maintenance should be prioritized for patients at high risk for recurrence (eg, high-grade T1 and CIS), especially in the early maintenance period (ie, 3 and 6 months post-induction).
- BCG maintenance for patients with intermediate-risk NMIBC can be risk adapted to prioritize patients with high-risk NMIBC.
- BCG maintenance for patients with high-risk NMIBC should be stopped at 1 year.
- Consider induction with alternative agents if BCG is completely not available.
 - ▶ Alternative options include: sequential gemcitabine/docetaxel, mitomycin, gemcitabine, epirubicin, valrubicin, docetaxel, or sequential gemcitabine/mitomycin.
- Consider a clinical trial if available.
- If feasible, the dose of BCG may be split (1/3 or 1/2 dose) so that multiple patients may be treated with a single vial (for induction or high-priority maintenance therapy).

[Continued](#)
[References](#)

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

BL-F
2 OF 4

**PRINCIPLES OF INSTILLATION THERAPY**

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

Topical or Percutaneous Administration of Chemotherapy or BCG

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

Postsurgical Intraprostatic BCG for Urothelial Carcinoma of the Prostate

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

Postsurgical Intraurethral Therapy for Primary Carcinoma of the Urethra

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

Intrapelvic and Intravesical Therapy for Upper Tract Tumors

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

[References](#)

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

**PRINCIPLES OF INSTILLATION THERAPY – REFERENCES**

- ¹ Messing E, Tangen C, Lerner S, et al. Effect of intravesical instillation of gemcitabine vs saline immediately following resection of suspected low-grade non-muscle-invasive bladder cancer on tumor recurrence. *JAMA* 2018;319:1880-1888.
- ² Bosschiet J, Nieuwenhuijzen JA, van Ginkel T, et al. Value of an immediate intravesical instillation of mitomycin C in patients with non-muscle-invasive bladder cancer: A prospective multicentre randomised study in 2243 patients. *Eur Urol* 2018;73:226-232.
- ³ Sylvester RJ, Oosterlinck W, Holmang S, et al. Systematic review and individual patient data meta-analysis of randomized trials comparing a single immediate instillation of chemotherapy after transurethral resection with transurethral resection alone in patients with stage pTa-pT1 urothelial carcinoma of the bladder: Which patients benefit from the instillation? *Eur Urol* 2016;69:231-244.
- ⁴ Lamm DL, Blumenstein BA, Crissman JD, et al. Maintenance bacillus Calmette-Guerin immunotherapy for recurrent TA, T1 and carcinoma in situ transitional cell carcinoma of the bladder: a randomized Southwest Oncology Group Study. *J Urol* 2000;163:1124-1129.
- ⁵ Hillyard RW, Jr, Ladaga L, Schellhammer PF. Superficial transitional cell carcinoma of the bladder associated with mucosal involvement of the prostatic urethra: results of treatment with intravesical bacillus Calmette-Guerin. *J Urol* 1988;139:290-293.
- ⁶ Canda AE, Tuzel E, Mungan MU, et al. Conservative management of mucosal prostatic urethral involvement in patients with superficial transitional cell carcinoma of the bladder. *Eur Urol* 2004;45:465-469; discussion 469-470.
- ⁷ Palou J, Xavier B, Laguna P, et al. In situ transitional cell carcinoma involvement of prostatic urethra: bacillus Calmette-Guerin therapy without previous transurethral resection of the prostate. *Urology* 1996;47:482-484.
- ⁸ Schellhammer PF, Ladaga LE, Moriarty RP. Intravesical bacillus Calmette-Guerin for the treatment of superficial transitional cell carcinoma of the prostatic urethra in association with carcinoma of the bladder. *J Urol* 1995;153:53-56.
- ⁹ Bretton PR, Herr HW, Whitmore WF, Jr, et al. Intravesical bacillus Calmette-Guerin therapy for in situ transitional cell carcinoma involving the prostatic urethra. *J Urol* 1989;141:853-856.
- ¹⁰ Orihuela E, Herr HW, Whitmore WF, Jr. Conservative treatment of superficial transitional cell carcinoma of prostatic urethra with intravesical BCG. *Urology* 1989;34:231-237.
- ¹¹ Solsona E, Iborra I, Ricos JV, et al. Recurrence of superficial bladder tumors in prostatic urethra. *Eur Urol* 1991;19:89-92.
- ¹² Cutress ML, Stewart GD, Zakikhani P, et al. Ureteroscopic and percutaneous management of upper tract urothelial carcinoma (UTUC): systematic review. *BJU Int* 2012;110:614-628.
- ¹³ Hayashida Y, Nomata K, Noguchi M, et al. Long-term effects of bacille Calmette-Guerin perfusion therapy for treatment of transitional cell carcinoma in situ of upper urinary tract. *Urology* 2004;63:1084-1088.
- ¹⁴ Audenet F, Traxer O, Bensalah K, Roupert M. Upper urinary tract instillations in the treatment of urothelial carcinomas: a review of technical constraints and outcomes. *World J Urol* 2013;31:45-52.
- ¹⁵ O'Brien T, Ray E, Singh R, et al. Prevention of bladder tumours after nephroureterectomy for primary upper urinary tract urothelial carcinoma: a prospective, multicentre, randomised clinical trial of a single postoperative intravesical dose of mitomycin C (the ODMIT-C Trial). *Eur Urol* 2011;60:703-710.
- ¹⁶ Ito A, Shintaku I, Satoh M, et al. Intravesical seeding of upper urinary tract urothelial carcinoma cells during nephroureterectomy: an exploratory analysis from the THPMG trial. *Jpn J Clin Oncol* 2013;43:1139-1144.
- ¹⁷ Yoo SH, Jeong CW, Kwak C, et al. Intravesical chemotherapy after radical nephroureterectomy for primary upper tract urothelial carcinoma: A systematic review and network meta-analysis. *J Clin Med* 2019;8:1059.
- ¹⁸ Freifeld Y, Ghandour R, Singla N, et al. Intraoperative prophylactic intravesical chemotherapy to reduce bladder recurrence following radical nephroureterectomy. *Urol Oncol* 2020;38:737.e11-737.e16.

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



PRINCIPLES OF SYSTEMIC THERAPY

Neoadjuvant Chemotherapy (preferred for bladder)	
<u>Preferred regimen</u> <ul style="list-style-type: none">• DDMVAC (dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin) with growth factor support for 3–6 cycles^{1,2} <u>Useful in certain circumstances</u> <ul style="list-style-type: none">• Gemcitabine and cisplatin for 4 cycles^{3,4}	

Perioperative/Sandwich Therapy	
<u>Preferred regimen</u> <ul style="list-style-type: none">• Gemcitabine + cisplatin + durvalumab prior to cystectomy, then durvalumab after cystectomy⁵ (for bladder cancer only) (category 1)	

Adjuvant Therapy	
No previous platinum-based neoadjuvant therapy (pT3, pT4a, pN+)	Previous platinum-based neoadjuvant therapy (ypT2–ypT4a or ypN+)
<u>Preferred regimen</u> <ul style="list-style-type: none">• DDMVAC with growth factor support for 3–6 cycles^{1,2} <u>Other recommended regimens</u> <ul style="list-style-type: none">• Gemcitabine and cisplatin for 4 cycles^{3,4}• Nivolumab⁶• Pembrolizumab⁷	<u>Other recommended regimen</u> <ul style="list-style-type: none">• Nivolumab⁶• Pembrolizumab⁷

- For patients who are not candidates for cisplatin, there are no data to support a recommendation for perioperative chemotherapy.
- Randomized trials and meta-analyses show a survival benefit for cisplatin-based neoadjuvant chemotherapy (3 or 4 cycles) for MIBC.^{1,8,9}
- Meta-analysis suggests overall survival benefit with adjuvant cisplatin-based chemotherapy for pathologic T3, T4 or N+ disease at cystectomy, if it was not given as neoadjuvant.⁹
- Neoadjuvant chemotherapy is preferred over adjuvant-based chemotherapy on a higher level of evidence data.
- DDMVAC is preferred over standard MVAC based on category 1 evidence for metastatic disease showing DDMVAC to be better tolerated and more effective than conventional MVAC in advanced disease.^{2,10} Based on these data, the traditional dose and schedule for MVAC is no longer recommended.
- Perioperative gemcitabine and cisplatin is a reasonable alternative to DDMVAC based on category 1 evidence for metastatic disease showing equivalence to conventional MVAC in the setting of advanced disease.^{4,11}
- For gemcitabine/cisplatin, a 21-day cycle is preferred. Better dose adherence may be achieved with fewer delays in dosing using the 21-day schedule.¹²
- Neoadjuvant chemotherapy is preferred for patients with UTUC, particularly for higher stage and/or grade tumors or concerning radiographic findings, as renal function will decline after nephroureterectomy and may preclude adjuvant therapy.
 - Multicenter data support the use of neoadjuvant, split-dose cisplatin-based chemotherapy (gemcitabine and cisplatin) for patients with high-grade UTUC.¹³ Staging for UTUC is less precise than for bladder cancers and understaging is common, necessitating discussion on the risk of under- versus over-treatment.
 - Adjuvant therapy should be considered if neoadjuvant therapy was not given for UTUC.¹⁴
- Carboplatin should not be substituted for cisplatin in the perioperative bladder cancer setting.
 - For patients with borderline renal function or minimal dysfunction, a split-dose administration of cisplatin may be considered (such as 35 mg/m² on days 1 and 2 or days 1 and 8) (category 2B). While safer, the relative efficacy of the cisplatin-containing combination administered with such modifications remains undefined.
- For patients with borderline renal function, estimate GFR to assess eligibility for cisplatin. Consider timed urine collection, which may more accurately determine eligibility for cisplatin.
- Nivolumab and hyaluronidase-nvhy subcutaneous injection may be substituted for IV nivolumab. Nivolumab and hyaluronidase-nvhy has different dosing and administration instructions compared to IV nivolumab.

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

[Continued](#)
[References](#)



PRINCIPLES OF SYSTEMIC THERAPY

First-Line Systemic Therapy for Locally Advanced or Metastatic Disease (Stage IV)		
Preferred regimen <ul style="list-style-type: none">• Enfortumab vedotin-ejfv^{15,16} and pembrolizumab (category 1)	Other recommended regimens <ul style="list-style-type: none">• Gemcitabine and cisplatin⁴ (category 1) followed by avelumab maintenance therapy (category 1)^{a,17}• Gemcitabine, cisplatin, and nivolumab (category 1) followed by nivolumab maintenance therapy¹⁸ (category 1)• DDMVAC with growth factor support^{2,10} (category 1) followed by avelumab maintenance therapy (category 1)^{a,17}	Useful in certain circumstances (cisplatin-ineligible) <ul style="list-style-type: none">• Gemcitabine and carboplatin¹⁹ followed by avelumab maintenance therapy (category 1)^{a,17}• Pembrolizumab (for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for any platinum-containing chemotherapy)²⁰• Atezolizumab²¹ (only for patients whose tumors express PD-L1^b or who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression) (category 2B)

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

^a Maintenance therapy with avelumab only if there is no progression on first-line platinum-containing chemotherapy.

^b Atezolizumab: SP142 assay, PD-L1–stained tumor-infiltrating immune cells covering ≥5% of the tumor area.

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



NCCN Guidelines Version 1.2025

Bladder Cancer

PRINCIPLES OF SYSTEMIC THERAPY

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

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

Preferred regimens <ul style="list-style-type: none"> • DDMVAC with growth factor support² • Gemcitabine and cisplatin⁴ • Gemcitabine and carboplatin (category 2B) • Biomarker-directed therapy (see biomarker-directed therapy table, BL-G 4 of 7) 	Other recommended regimens <ul style="list-style-type: none"> • Paclitaxel²² or docetaxel²³ • Gemcitabine²⁴ 	Useful in certain circumstances <ul style="list-style-type: none"> • Gemcitabine, cisplatin, and nivolumab (category 2B)
---	---	--

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

Preferred regimens <ul style="list-style-type: none"> • Pembrolizumab (category 1 post-platinum)²⁵ • Enfortumab vedotin-ejfv and pembrolizumab¹⁶ • Enfortumab vedotin-ejfv²⁶ • Nivolumab²⁷ (category 2B) • Avelumab^{28,29} (category 2B) • Biomarker-directed therapy (see biomarker-directed therapy table, BL-G 4 of 7) 	Other recommended regimens <ul style="list-style-type: none"> • Paclitaxel²² or docetaxel²³ • Gemcitabine²⁴ 	Useful in certain circumstances <ul style="list-style-type: none"> • DDMVAC with growth factor support² (category 2B) • Ifosfamide, doxorubicin, and gemcitabine³⁰ (category 2B) • Gemcitabine and paclitaxel³¹ (category 2B) • Gemcitabine and cisplatin⁴ (category 2B)
---	---	---

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

Preferred regimens <ul style="list-style-type: none"> • Enfortumab vedotin-ejfv²⁶ • Enfortumab vedotin-ejfv and pembrolizumab • Gemcitabine and carboplatin • Gemcitabine and cisplatin⁴ • DDMVAC with growth factor support² • Biomarker-directed therapy (see biomarker-directed therapy table, BL-G 4 of 7) 	Other recommended regimens <ul style="list-style-type: none"> • Paclitaxel²² or docetaxel²³ • Gemcitabine²⁴ 	Useful in certain circumstances <ul style="list-style-type: none"> • Gemcitabine, cisplatin, and nivolumab (category 2B) • Ifosfamide, doxorubicin, and gemcitabine³⁰ (category 2B) • Gemcitabine and paclitaxel³¹ (category 2B)
--	---	--

Previous chemotherapy and immunotherapy (no previous enfortumab vedotin-ejfv)^{d,e}

Preferred regimens <ul style="list-style-type: none"> • Enfortumab vedotin-ejfv^{32,33} (category 1) • Biomarker-directed therapy (see biomarker-directed therapy table, BL-G 4 of 7) 	Other recommended regimens <ul style="list-style-type: none"> • Enfortumab vedotin-ejfv and pembrolizumab • Paclitaxel²² or docetaxel²³ • Gemcitabine²⁴ • Gemcitabine and cisplatin⁴ • DDMVAC with growth factor support² • Ifosfamide, doxorubicin, and gemcitabine³⁰ (category 2B) • Gemcitabine and paclitaxel³¹ (category 2B) 	Useful in certain circumstances <ul style="list-style-type: none"> • Sacituzumab govitecan-hziy³⁴
--	--	--

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

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

[Footnotes](#) [References](#)

BL-G
3 OF 7



NCCN Guidelines Version 1.2025

Bladder Cancer

PRINCIPLES OF SYSTEMIC THERAPY

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

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

^c If progression-free survival >12 months after platinum (eg, cisplatin or carboplatin), consider re-treatment with platinum if the patient is still platinum eligible.

^d Patient should have already received platinum and a checkpoint inhibitor, if eligible.

^e These therapies are appropriate for patients who received a first-line platinum-containing chemotherapy followed by checkpoint inhibitor maintenance therapy or first-line therapy containing both platinum chemotherapy and an immune checkpoint inhibitor.

^f Category 1 for patients who have already received platinum and a checkpoint inhibitor if eligible.

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



PRINCIPLES OF SYSTEMIC THERAPY

Radiosensitizing Chemotherapy Regimens ⁹		
Preferred regimens <ul style="list-style-type: none">• Cisplatin^h alone^{37,38}• Low-dose gemcitabine³⁹⁻⁴¹• 5-FU and mitomycin⁴²	Other recommended regimens <ul style="list-style-type: none">• Cisplatin and 5-FU^{39,43}• Cisplatin and paclitaxel^{39,44}	Useful in certain circumstances (not generally used for curative-intent chemoradiotherapy for organ preservation) <ul style="list-style-type: none">• Taxane (docetaxel or paclitaxel) (category 2B)• 5-FU (category 2B)• Capecitabine (category 3)

⁹ In select cases these regimens may be used with palliative intent.

^h Carboplatin is not an effective radiation sensitizer and should not be substituted for cisplatin with radiation (Rödel C, Grabenbauer GG, Kühn R, et al. Combined-modality treatment and selective organ preservation in invasive bladder cancer: long-term results. J Clin Oncol 2002;20:3061-3071).

References

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

**PRINCIPLES OF SYSTEMIC THERAPY – REFERENCES**

- ¹ Grossman HB, Natale RB, Tangen CM, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. *N Engl J Med* 2003;349:859-866.
- ² Sternberg CN, de Mulder PH, Schornagel JH, et al. Randomized phase III trial of high-dose-intensity methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) chemotherapy and recombinant human granulocyte colony-stimulating factor versus classic MVAC in advanced urothelial tract tumors: European Organization for Research and Treatment of Cancer Protocol no. 30924. *J Clin Oncol* 2001;19:2638-2646.
- ³ Dash A, Pettus JA, Herr HW, et al. A role for neoadjuvant gemcitabine plus cisplatin in muscle-invasive urothelial carcinoma of the bladder: a retrospective experience. *Cancer* 2008;113:2471-2477.
- ⁴ Von der Maase H, Hansen SW, Roberts JT, et al. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. *J Clin Oncol* 2000;18:3068-3077.
- ⁵ Powles T, Catto JWF, Galsky MD, et al. Perioperative durvalumab with neoadjuvant chemotherapy in operable bladder cancer. *N Engl J Med* 2024;391:1773-1786.
- ⁶ Bajorin D, Witjes JA, Gschwend J, et al. Adjuvant nivolumab versus placebo in muscle-invasive urothelial carcinoma. *N Engl J Med* 2021;384:2102-2114.
- ⁷ Apolo AB, Ballman KV, Sonpavde G, et al. Adjuvant Pembrolizumab versus Observation in Muscle-Invasive Urothelial Carcinoma. *N Engl J Med*. 2025;392(1):45-55
- ⁸ Advanced Bladder Cancer Meta-analysis Collaboration. Neoadjuvant chemotherapy in invasive bladder cancer: Update of a systematic review and meta-analysis of individual patient data advanced bladder cancer (ABC) meta-analysis collaboration. *Eur Urol* 2005;48:202-205; discussion 205-206.
- ⁹ Advanced Bladder Cancer Meta-analysis Collaboration. Adjuvant chemotherapy in invasive bladder cancer: A systematic review and meta-analysis of individual patient data Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. *Eur Urol* 2005;48:189-199; discussion 199-201.
- ¹⁰ Sternberg CN, de Mulder P, Schornagel JH, et al. Seven year update of an EORTC phase III trial of high-dose intensity M-VAC chemotherapy and G-CSF versus classic M-VAC in advanced urothelial tract tumours. *Eur J Cancer* 2006;42:50-54.
- ¹¹ von der Maase H, Sengelov L, Roberts JT, et al. Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. *J Clin Oncol* 2005;23:4602-4608.
- ¹² Soto Parra H, Cavina R, Latteri F, et al. Three-week versus four-week schedule of cisplatin and gemcitabine: results of a randomized phase II study. *Ann Oncol* 2002;13:1080-1086.
- ¹³ Coleman J, Yip W, Wong N, et al. Multicenter phase II clinical trial of gemcitabine and cisplatin as neoadjuvant chemotherapy for patients with high-grade upper tract urothelial carcinoma. *J Clin Oncol* 2023;41:1618-1625.
- ¹⁴ Birtle A, Johnson M, Chester J, et al. Adjuvant chemotherapy in upper tract urothelial carcinoma (the POUT trial): a phase 3, open-label, randomised controlled trial. *Lancet* 2020;395:1268-1277.
- ¹⁵ Powles T, Valderrama B, Gupta S, et al. Enfortumab vedotin and pembrolizumab in untreated advanced urothelial cancer. *N Engl J Med* 2024;390:875-888.
- ¹⁶ Hoimes C, Flaig T, Milowsky M, et al. Enfortumab vedotin plus pembrolizumab in previously untreated advanced urothelial cancer. *J Clin Oncol* 2023;41:22-31.
- ¹⁷ Powles T, Park SH, Voog E, et al. Avelumab maintenance therapy for advanced or metastatic urothelial carcinoma. *N Engl J Med* 2020;383:1218-1230.
- ¹⁸ van der Heijden MS, Sonpavde G, Powles T, et al. Nivolumab plus gemcitabine-cisplatin in advanced urothelial carcinoma. *N Engl J Med* 2023;389:1778-1789.
- ¹⁹ De Santis M, Bellmunt J, Mead G, et al. Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC study 30986. *J Clin Oncol* 2012;30:191-199.
- ²⁰ Powles T, Csőszi T, Özgüroğlu M, et al. Pembrolizumab alone or combined with chemotherapy versus chemotherapy as first-line therapy for advanced urothelial carcinoma (KEYNOTE-361): a randomised, open-label, phase 3 trial. *Lancet Oncol* 2021;22:931-945.
- ²¹ Balar AV, Galsky MD, Rosenberg JE, et al. Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial. *Lancet* 2017;389:67-76.
- ²² Sideris S, Auon F, Zanaty M, et al. Efficacy of weekly paclitaxel treatment as a single agent chemotherapy following first-line cisplatin treatment in urothelial bladder cancer. *Mol Clin Oncol* 2016;4:1063-1067.
- ²³ McCaffrey JA, Hilton S, Mazumdar M, et al. Phase II trial of docetaxel in patients with advanced or metastatic transitional-cell carcinoma. *J Clin Oncol* 1997;15:1853-1857.

Note: All recommendations are category 2A unless otherwise indicated.[Continued](#)

**PRINCIPLES OF SYSTEMIC THERAPY – REFERENCES**

- ²⁴ Stadler WM, Kuzel T, Roth B, et al: Phase II study of single-agent gemcitabine in previously untreated patients with metastatic urothelial cancer. *J Clin Oncol* 1997;15:3394-3398.
- ²⁵ Bellmunt, de Wit R, Vaughn D, et al: Pembrolizumab as second-line therapy for advanced urothelial carcinoma. *N Engl J Med* 2017;376:1015-1026.
- ²⁶ Yu E, Petrylak D, O'Donnell P, et al: Enfortumab vedotin after PD-1 or PD-L1 inhibitors in cisplatin-ineligible patients with advanced urothelial carcinoma (EV 201): a multicentre, single-arm, phase 2 trial. *Lancet Oncol* 2021;22:872-882.
- ²⁷ Sharma P, Retz M, Siefker-Radtke A, et al: Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): A multicentre, single-arm, phase 2 trial. *Lancet Oncol* 2017;18:312-322.
- ²⁸ Apolo AB, Infante JR, Patel MR, et al: Avelumab, an anti-programmed death-ligand 1 antibody, in patients with refractory metastatic urothelial carcinoma: Results from a multicenter, phase Ib study. *J Clin Oncol* 2017;35:2117-2124.
- ²⁹ Patel M, Ellerton J, Infante J, et al: Avelumab in metastatic urothelial carcinoma after platinum failure (JAVELIN Solid Tumor): pooled results from two expansion cohorts or an open-label, phase 1 trial. *Lancet Oncol* 2018;19:51-64.
- ³⁰ Siefker-Radtke AO, Dinney CP, Shen Y, et al: A phase 2 clinical trial of sequential neoadjuvant chemotherapy with ifosfamide, doxorubicin, and gemcitabine followed by cisplatin, gemcitabine, and ifosfamide in locally advanced urothelial cancer: final results. *Cancer* 2013;119:540-547.
- ³¹ Albers P, Park SI, Niegisch G, et al: Randomized phase III trial of 2nd line gemcitabine and paclitaxel chemotherapy in patients with advanced bladder cancer: short-term versus prolonged treatment [German Association of Urological Oncology (AUO) trial AB 20/99]. *Ann Oncol* 2011; 22:288-294.
- ³² Rosenberg JE, O'Donnell PH, Balar AV, et al: Pivotal trial of enfortumab vedotin in urothelial carcinoma after platinum and anti-programmed death 1/programmed death ligand 1 therapy. *J Clin Oncol* 2019;37:2592-2600.
- ³³ Powles T, Rosenberg JE, Sonpavde G, et al: Enfortumab vedotin in previously treated advanced urothelial carcinoma. *N Engl J Med* 2021;384:1125-1135.
- ³⁴ Tagawa S, Balar AV, Petrylak DP, et al: TROPY-U-01: A phase II open-label study of sacituzumab govitecan in patients with metastatic urothelial carcinoma progressing after platinum based chemotherapy and checkpoint inhibitors. *J Clin Oncol* 2021;39:2474-2485.
- ³⁵ Loriot Y, Necchi A, Park SH, et al: Erdafitinib in locally advanced or metastatic urothelial carcinoma. *N Engl J Med* 2019;381:338-348.
- ³⁶ Meric-Bernstam F, Makker V, Oaknin A, et al: Efficacy and Safety of Trastuzumab Deruxtecan in Patients With HER2-Expressing Solid Tumors: Primary Results From the DESTINY-PanTumor02 Phase II Trial. *J Clin Oncol* 2024;42:47-58.
- ³⁷ Tester W, Caplan R, Heaney J, et al: Neoadjuvant combined modality program with selective organ preservation for invasive bladder cancer: results of Radiation Therapy Oncology Group phase II trial 8802. *J Clin Oncol* 1996;14:119-126.
- ³⁸ Shipley WU, Kaufman DS, Zehr E, et al: Selective bladder preservation by combined modality protocol treatment: long-term outcomes of 190 patients with invasive bladder cancer. *Urology* 2002;60:62-67; discussion 67-68.
- ³⁹ Mitin T, Hunt D, Shipley W, et al: Transurethral surgery and twice-daily radiation plus paclitaxel-cisplatin or fluorouracil-cisplatin with selective bladder preservation and adjuvant chemotherapy for patients with muscle invasive bladder cancer (RTOG 0233): a randomized multicentre phase 2 trial. *Lancet Oncol* 2013;14:863-872.
- ⁴⁰ Kent E, Sandler H, Montie J, et al: Combined-modality therapy with gemcitabine and radiotherapy as a bladder preservation strategy: results of a phase I trial. *J Clin Oncol* 2004;22:2540-2545.
- ⁴¹ Choudhury A, Swindell R, Logue JP, et al: Phase II study of conformal hypofractionated radiotherapy with concurrent gemcitabine in muscle-invasive bladder cancer. *J Clin Oncol* 2011; 29:733-738.
- ⁴² James ND, Hussain SA, Hall E, et al; BC2001 Investigators: Radiotherapy with or without chemotherapy in muscle-invasive bladder cancer. *N Engl J Med* 2012;366:1477-1488.
- ⁴³ Coen JJ, Zhang P, Saylor PJ, et al: Bladder preservation with twice-a-day radiation plus fluorouracil/cisplatin or once daily radiation plus gemcitabine for muscle-invasive bladder cancer: NRG/RTOG 0712-A randomized phase II trial. *J Clin Oncol* 2019;37:44-51.
- ⁴⁴ Efstathiou JA, Spiegel DY, Shipley WU, et al: Long-term outcomes of selective bladder preservation by combined-modality therapy for invasive bladder cancer: The MGH experience. *Eur Urol* 2012; 61:705-711.

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

**PRINCIPLES OF RADIATION MANAGEMENT OF INVASIVE DISEASE**

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

- Precede RT alone or concurrent chemoradiotherapy by maximal TUR of the tumor when safely possible.
- Simulating and treating patients when they have an empty bladder is preferred for daily reproducibility (bladder full for tumor boosts is acceptable with image guidance).
- Use multiple fields from high-energy linear accelerator beams.
- For invasive tumors, consider low-dose preoperative RT prior to segmental cystectomy (category 2B).
- Concurrent chemoradiotherapy or RT alone is most successful for patients without moderate/severe hydronephrosis and without extensive CIS associated with their muscle-invading tumor.
- For patients with stage Ta, T1, or CIS, external beam RT (EBRT) alone is rarely appropriate. For patients with recurrent Ta–T1 disease usually following BCG therapy but without extensive CIS who are not candidates for cystectomy, concurrent chemoradiotherapy may be considered as a potentially curative alternative to radical cystectomy, which is the standard treatment by NCCN Guidelines.
- Treat the whole bladder with or without pelvic nodal RT 39.6–50.4 Gy using conventional or accelerated hyperfractionation. Elective treatment to the lymph nodes is optional and should take into account patient comorbidities and the risks of toxicity to adjacent critical structures. Then boost either the whole or partial bladder between 60–66 Gy. For node-positive disease, consider boosting grossly involved nodes to the highest achievable dose that does not violate dose-volume histogram (DVH) parameters based on the clinical scenario. Reasonable alternatives to conventional fractionation include taking the whole bladder to 55 Gy in 20 fractions, or using simultaneous integrated boosts to sites of gross disease.
- When irradiating the bladder only or bladder tumor boost, consider daily image guidance.
- Concurrent chemoradiotherapy is recommended for added tumor cytotoxicity, and can be given without significant increased toxicity over RT alone. Concurrent 5-FU and mitomycin C or low-dose gemcitabine can be used instead of cisplatin-containing regimens in patients with low or moderate renal function. Such therapy is optimally given by dedicated multidisciplinary teams.
- Concurrent chemoradiotherapy (preferred) or RT alone should be considered as potentially curative therapy for patients who are medically inoperable. Concurrent chemoradiotherapy or RT alone should be considered for local palliation in patients with metastatic disease.
- When giving palliative radiation for metastatic bladder cancer or for recurrent pelvic tumor, combining radiation with radiosensitizing chemotherapy should be considered. See [BL-G 5 of 7](#) for agents. Chemotherapy should not be used concurrently with high-dose (>3 Gy per fraction) palliative radiation.
- Treatment field should include whole bladder and all sites of gross disease plus or minus uninvolved regional lymph nodes. Regional lymph nodes include the hypogastric, obturator, internal and external iliac, perivesical, sacral, and presacral nodes. For involved nodal disease, the common iliac nodes are a site of secondary involvement.
- For patients with pT3/pT4 pN0–2 urothelial (pure urothelial or primary urothelial mixed with other subtypes) bladder cancer following radical cystectomy with ileal conduit, consider postoperative adjuvant pelvic RT (category 2B). Treatment field should encompass areas at risk for harboring residual microscopic disease based on pathologic findings at resection and may include cystectomy bed and pelvic lymph nodes with doses in the range of 45 to 50.4 Gy. Involved resection margins and areas of extranodal extension could be boosted to 54–60 Gy if feasible based on normal tissue constraints.
- Conduct tumor status assessment after completion of full-dose primary chemoradiotherapy. See Table 7 on [BL-E 5 of 6](#).
- In highly selected T4b tumor cases, may consider intraoperative RT.
- Concurrent chemoradiotherapy is generally most suitable for patients with solitary tumors, negative nodes, no extensive or multifocal CIS, no moderate/severe tumor-related hydronephrosis, and good pre-treatment bladder function.
- For palliative RT, consider a dose of 30 Gy in 10 fractions or 21 Gy in 3 fractions.
- A meta-analysis of individual patient data from two randomized phase III studies (BC2001 and BCON) found that a hypofractionated schedule of 55 Gy in 20 fractions over 4 weeks is noninferior to the standard fractionation schedule of 64 Gy in 32 fractions over 6.5 weeks for both invasive local control and toxicity and that the hypofractionated schedule is superior regarding invasive local control.

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

[Continued](#)
[References](#)

BL-H
1 OF 3

**PRINCIPLES OF RADIATION MANAGEMENT OF INVASIVE DISEASE**

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

- Data support the use of RT for urothelial carcinoma and squamous cell carcinoma of the urethra (case series and experience treating these carcinomas arising from other disease sites); radiation can also be considered for adenocarcinomas of the urethra.
- Definitive Radiation Therapy (organ preservation)
 - ▶ cT2 cN0
 - ◊ 66–70 Gy EBRT delivered to gross disease with a margin to encompass areas of potential microscopic spread. Concurrent chemotherapy with regimens used for bladder cancer is encouraged for added tumor cytotoxicity.
 - ◊ Strongly consider prophylactic radiation treatment of regional-nodal basins (inguinal and low pelvic nodes for female and distal male tumors; pelvic lymph nodes for proximal male tumors).
 - ▶ cT3–T4, or lymph node positive
 - ◊ 45–50.4 Gy EBRT delivered to gross disease with a margin to encompass areas of microscopic spread and to regional-nodal basins (inguinal and low pelvic nodes for female and distal male tumors; pelvic lymph nodes for proximal male tumors). Boost gross primary disease to 66–70 Gy and gross nodal disease to 54–66 Gy, if feasible. Dose delivered to gross nodal disease may be limited secondary to normal tissue dose constraints. Concurrent chemotherapy should be administered for added tumor cytotoxicity.
 - ▶ Postoperative adjuvant RT
 - ◊ Treatment field should encompass areas at risk for harboring residual microscopic disease based on pathologic findings at resection and may include resection bed, inguinal lymph nodes, and pelvic lymph nodes. Areas at risk for harboring residual microscopic disease should receive 45–50.4 Gy EBRT. Involved resection margins and areas of extranodal extension should be boosted to 54–60 Gy if feasible based on normal tissue constraints. Areas of gross residual disease should be boosted to 66–70 Gy, if feasible based on normal tissue constraints. Concurrent chemotherapy with regimens used for bladder cancer should be considered for added tumor cytotoxicity.
 - ▶ Recurrent disease
 - ◊ Clinical target volume (CTV) should include gross disease in any suspected areas of spread at 66–74 Gy (higher dose up to 74 Gy for larger tumor and non-urothelial histology) and consideration can be given to elective regional-nodal basins (45–50.4 Gy) as discussed above, if feasible based on normal tissue constraints.

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

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

References

**PRINCIPLES OF RADIATION MANAGEMENT OF INVASIVE DISEASE**
REFERENCES

- Baumann BC, Bosch WR, Bahl A, et al. Development and validation of consensus contouring guidelines for adjuvant radiation therapy for bladder cancer after radical cystectomy. *Int J Radiat Oncol Biol Phys* 2018;96:78-86.
- Baumann BC, He J, Hwang WT, et al. Validating a local failure risk stratification for use in prospective studies of adjuvant radiation therapy for bladder cancer. *Int J Radiat Oncol Biol Phys* 2018;95:703-706.
- Choudhury A, Porta N, Hall E, et al. Hypofractionated radiotherapy in locally advanced bladder cancer: an individual patient data meta-analysis of the BC2001 and BCON trials. *Lancet Oncol* 2021;22:246-255.
- Coen JJ, Zhang P, Saylor PJ, et al. Selective bladder preservation with twice-daily radiation plus 5-fluorouracil/cisplatin (FCT) or daily radiation plus gemcitabine (GD) for patients with muscle invasive bladder cancer: Primary results of NRG/RTOG 0712—A randomized phase 2 multicenter trial [Abstract]. *J Clin Oncol* 2018;36(Suppl):Abstract 408.
- Efstathiou JA, Spiegel DY, Shipley WU, et al. Long-term outcomes of selective bladder preservation by combined-modality therapy for invasive bladder cancer: the MGH experience. *Eur Urol* 2012;61:705-711.
- Efstathiou JA, Zietman AL. Bladder Cancer. In: Gunderson & Tepper, editors. *Clinical Radiation Oncology*. Churchill Livingstone Elsevier 2016.
- James ND, Hussain SA, Hall E, et al. Radiotherapy with or without chemotherapy in muscle-invasive bladder cancer. *N Engl J Med* 2012; 366:1477-1488.
- Kamat AM, Hahn NM, Efstathiou JA, et al. Bladder cancer. *Lancet* 2016;338:2796-2810.
- Mak RH, Hunt D, Shipley WU, et al. Long-term outcomes in patients with muscle-invasive bladder cancer after selective bladder-preserving combined-modality therapy: A pooled analysis of Radiation Therapy Oncology Group protocols 8802, 8903, 9506, 9706, 9906, and 0233. *J Clin Oncol* 2014;32:3801-3809.
- Mitin T, Hunt D, Shipley WU, et al. Transurethral surgery and twice-daily radiation plus paclitaxel-cisplatin or fluorouracil-cisplatin with selective bladder preservation and adjuvant chemotherapy for patients with muscle invasive bladder cancer (RTOG 0233): A randomised multicentre phase 2 trial. *Lancet Oncol* 2013;14:863-872.
- Ploussard G, Daneshmand S, Efstathiou JA, et al. Critical analysis of bladder sparing with trimodal therapy in muscle-invasive bladder cancer: a systematic review. *Eur Urol* 2014;66:120-137.
- Rödel C, Grabenbauer GG, Kühn R, et al. Combined-modality treatment and selective organ preservation in invasive bladder cancer: long-term results. *J Clin Oncol* 2002;20:3061-3071.
- Shipley WU, Prout GR, Kaufman SD, Perrone TL. Invasive bladder carcinoma. The importance of initial transurethral surgery and other significant prognostic factors for improved survival with full-dose irradiation. *Cancer* 1987;60:514-520.
- Weiss C, Wolze C, Engehausen DG, et al. Radiochemotherapy after transurethral resection for high-risk T1 bladder cancer: An alternative to intravesical therapy or early cystectomy? *J Clin Oncol* 2006;24:2318-2324.
- Zaghloul MS, Christodouleas JP, Smith A, et al. Adjuvant sandwich chemotherapy plus radiotherapy vs adjuvant chemotherapy alone for locally advanced bladder cancer after radical cystectomy: A randomized phase 2 trial. *JAMA Surg* 2018;153:e174591.

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

**PRINCIPLES OF ALTERNATIVE RISK CLASSIFIERS AND BIOMARKERS**

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

Prognostic Biomarkers

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

Predictive Biomarkers

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

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



PRINCIPLES OF ALTERNATIVE RISK CLASSIFIERS AND BIOMARKERS

Disease Contexts

• Germline Testing

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

• Non–Muscle-Invasive Bladder Cancer (NMIBC)

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

• Muscle-Invasive Bladder Cancer (MIBC)/Resectable:

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

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

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



PRINCIPLES OF ALTERNATIVE RISK CLASSIFIERS AND BIOMARKERS

Disease Contexts (cont.)

- **Locally Advanced Unresectable/Metastatic Bladder Cancer:**

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

- **Advanced Disease**

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

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

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



NCCN Guidelines Version 1.2025

Upper GU Tract Tumors

WORKUP

- Imaging of upper tract collecting system^a
- Cytology
- Cystoscopy
- Uteroscopy and biopsy or percutaneous biopsy and/or selective washings
- Renal function tests
- Chest x-ray or CT
- CBC, chemistry profile
- Nuclear medicine renal scan (optional)
- Bone scan^a if clinical suspicion or symptoms of bone metastases
- Consider germline testing and genetic counselor referral if younger age at presentation and/or personal or family history of Lynch syndrome-related cancers^b

Renal pelvis →

Non-metastatic

Low grade^cHigh grade,^c large, or parenchymal invasion

Metastatic

PRIMARY TREATMENT^d

Endoscopic resection^e
± postsurgical intrapelvic chemotherapy^f
or
Nephroureterectomy with cuff of bladder ± perioperative intravesical chemotherapy^f

Nephroureterectomy with cuff of bladder + regional lymphadenectomy ± perioperative intravesical chemotherapy^f and cisplatin based neoadjuvant chemotherapy^g in selected patients

Systemic therapy^h

Adjuvant Treatment and Follow-up
([UTT-3](#))

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

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

^c Montironi R, Lopez-Beltran A. The 2004 WHO classification of bladder tumors: A summary and commentary. Int J Surg Pathol 2005;13:143-153. See [Principles of Pathology Management \(BL-C\)](#).

^d [Principles of Surgical Management \(BL-B\)](#).

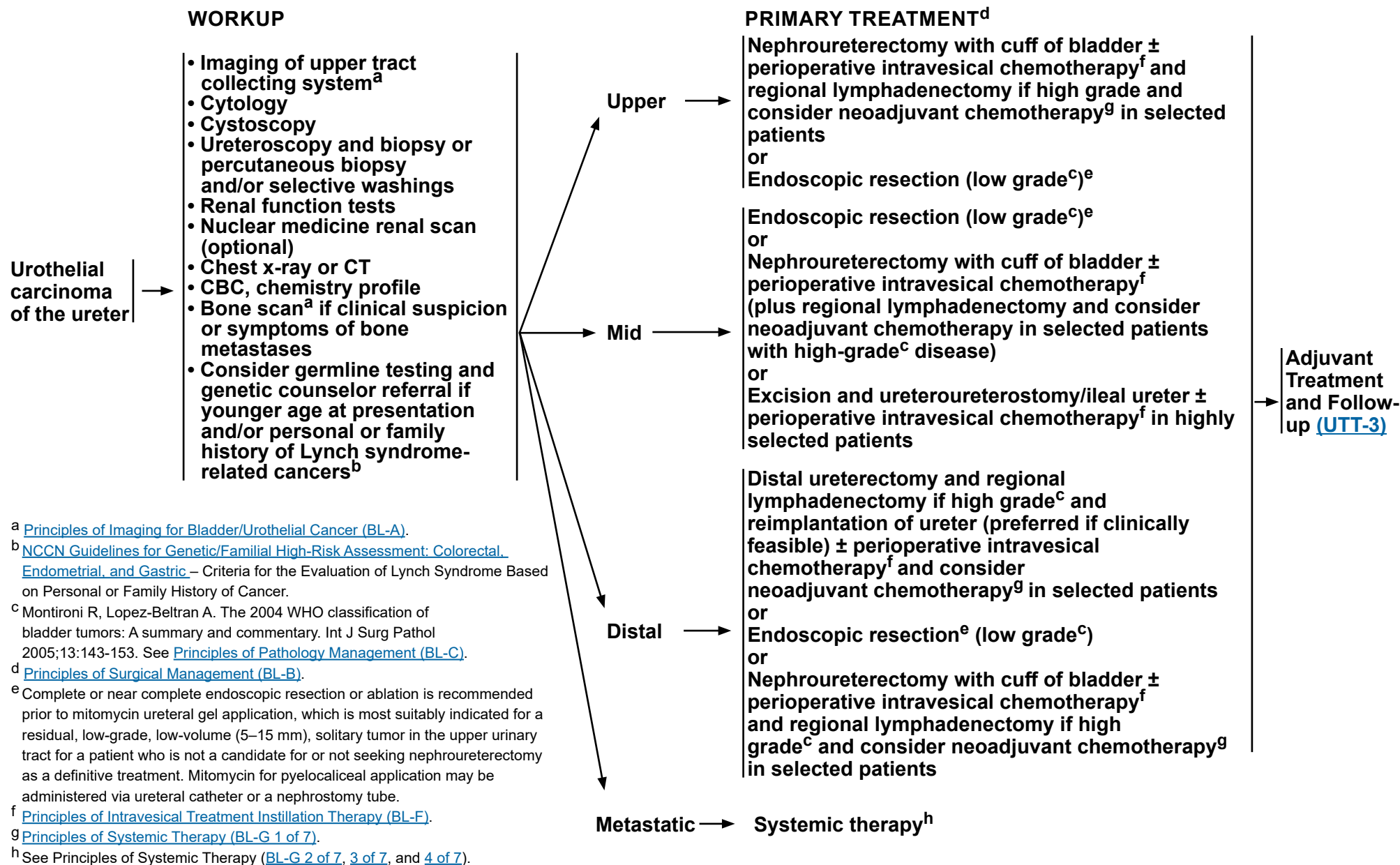
^e Complete or near complete endoscopic resection or ablation is recommended prior to mitomycin ureteral gel application, which is most suitably indicated for a residual, low-grade, low-volume (5–15 mm), solitary tumor in the upper urinary tract for a patient who is not a candidate for or not seeking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

^f [Principles of Instillation Therapy \(BL-F\)](#).

^g [Principles of Systemic Therapy \(BL-G 1 of 7\)](#).

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

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



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



NCCN Guidelines Version 1.2025

Upper GU Tract Tumors

PATHOLOGIC
STAGINGⁱ

ADJUVANT TREATMENT

FOLLOW-UP

Adjuvant treatment for
renal pelvis
and
urothelial carcinoma
of the ureter

pT0, pT1

None

- Cystoscopy and consider cytology for high grade every 3 months for 1 year, then at longer intervals
- If nephron-sparing surgery, imaging of upper tract collecting system^a or ureteroscopy at 3- to 12-month intervals ± abdomen/pelvis CT or MRI with and without contrast

pT2, pT3,
pT4, pN+

- If no platinum neoadjuvant treatment given and pT3, pT4, or pN+
 - Adjuvant platinum-based chemotherapy should be discussed^{g,j} or
 - Consider adjuvant nivolumab^{g,j,k} (category 2B)
- or
- If platinum neoadjuvant chemotherapy given and ypT2-ypT4 or ypN+, consider adjuvant nivolumab^{g,j,k}

- Cystoscopy and cytology every 3 months for 1 year, then at longer intervals
- If nephron-sparing surgery, imaging of upper tract collecting system^a or ureteroscopy at 3- to 12-month intervals + abdomen/pelvis CT or MRI with and without contrast + chest imaging

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

^g [Principles of Systemic Therapy \(BL-G 1 of 7\).](#)

ⁱ The modifier “p” refers to pathologic staging based on surgical resection and lymph node dissection.

^j Follow recommendations for adjuvant chemotherapy after ensuring that patient is fully staged to rule out metastatic disease.

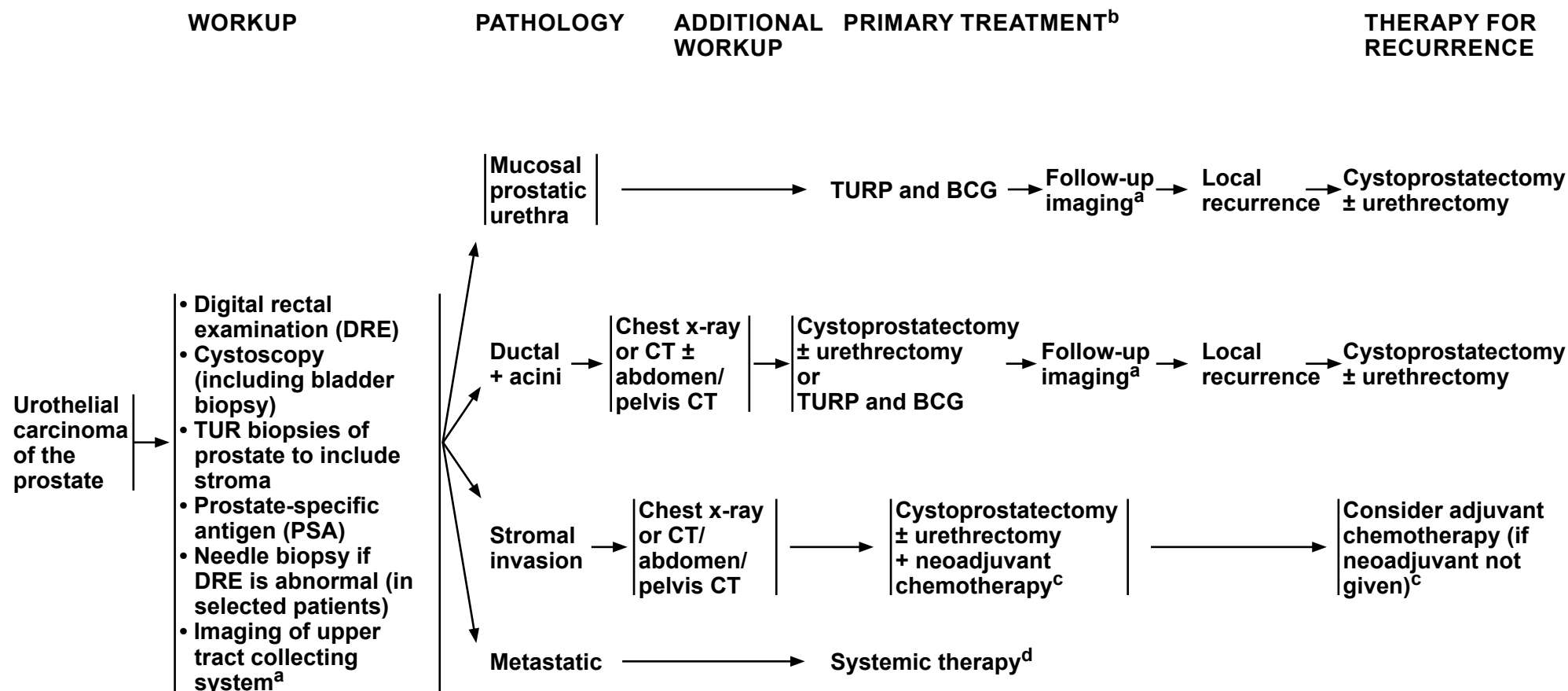
^k Most appropriate for patients who value an opportunity to delay recurrence even if the chance of cure was not improved, and for whom the risk of side effects was acceptable.

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



NCCN Guidelines Version 1.2025

Urothelial Carcinoma of the Prostate


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

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



NCCN Guidelines Version 1.2025

Primary Carcinoma of the Urethra

WORKUP^a

Suspicion of carcinoma
of the urethra

- Cystourethroscopy
 - EUA
 - TUR or transvaginal biopsy
- Chest x-ray or CT
- MRI of pelvis with and without contrast^b

DIAGNOSIS

Urothelial carcinoma of prostate

[UCP-1](#)

Primary carcinoma of
non-prostatic male urethra
or female urethra

CIS Ta, T1

[PCU-2](#)

T2

T3, T4

Palpable
inguinal
lymph nodes

[PCU-3](#)

Distant
metastasis

^a Referral to a specialized center is recommended.

^b [Principles of Imaging for Bladder/Urothelial Cancer \(BL-A\)](#).

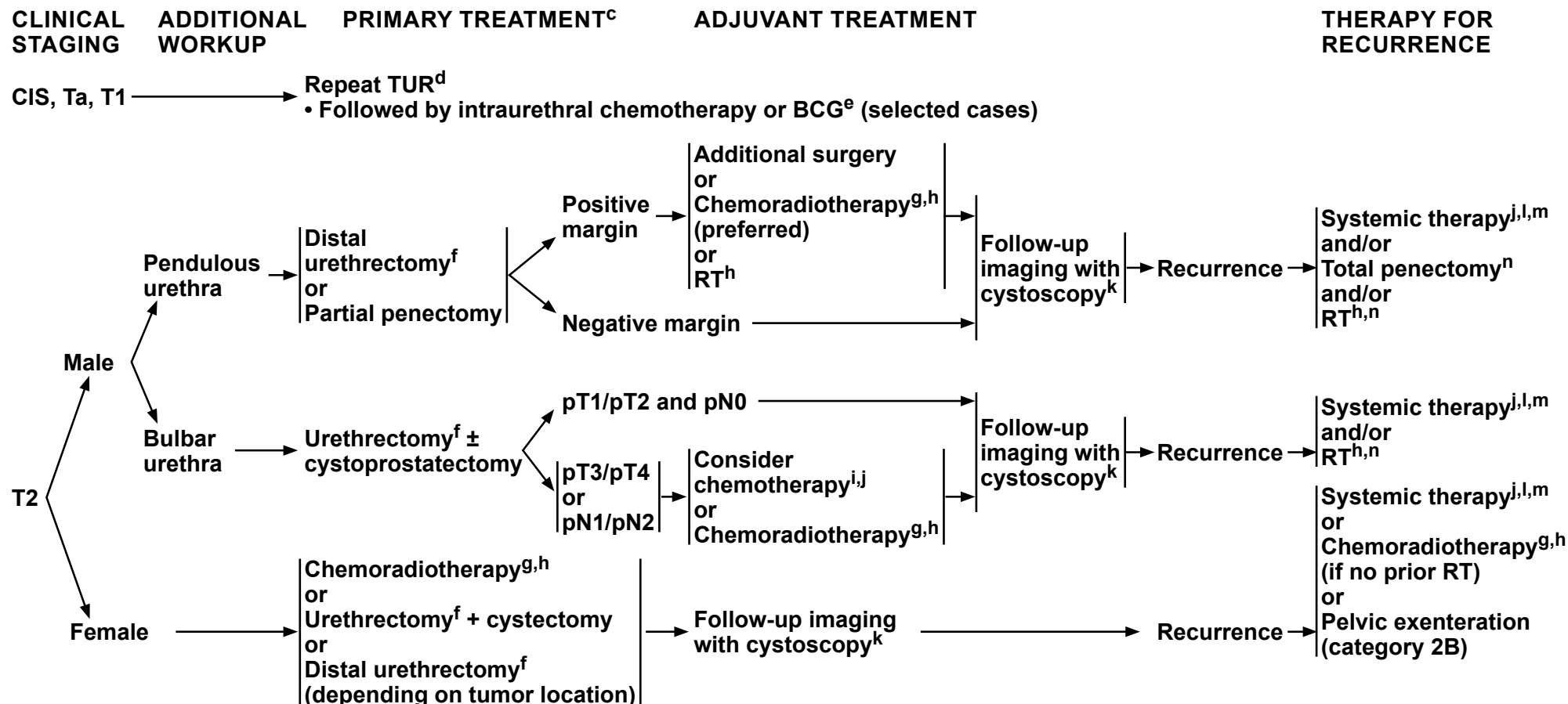
NCCN recommendations have been developed to be inclusive of individuals of all sexual and gender identities to the greatest extent possible. On this page, the terms male and female refer to sex assigned at birth.

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



NCCN Guidelines Version 1.2025

Primary Carcinoma of the Urethra

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

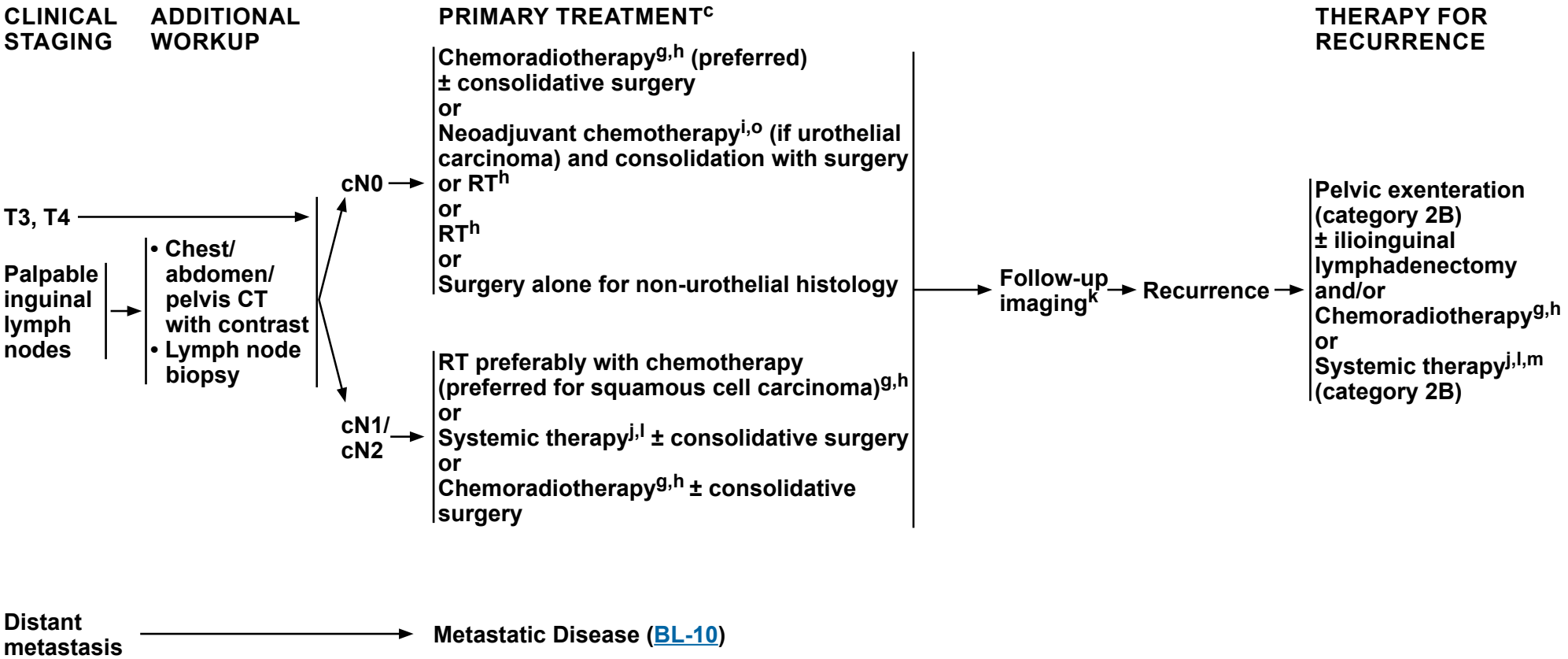
NCCN recommendations have been developed to be inclusive of individuals of all sexual and gender identities to the greatest extent possible. On this page, the terms male and female refer to sex assigned at birth.

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



NCCN Guidelines Version 1.2025

Primary Carcinoma of the Urethra



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

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



NCCN Guidelines Version 1.2025

Bladder Cancer

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

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

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

N	Regional Lymph Nodes
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		T1-T4a	N1	M0
Stage 0is	CIS (Tis)	N0	M0	Stage IIIB	T1-T4a	N2,N3	M0
Stage I	T1	N0	M0	Stage IVA	T4b	Any N	M0
Stage II	T2a	N0	M0		Any T	Any N	M1a
	T2b	N0	M0	Stage IVB	Any T	Any N	M1b
Stage IIIA	T3a	N0	M0				
	T3b	N0	M0				
	T4a	N0	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.



NCCN Guidelines Version 1.2025

Bladder Cancer

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

T	Primary Tumor
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Papillary noninvasive carcinoma
CIS (Tis)	Carcinoma <i>in situ</i>
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	CIS (Tis)	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
Stage IV	T4	NX, N0	M0
	Any T	N1	M0
	Any T	N2	M0
	Any T	Any N	M1

[Continued](#)

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



NCCN Guidelines Version 1.2025

Bladder Cancer

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

Male Penile Urethra and Female Urethra

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

Prostatic Urethra

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

N	Regional Lymph Nodes
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Single regional lymph node metastasis in the inguinal region or true pelvis [perivesical, obturator, internal (hypogastric) and external iliac], or presacral lymph node
N2	Multiple regional lymph node metastasis in the inguinal region or true pelvis [perivesical, obturator, internal (hypogastric) and external iliac], or presacral lymph node
M	Distant Metastasis
M0	No distant metastasis
M1	Distant metastasis

Histologic Grade (G)	
Grade is reported by the grade value. For urothelial histology, a low- and high-grade designation is used to match the current WHO/ISUP recommended grading system:	
LG	Low grade
HG	High grade
For squamous cell carcinoma and adenocarcinoma, the following grading schema is recommended:	
GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated

Table 6. AJCC Prognostic Groups

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

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



ABBREVIATIONS

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



NCCN Categories of Evidence and Consensus

Category 1	Based upon high-level evidence (≥ 1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus ($\geq 85\%$ support of the Panel) that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus ($\geq 85\%$ support of the Panel) that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus ($\geq 50\%$, but $< 85\%$ support of the Panel) that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

NCCN Categories of Preference

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

All recommendations are considered appropriate.



NCCN Guidelines Version 1.2025

Bladder Cancer

Discussion

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

Table of Contents

Overview	MS-2	Adjuvant Systemic Therapy	MS-19
Guidelines Update Methodology	MS-2	Adjuvant Radiation	MS-21
Literature Search Criteria	MS-2	Bladder Preservation	MS-21
Sensitive/Inclusive Language Usage	MS-3	NCCN Recommendations for Treatment of Muscle Invasive Bladder Cancer	MS-24
Clinical Presentation and Workup	MS-3	Follow-up	MS-26
Pathology and Staging	MS-4	Recurrent or Persistent Disease	MS-26
Enhanced Cystoscopy	MS-5	Metastatic (Stage IVB) Urothelial Bladder Cancer	MS-27
Histology	MS-7	Evaluation of Metastatic Disease	MS-27
Non-Muscle Invasive Urothelial Bladder Cancer	MS-8	Metastasectomy for Oligometastatic Disease	MS-27
Intravesical Therapy.....	MS-8	Molecular/Genomic Testing	MS-28
BCG Shortage.....	MS-10	First-Line Systemic Therapy for Metastatic Disease	MS-29
Treatments for BCG-Unresponsive or BCG-Intolerant NMIBC	MS-11	Second-Line and Subsequent Therapy for Metastatic Disease	MS-33
NCCN Recommendations for Treatment of NMIBC	MS-12	NCCN Recommendations for Systemic Therapy of Metastatic Disease	MS-37
Surveillance	MS-14	Non-Urothelial Carcinomas of the Bladder	MS-39
Posttreatment of Recurrent or Persistent Disease	MS-15	Upper Tract Urothelial Carcinoma	MS-39
Muscle Invasive Urothelial Bladder Cancer	MS-16	Urothelial Carcinomas of the Prostate	MS-43
Additional Workup	MS-16	Primary Carcinoma of the Urethra	MS-44
Cystectomy	MS-16	Summary	MS-45
Neoadjuvant Chemotherapy	MS-17	References	MS-47



NCCN Guidelines Version 1.2025

Bladder Cancer

Overview

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

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

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

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

Guidelines Update Methodology

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

Literature Search Criteria

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

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



Sensitive/Inclusive Language Usage

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

Clinical Presentation and Workup

The most common presenting symptom in patients with bladder cancer is microscopic or gross hematuria, although urinary frequency due to irritation or reduced bladder capacity can also develop. Less commonly, the presenting symptom is a urinary tract infection. Upper tract obstruction or pain may occur in patients with a more advanced lesion. Patients presenting with these symptoms should be evaluated with office cystoscopy to determine if a lesion is present. Enhanced cystoscopy may be used if available. If a lesion is documented, the patient should be scheduled for a transurethral resection of the bladder

tumor (TURBT) to confirm the diagnosis and determine the extent of disease within the bladder. Urine cytology may also be obtained around the time of cystoscopy. Because smoking is a major risk factor for bladder cancer,¹¹ screening for smoking and initiation of treatment for smoking cessation, if appropriate, is recommended during the initial evaluation (see [NCCN Guidelines for Smoking Cessation](#)).

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

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

TURBT with a bimanual examination under anesthesia (EUA) is performed to resect visible tumor and to sample muscle within the area of the tumor to assess invasion. In a case where the tumor is clearly not invasive (eg, multiple small papillary tumors), EUA would not be



necessary. The goal of TURBT is to correctly identify the clinical stage and grade of disease while completely resecting all visible tumor. Therefore, an adequate sample that includes bladder muscle (ie, muscularis propria) preferentially should be obtained in the resection specimen, most notably in high-grade disease. A small fragment of tumor with few muscle fibers is inadequate for assessing the depth of invasion and guiding treatment recommendations. When a large papillary lesion is noted, more than one session may be needed to completely resect the tumor. With carcinoma in situ (CIS), biopsy of sites adjacent to the tumor and multiple random biopsies may be performed to assess for a field change. Single-dose intravesical gemcitabine or mitomycin (both category 1, although gemcitabine is preferred due to better tolerability and lower cost) within 24 hours of TURBT is recommended if non-muscle invasive disease is suspected (see *Intravesical Therapy*). Existing data support this approach largely for low-volume, low-grade disease.¹³⁻¹⁵

Mapping or random biopsies of normal-appearing urothelium rarely yield positive results and lack sensitivity for CIS, especially for low-risk tumors.¹⁶⁻¹⁹ In addition, these biopsies often cause additional damage to the bladder without benefit to the patient. Therefore, mapping biopsies of normal-appearing urothelium are not recommended for most patients.

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

Clinical investigation of the specimen obtained by TURBT or biopsy is an important step in the diagnosis and subsequent management of bladder cancer. The modifier “c” before the stage refers to clinical staging based on bimanual EUA, endoscopic surgery (biopsy or

TURBT), and imaging studies. A modifier “p” would refer to pathologic staging based on cystectomy and lymph node dissection.

Pathology and Staging

The most commonly used staging system is the tumor, node, metastasis (TNM) staging system by the AJCC²⁰ (see *Staging* in the algorithm). The NCCN Guidelines® for Bladder Cancer divide treatment recommendations for urothelial carcinoma of the bladder according to non-muscle invasive disease (Ta, T1, and CIS) and muscle invasive disease (≥T2 disease). Management of bladder cancer is based on the findings of the biopsy and TURBT specimens, with attention to histology, grade, and depth of invasion. These factors are used to estimate the probability of recurrence and progression to a more advanced stage. Patient bladder function, comorbidities, and life expectancy are also important considerations.

Approximately 75% of newly detected cases are non-muscle invasive disease—exophytic papillary tumors confined largely to the mucosa (Ta) (70%–75%) or, less often, to the lamina propria (T1) (20%–25%) or flat high-grade lesions (CIS, 5%–10%).²¹ These tumors tend to be friable and have a high propensity for bleeding. Their natural history is characterized by a tendency to recur in the bladder, and these recurrences can either be at the same stage as the initial tumor or at a more advanced stage. While not fully endorsed by the AJCC staging system, there are data to support that pT1 sub-staging may have prognostic value, with microscopic or focal invasion into the lamina propria showing better outcomes than more extensive pT1 disease.²²⁻²⁴ If feasible, pT1 sub-staging may be useful for prognostication, although it is currently not widely utilized and relies on specialized pathology review, which may not be available at all centers.



Papillary tumors confined to the mucosa or submucosa are generally managed endoscopically with complete resection. Progression to a more advanced stage may result in local symptoms or, less commonly, symptoms related to metastatic disease. An estimated 31% to 78% of patients with a tumor confined to the mucosa or submucosa will experience a recurrence or new occurrence of urothelial carcinoma within 5 years.²⁵ These probabilities of recurrence vary as a function of the initial stage and grade, size, and multiplicity. Refining these estimates for individual patients is an area of active research.

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

The 8th edition of the AJCC Cancer Staging Manual includes changes to the staging of urinary bladder carcinoma, including the subdivision of stages III and IV disease (stage III into stage IIIA and stage IIIB; stage IV into stage IVA and stage IVB).²⁰ Notably, the new staging system groups T1–T4a, N1 within stage IIIA and T1–T4a, N2–3 within stage IIIB; N1–3 was previously grouped within stage IV, regardless of T stage.^{20,26} The NCCN Guidelines for Bladder Cancer were updated to reflect appropriate treatment options based on this new staging system (see *Treatment of Stage II and IIIA Tumors*, *Treatment of Stage IIIB Tumors*, and *Treatment of Stage IVA Tumors*).

Enhanced Cystoscopy

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

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

Blue Light Cystoscopy

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

Several prospective clinical studies have evaluated BLC in conjunction with WLC and found higher detection rates of non-muscle invasive lesions with BLC.^{27–32} Particularly CIS, which is often missed by WLC, was detected at a higher rate. A meta-analysis of BLC TURBT in NMIBC included 12 randomized controlled trials with a total of 2258 patients.³³ A lower recurrence rate was observed (overall response [OR], 0.5; $P < .00001$) with a delayed time to first recurrence by 7.39 weeks ($P < .0001$). Recurrence-free survival (RFS) was improved at 1 year (hazard ratio [HR], 0.69; $P < .00001$) and at 2 years (HR, 0.65;



$P = .0004$). However, no significant reduction in the rate of progression to muscle invasive bladder cancer was seen (OR, 0.85; $P = .39$).

In a meta-analysis from Burger et al,³⁴ 1345 patients with Ta, T1, or CIS disease showed improved detection of bladder tumors and a reduction in recurrence.³⁴ Compared to WLC, BLC detected more Ta tumors (14.7%; $P < .001$; OR, 4.898; 95% CI, 1.937–12.390) and CIS lesions (40.8%; $P < .001$; OR, 12.372; 95% CI, 6.343–0.924). Importantly, 24.9% of patients had at least one additional Ta/T1 tumor detected ($P < .001$), and improved detection was seen in both primary (20.7%; $P < .001$) and recurrent disease (27.7%; $P < .001$). Another review of the literature included 26 studies with 5-ALA, 15 studies with HAL, and two studies that used both methodologies. The results from this review also support greater detection and reduced recurrence but no reduction in disease progression.³⁵

Although most studies have found no significant reduction in disease progression, a recent analysis reported a trend towards a lower rate with the use of BLC compared to WLC (12.2% vs. 17.6%, respectively; $P = .085$) with a longer time to progression ($P = .05$).³⁶ Although BLC has demonstrated improved detection and reduced recurrence, the value of this technique in reducing disease progression remains less established. Therefore, BLC may have the greatest advantage in detecting difficult-to-visualize tumors (eg, CIS tumors) that may be missed by WLC but has more limited applicability in disease monitoring. Other impediments to BLC include the need for appropriate expertise and equipment to use this new technology. High false positives are also attributed to this method and may be increased in patients who have had a recent TURBT or bacillus Calmette-Guérin (BCG) instillation, or who have inflammation.³⁵ The limitations of BLC require judicious application of this additional diagnostic tool.

Narrow-Band Imaging

NBI uses two narrow bands of light at 415 nanometers and 540 nanometers that are absorbed by hemoglobin. The shorter wavelength provides analysis of the mucosa and the longer wavelength allows for evaluation of the deeper submucosal blood vessels. Studies suggest that there is an increase in bladder tumor detection compared with WLC, although the rate of false positives is higher.³⁷⁻⁴¹

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

A randomized prospective trial followed patients for 1 year after NBI- or WLC-guided transurethral resection (TUR) to evaluate recurrence. NBI had a reduced 1-year recurrence rate (32.9%; 25 of 76 patients) compared to WLC (32.9% vs. 51.4%, respectively; OR, 0.62).⁴² However, the small number of patients in this study is limiting. A larger international, multicenter, randomized controlled trial compared 1-year recurrence rates in 965 patients who received either NBI- or WLC-



guided TUR for treatment of NMIBC. This study found that while recurrence rates were similar between the two groups in the study population overall, NBI-guided TUR significantly reduced the likelihood of disease recurrence at 1 year in patients with low-risk disease (5.6% for NBI vs. 27.3% for WLC; $P = .002$).⁴³ These results are supported by the systemic reviews and meta-analyses that have also shown reduced recurrence rates following NBI-guided TUR compared to WLC-guided TUR.^{44,45}

A benefit of NBI is that it does not require a contrast agent and can therefore be used as part of office cystoscopy. Higher detection rates of flat lesions and a reduction in tumor recurrence have been reported.⁴³⁻⁴⁶

Histology

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

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

Urothelial (transitional cell) carcinoma is the most common histologic subtype of bladder cancer in the United States and Europe and may develop anywhere urothelium is present, from the renal pelvis to the

ureter, bladder, and proximal two thirds of the urethra. The fifth edition of the World Health Organization (WHO) Classification of Tumors of the Urinary System and Male Genital Organs, published in November 2022, provided new information into the grading of invasive urothelial carcinomas, as well as noninvasive urothelial neoplasms, and the definition of precursor lesions.⁴⁷

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

Squamous cell neoplasms of the urothelial tract constitute 3% of the urinary tumors diagnosed in the United States. In regions where *Schistosoma* is endemic, this subtype is more prevalent and may account for up to 75% of bladder cancer cases. The distal third of the urethra is dominated by squamous epithelium. The diagnosis of squamous cell tumors requires the presence of keratinization in the pathologic specimen.⁵³ Squamous cell carcinoma of the bladder is



morphologically indistinguishable from squamous cell carcinoma of other sites and generally presents at an advanced stage. The three variants within this subtype are pure squamous cell carcinoma, verrucous carcinoma, and squamous cell papilloma.

Other histologic subtypes derived from cells of urothelial origin include glandular neoplasms, epithelial tumors of the upper urinary tract, and tumors arising in a bladder diverticulum. Glandular neoplasms include adenocarcinoma and villous adenoma. Urachal tumors are non-urothelial tumors, most commonly adenocarcinomas, which arise from the urachal ligament and secondarily involve the midline/dome of the bladder.⁵⁴ Tumors arising within the genitourinary tract but that are not of urothelial origin (eg, tumors of Müllerian type, melanocytic tumors, mesenchymal tumors) are beyond the scope of these guidelines.

Non-Muscle Invasive Urothelial Bladder Cancer

Non-muscle invasive tumors were previously referred to as *superficial*, which is an imprecise term that should be avoided. Treatment for non-muscle invasive disease often includes intravesical therapy or, for those with particularly high-risk disease, cystectomy.

Intravesical Therapy

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

Immediate Intravesical Therapy Post TURBT

An immediate intravesical instillation of chemotherapy may be given within 24 hours of TURBT to prevent tumor cell implantation and early recurrence. Immediate intravesical chemotherapy has been shown to decrease recurrence in select subgroups of patients. A systematic review and meta-analysis of 13 randomized trials demonstrated a decreased risk of recurrence by 35% (HR, 0.65; 95% CI, 0.58–0.74; $P <$

.001) and a decreased 5-year recurrence rate from 58.8% to 44.8% when comparing immediate intravesical chemotherapy following TURBT to TURBT alone, although the instillation did not prolong the time to progression or time to death from bladder cancer.¹⁵ This study also found that the instillation did not reduce recurrences in patients who had a prior recurrence rate of greater than one recurrence per year or with a European Organization for Research and Treatment of Cancer (EORTC) recurrence score greater than or equal to 5.

Phase III trials have reported a reduced risk of recurrence for patients with suspected non-muscle invasive disease who are treated with immediate postoperative gemcitabine or mitomycin. A randomized, double-blind, phase III trial of 406 patients with suspected low-grade NMIBC based on cystoscopic appearance showed that immediate post-TURBT instillation of gemcitabine reduced the rate of recurrence compared to saline instillation (placebo).¹³ In the intention to treat (ITT) analysis, 35% of patients treated with gemcitabine and 47% of those who received placebo had disease recurrence within 4 years (HR, 0.66; 95% CI, 0.48–0.90; $P < .001$).¹³ Intravesical therapy for a previous NMIBC was allowed in the study if received at least 6 months prior to enrollment. Another phase III, prospective, multicenter, randomized study of 2844 patients with NMIBC showed that an immediate instillation of mitomycin C after TURBT reduces recurrence regardless of the number of adjuvant instillations. Recurrence risk was 27% for immediate instillation versus 36% for delayed instillation ($P < .001$) for all patients in the study, with the benefit of immediate instillation present across risk groups.¹⁴ Previous intravesical chemotherapy was permitted in study participants as long as it was received at least 3 years prior to participation. For both studies, the rate of AEs did not significantly differ between the treatment and control groups, indicating that immediate intravesical instillation of gemcitabine or mitomycin was well tolerated.^{13,14} Gemcitabine is preferred over mitomycin based on toxicity



profiles and lower cost.⁵⁵ For tumors with an intermediate or high risk of progression, subsequent treatment with intravesical induction (adjuvant) therapy may be given. Perioperative intravesical treatment should not be given if there is extensive TURBT or concern for bladder perforation.

Induction (Adjuvant) Intravesical Chemotherapy or BCG

Although only intravesical chemotherapy is recommended in the immediate postoperative setting, both intravesical chemotherapy and BCG have been given as induction therapy in patients with NMIBC.⁵⁶ The most commonly used chemotherapy agents are mitomycin C and gemcitabine, although gemcitabine is preferred over mitomycin due to better tolerability and cost. In addition, in systematic reviews and meta-analyses, gemcitabine has shown superior efficacy compared to mitomycin, in that it demonstrated reduced rates of recurrence and progression.^{57,58}

Induction BCG has been shown to decrease the risk of bladder cancer recurrence following TURBT. BCG therapy is commonly given once a week for 6 weeks, followed by a rest period of 4 to 6 weeks, with a full re-evaluation at week 12 (ie, 3 months) after the start of therapy.⁵⁹ There are several meta-analyses demonstrating that BCG after TURBT is superior to TURBT alone, or TURBT and chemotherapy in preventing recurrences of high-grade Ta and T1 tumors.⁶⁰⁻⁶³ A meta-analysis including nine trials of 2820 patients with NMIBC reported that mitomycin C was superior to BCG without maintenance in preventing recurrence, but inferior to BCG in trials using BCG maintenance.⁶⁴ Using the SEER database, a reduction in mortality of 23% was reported in patients receiving BCG therapy.⁶⁵ Other studies have also reported that BCG was better at reducing recurrence in intermediate- and high-risk NMIBC when compared to mitomycin C.^{66,67}

BCG has also been compared to gemcitabine and epirubicin. A prospective, randomized phase II trial compared the quality of life in

patients receiving either BCG (n = 59) or intravesical gemcitabine (n = 61) and found no significant difference.⁶⁸ There were more frequent local and systemic side effects in the BCG arm; however, they were mild to moderate and the treatment was well tolerated in both groups. The benefit of BCG with or without isoniazid compared to epirubicin alone in a long-term study of 957 patients with intermediate- or high-risk Ta or T1 disease was measured by a reduced recurrence, greater time to distant metastases, and greater overall survival (OS) and disease-specific survival (DSS); progression was similar.⁶⁹ Long-term data comparing BCG to epirubicin in combination with interferon^{69,70} in patients with T1 disease showed a better reduction in recurrence with BCG; however, no differences in progression or AEs were seen.⁷⁰ Patients in both studies received 2 to 3 years of maintenance therapy.

Maintenance Therapy

Maintenance intravesical therapy may be considered following induction with chemotherapy or BCG. The role of maintenance chemotherapy is controversial. When given, maintenance chemotherapy is generally monthly. The role of maintenance BCG in those patients with intermediate- to high-risk NMIBC is more established, although the exact regimens have varied across studies. Some of the previous controversy over the effectiveness of BCG maintenance reflects the wide array of schedules and conflicting reports of efficacy. Quarterly and monthly installations as well as 3- and 6-week schedules have been evaluated. To date, the strongest data support the 3-week BCG regimen used in the SWOG trial that demonstrated reduced disease progression and metastasis.⁷¹ The 3-week timing of BCG has shown improved outcomes compared with epirubicin⁷⁰ or isoniazid.⁶⁹ Most patients receive maintenance BCG for 1 to 3 years. In an evaluation of randomized controlled trials and meta-analyses, limited evidence was found for 1 year of BCG maintenance.⁷² A study of 1355 patients with a median follow-up of 7.1 years found no benefit in 3 years of



maintenance BCG compared to 1 year for patients with intermediate-risk disease.⁷³ Conversely, 3-year maintenance BCG reduced recurrence compared to 1-year maintenance but did not impact progression or survival in patients with high-risk disease. These data suggest that 1 year may be suitable for patients at intermediate risk while 3 years of maintenance is preferred for high-risk disease. It should also be noted that duration of treatment may be limited by toxicity and patient refusal to continue.

For patients showing no residual disease at the follow-up cystoscopy, whether 1 or 2 courses of induction therapy were administered, maintenance therapy with BCG is preferred. This recommendation is based on findings that an induction course of intravesical therapy followed by a maintenance regimen produced better outcomes than intravesical chemotherapy.^{56,60,61,71,74,75}

BCG Toxicity

There are concerns regarding potentially severe local and systemic side effects and the inconsistent availability of BCG. BCG induces a systemic, nonspecific, immunostimulatory response leading to secretion of proinflammatory cytokines. This causes patients to experience flu-like symptoms that may last 48 to 72 hours.⁷⁶ Installation of BCG into the bladder can mimic a urinary tract infection and may produce intense local discomfort. The side effects of treatment have translated to discontinuation of BCG therapy. Dysuria has been reported in 60% of patients in clinical trials.⁷⁶ However, the side effects are treatable in almost all cases⁷⁷ and no increase in toxicity has been reported with cumulative doses. Symptom management with single-dose, short-term quinolones and/or anticholinergics have been reported to reduce AEs.^{78,79}

A reduced (one-third) dose of BCG was evaluated for the possible reduction of side effects. In a phase III study, 1316 patients with

intermediate- or high-risk Ta, T1 papillary carcinoma of the bladder were randomized to receive reduced- or full-dose BCG with either 1 or 3 years of maintenance.⁸⁰ Among all four groups, the percentage of patients with greater than or equal to one side effect was similar ($P = .41$). Although the one-third dose of BCG was effective, side effects were not reduced. Conversely, other publications suggest that the one-third dose may reduce side effects.⁸¹⁻⁸³ Full-dose BCG is recommended by the panel until more data are available to evaluate the low-dose BCG regimen. However, dose reduction may be used if there are substantial local symptoms during maintenance.

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

BCG Shortage

An ongoing shortage of BCG has existed in the United States, necessitating development of strategies to prioritize use of intravesical BCG and identify alternative treatment approaches for some patients with NMIBC.⁸⁵ Several organizations, including the American Urological Association (AUA), American Association of Clinical Urologists (AACU), Bladder Cancer Advocacy Network (BCAN), Society of Urologic



Oncology (SUO), the Large Urology Group Practice Association (LUGPA), and the Urology Care Foundation (UCF), issued a [notice](#) outlining strategies to maximize care for patients with NMIBC in the context of this shortage.⁸⁶ NCCN Panel Members recommend several strategies to help alleviate problems associated with this shortage.

In the event of a BCG shortage, priority for treatment should be to provide patients with high-risk NMIBC (cT1 high grade or CIS) with induction BCG. For patients who do not receive BCG, intravesical chemotherapy may be used as an alternative. The intravesical chemotherapies most commonly used for this purpose are gemcitabine^{55,87} and mitomycin.⁸⁸ Two separate meta-analyses of randomized trials reported that there were no differences in risk of recurrence between BCG and mitomycin,^{56,89} although BCG may show more favorable outcomes from maintenance regimens.⁵⁶ Other options include epirubicin,^{69,90} valrubicin,⁹¹ docetaxel,⁹² sequential gemcitabine/docetaxel,⁹³ or gemcitabine/mitomycin.⁹⁴ Another alternative to intravesical BCG for patients with NMIBC at high risk of recurrence and, particularly, at high risk of progression, is initial radical cystectomy.⁹⁵

Another option during a shortage is splitting the dose of BCG so that multiple patients may be treated using a single vial. While several randomized trials have reported that one-third-dose BCG showed similar outcomes when compared to full-dose BCG,^{82,96,97} a phase 3 trial of 1355 patients with intermediate- or high-risk NMIBC reported that patients receiving the full dose of BCG show a longer disease-free interval, compared with those receiving the one-third dose.⁷³ In this study, the 5-year disease-free rate was 58.5% for the one-third dose compared to 61.7% for the full dose; therefore, the null hypothesis of inferiority for duration of the disease-free interval of one-third-dose BCG could not be rejected (HR, 1.15; 95% CI, 0.98–1.35; $P = .045$), although

there were no differences in progression or survival rates.⁷³ Based on these data, the panel recommends that one-half or one-third dose may be considered for BCG induction during a shortage and should be used for BCG maintenance, if supply allows. Maintenance BCG should be prioritized for patients with high-risk NMIBC (cT1 high grade and/or CIS) in the early maintenance period (eg, 3 and 6 months post-induction), although in cases of shortage, BCG induction therapy should be prioritized over maintenance BCG.

Treatments for BCG-Unresponsive or BCG-Intolerant NMIBC

Nadofaragene Firadenovec-vncg

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



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

Nogapendekin alfa inbakicept-pmIn (N-803)

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

Pembrolizumab for NMIBC

Pembrolizumab is a programmed cell death protein 1 (PD-1) inhibitor that has been evaluated as systemic therapy for BCG-unresponsive NMIBC with CIS in the single-arm, phase II KEYNOTE-057 study (pembrolizumab is also indicated for treatment of metastatic urothelial carcinoma; see section on *Metastatic (Stage IVB) Urothelial Bladder Cancer*, below). In the KEYNOTE-057 study, 101 patients with high-risk CIS, with or without papillary tumor, who received previous BCG therapy and were either unable or unwilling to undergo cystectomy were treated with pembrolizumab.¹⁰³ Ninety-six patients were eligible for inclusion in the efficacy analysis. The 12-month complete response rate was 19% (18 of 96 total patients on the study), and the median duration of response (DOR) from time of onset was 16.2 months (95% CI, 6.7–36.2). Grade ≥3 treatment-related AEs were reported in 13% of patients, with arthralgia and hyponatremia being the most common. Serious treatment-related AEs occurred in 8% of patients.

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

NCCN Recommendations for Treatment of NMIBC

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



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

After the initial TURBT shows NMIBC, a repeat TURBT is recommended for visually incomplete or high-volume tumors and for high-grade NMIBC, which is found to be T1 on the initial TURBT.¹⁰⁷ This is supported by a trial that prospectively randomized 142 patients with pT1 tumors to a second TURBT within 2 to 6 weeks of the initial TURBT or no repeat TURBT.¹⁰⁸ All patients received adjuvant intravesical therapy. Although OS was similar, the 3-year recurrence-free survival was significantly higher in the repeat TURBT arm versus the control arm (69% vs. 37%, respectively), especially among patients with high-grade tumors. Similarly, a randomized 10-year extension trial of 210 patients with pT1 NMIBC found that patients who underwent repeat TURBT had a significantly higher 5-, 7-, and 10-year RFS and PFS and, in addition, the 10-year OS rate was significantly higher in patients with repeat TURBT (59.1% vs. 40.8%; $P = .004$).¹⁰⁹ Repeat TURBT was found to be an independent determinant of prolonged OS on multivariate analysis.

Repeat TURBT may also be considered for select patients with high-grade Ta on initial TURBT, particularly if the tumor is large and/or there was no muscle present in the initial TURBT specimen. Restaging TURBT detected residual disease in 27% of Ta patients when muscle was present in the original TURBT.¹¹⁰ In the absence of muscularis propria in the initial TURBT specimen, 49% of patients with non-muscle invasive disease will be understaged versus 14% if muscle is present.¹¹¹

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

Treatment of Low-Risk NMIBC

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

Treatment of Intermediate-Risk NMIBC

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



The value of an induction course of intravesical therapy depends on the patient's prognosis and likelihood of disease recurrence. Factors to consider include the size, number, T category, and grade of the tumor(s), as well as concomitant CIS and prior recurrence.²⁵

Meta-analyses have confirmed the efficacy of adjuvant (induction) intravesical chemotherapy in reducing the risk of recurrence.^{114,115} In the literature, there are four meta-analyses confirming that BCG after TURBT is superior to TURBT alone, or TURBT and chemotherapy in preventing recurrences of Ta and T1 tumors.⁶⁰⁻⁶³ Close follow-up of all patients is needed, although the risk for progression to a more advanced stage is low (see *Surveillance* in the discussion and algorithm).

Treatment of High-Risk NMIBC

High-risk NMIBC has a relatively high risk for recurrence and progression towards more invasiveness. According to the AUA/SUO risk stratification, high-risk NMIBC includes high-grade urothelial carcinoma that has any of the following characteristics: CIS, T1, size greater than 3 cm, or multifocal. In addition, a subgroup of very-high-risk features includes BCG unresponsiveness, variant histologies, lymphovascular invasion, and prostatic urethral invasion.¹⁰⁵ Based on the histologic differentiation, most cT1 lesions are high grade and considered to be potentially dangerous with a higher risk for recurrence and progression. These tumors may occur as solitary lesions or as multifocal tumors with or without an associated CIS component. The presence of CIS is associated with an increased risk of invasive disease, including increased cancer progression rates and worse cancer-specific outcomes.²⁰ If untreated, 50% of CIS progresses to muscle invasive disease within 5 years and, even with treatment, 30% to 40% progresses within 10 years.¹¹⁶

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

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

Surveillance

For intermediate and high-risk NMIBC, follow-up is recommended with a urinary cytology and cystoscopy at 3- to 6-month intervals for the first 2 years, and at longer intervals as appropriate thereafter. Imaging of the upper tract should be considered every 1 to 2 years for high-risk tumors (see *Follow-up* in the algorithm). Urine molecular tests for urothelial tumor markers are now available.¹²⁰ Many of these tests have a better



sensitivity for detecting bladder cancer than urinary cytology, but specificity is lower. Considering this, evaluation of urinary urothelial tumor markers may be considered during surveillance of high-risk NMIBC. However, it remains unclear whether these tests offer additional useful information for detection and management of non-muscle invasive bladder tumors. Therefore, the panel considers this to be a category 2B recommendation.

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

Posttreatment of Recurrent or Persistent Disease

Treatment of Patients with Positive Cystoscopy

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

Treatment of Patients with Positive Cytology

In patients without a documented recurrence but with initial positive cytology and negative cystoscopy and imaging, it may be appropriate to repeat the cytology test within 3 months. If subsequent cytology tests are positive, selected mapping biopsies including transurethral resection of the prostate (TURP) may be considered. In addition, the upper tract must be evaluated and ureteroscopy may be considered for detecting tumors of the upper tract. If available, enhanced cystoscopy should be considered (see *Enhanced Cystoscopy*, above). With persistent positive

cytology and no demonstrable clinical disease in the urinary tract, evaluation of the contiguous organs (eg, vagina, cervix, uterus, or anorectum) via referral to an appropriate specialist may be warranted. Several case reports have described the detection of urothelial carcinoma spread to the vagina, cervix, or vulva.¹²¹⁻¹²³ It has also been reported that as many as 14% of patients with a positive urine cytology and no visible disease in the bladder had tumors in contiguous organs as the source of the positive cytology finding.¹²⁴ If the bladder, prostate, and upper tract continue to show negative results on further evaluation, additional follow-up is indicated after 3 months, then at longer intervals. If BCG was given previously, maintenance BCG may be considered.

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

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

In a phase II multicenter study of NMIBC that recurred following two courses of BCG, intravesical gemcitabine demonstrated activity that was relegated to high-risk NMIBC.¹²⁵ In the 47 patients with evaluable response, 47% had DFS at 3 months. The 1-year RFS was 28% with all cases except for two attributed to the high-risk group. The 2-year RFS was 21%. Intravesical gemcitabine had some activity in the high-risk group, and may be an option if a candidate is not eligible for a cystectomy; however, the study results indicate that cystectomy is preferred when possible. Similarly, for patients with recurrence of high-grade cT1 disease after TURBT and induction BCG, cystectomy is the recommended option with the best data for cure.¹²⁶ Surveillance



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

Muscle Invasive Urothelial Bladder Cancer

Additional Workup

Several workup procedures are recommended to accurately determine clinical staging of muscle invasive disease. Laboratory studies, such as a complete blood count (CBC) and chemistry profile, including alkaline phosphatase, must be performed. Since cisplatin-based chemotherapy is a preferred approach both for neoadjuvant therapy prior to cystectomy and as part of trimodal therapy for bladder preservation, an estimated glomerular filtration rate (GFR) should be obtained to assess patient eligibility for cisplatin. For patients with borderline GFR results, a timed or measured urine collection may be considered to more accurately determine cisplatin eligibility.¹³⁰

Patients should also be assessed for regional or distant metastases. This evaluation should include chest imaging (CT [preferred], x-ray, or fluorodeoxyglucose [FDG]-PET/CT [category 2B]) and evaluation for suspected bone metastasis in patients with symptoms or clinical suspicion of bone metastasis (eg, elevated alkaline phosphatase, focal bone pain). Chest imaging with CT is preferred over chest x-ray based on studies showing better sensitivity of CT for detection of metastatic disease.^{131,132} Bone imaging may include a bone scan, MRI, or FDG-PET/CT (category 2B). Imaging studies help assess the extent of tumor spread to lymph nodes or distant organs.^{133,134} An abdominal/pelvic CT or MRI is used to assess the local and regional extent of disease.^{135,136}

Unfortunately, CT scans, ultrasound, and MRI cannot accurately predict the true depth of invasion.

The overwhelming majority of muscle invasive tumors are high-grade urothelial carcinomas. Further treatment following initial TURBT is often required for muscle invasive tumors, although select patients may be treated with TURBT alone.^{137,138} Different treatment modalities are discussed below. These include radical cystectomy, partial cystectomy, neoadjuvant or adjuvant therapy, bladder-preserving approaches, and systemic therapy for advanced disease.

Cystectomy

Radical Cystectomy

Radical surgical treatment of bladder cancer involves a cystoprostatectomy or a cystectomy and commonly a hysterectomy for those with a uterus, followed by the formation of a urinary diversion, although in appropriately selected patients, approaches that preserve the uterus, vagina, fallopian tubes, and/or ovaries may be used.^{139,140} This surgery can be performed in an open or robotic manner.¹⁴¹⁻¹⁴⁴ Prostatectomy includes removal of the prostate, seminal vesicles, proximal vas deferens, and proximal urethra. Hysterectomy should include removal of the uterus, ovaries, fallopian tubes, urethra, and part of the vagina. Forms of urinary diversion include an ileal conduit or directing urine to an internal urinary reservoir (such as a continent pouch), with drainage to the abdominal wall or the urethra (orthotopic neobladder). Relative contraindications to urethral drainage include CIS in the prostatic ducts or positive urethral margin. Orthotopic diversion or a neobladder provides the closest bladder function to that of a native bladder albeit with an increased risk for nighttime incontinence as well as urinary retention requiring intermittent self-catheterization.



Unfortunately, the accuracy of the staging cystoscopy, EUA, and TURBT is modest, even when combined with cross-sectional imaging and when understaging is frequently encountered. A retrospective study of 778 patients with bladder cancer found that 42% of patients were upstaged following cystectomy.¹⁴⁵ A pelvic lymph node dissection (PLND) is considered an integral part of the surgical management of bladder cancer. A more extensive PLND, which may include the common iliac or even lower para-aortic or para-caval nodes, yields more nodes to be examined, increases yield of positive nodes, and may be associated with better survival and a lower pelvic recurrence rate.¹⁴⁶⁻¹⁵⁰ Conversely, a 2019 prospective, randomized trial concluded that an extended LND did not show a significant advantage over limited LND for RFS, cancer-specific survival, or OS.¹⁵¹ However, differing definitions of “extended” versus “limited” LND between studies and specifics on how the study was powered complicate these results. Therefore, additional information will be needed to determine whether extended LND leads to improved outcomes. Results from the SWOG-1011 trial, which is fully accrued but not yet reported, may help to further answer this question.¹⁵² Patient factors that may preclude a PLND include severe scarring secondary to previous treatments or surgery, advanced age, or severe comorbidities.

Partial Cystectomy

In fewer than 5% of cases, an initial invasive tumor develops in an area of the bladder where an adequate margin of soft tissue and an adequate amount of noninvolved urothelium can be removed along with the tumor without compromising continence or significantly reducing bladder capacity. Partial cystectomy is most frequently recommended for lesions that develop on the dome of the bladder and have no associated CIS in other areas of the urothelium. Relative contraindications to this procedure are lesions that occur in the trigone or bladder neck. The requirement for a ureteral reimplantation, however,

is not an absolute contraindication. Outcomes data on partial cystectomy are varied and, in general, partial cystectomy is not considered the standard surgical treatment of muscle invasive bladder cancer. Ideal candidates are patients with cancer in a diverticulum or with significant medical comorbidities.

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

Neoadjuvant Chemotherapy

One of the most noteworthy issues in the treatment of bladder cancer is the optimal use of perioperative chemotherapy for muscle invasive disease. Data support the role of neoadjuvant chemotherapy before cystectomy for stage II and IIIA lesions.¹⁵³⁻¹⁵⁸ In a SWOG randomized trial of 307 patients with muscle invasive disease, radical cystectomy alone versus 3 (28-day) cycles of neoadjuvant methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) followed by radical cystectomy were compared. Neoadjuvant chemotherapy increased median survival (77 vs. 46 months; $P = .06$) and lowered the rate of residual disease (15% vs. 38%; $P < .001$) with no apparent increase in treatment-related morbidity or mortality.¹⁵³ In a meta-analysis of 11 trials involving 3005 patients, cisplatin-based multiagent neoadjuvant chemotherapy was associated with improved 5-year OS and DFS (5% and 9% absolute improvement, respectively).¹⁵⁷ The randomized, phase III JCOG0209 study comparing neoadjuvant MVAC to no neoadjuvant chemotherapy also found no difference in health-related quality of life



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

Since the neoadjuvant trial with MVAC, the use of dose-dense MVAC (ddMVAC) with growth factor support in the metastatic setting has been shown to have good comparable tolerance with an increased complete response rate compared to standard (28-day) dosing of MVAC (11% vs. 25%; 2-sided $P = .006$).¹⁶¹ Based on these findings, ddMVAC has also been investigated in the neoadjuvant setting. In a multicenter prospective phase II trial, patients with cT2 to cT4a tumor staging and N0 or N1 muscle invasive bladder cancer ($n = 44$) were given 3 cycles of ddMVAC with pegfilgrastim followed by radical cystectomy and lymph node dissection.¹⁶² ddMVAC was anticipated to have a safer profile, a shorter time to surgery, and a similar pathologic complete response rate compared to historical control data for neoadjuvant MVAC chemotherapy given in previous studies. Patients receiving ddMVAC had no grade 3 or 4 renal toxicities and no toxicity-related deaths. Grade 1 or 2 treatment-related toxicities were seen in 82% of patients. The median time to cystectomy was 9.7 weeks from the start of chemotherapy.¹⁶² A separate single-arm phase II study also reported pathologic downstaging in 49% of patients receiving neoadjuvant ddMVAC with a similar safety profile.¹⁶³ An additional neoadjuvant clinical trial of ddMVAC with bevacizumab reported 5-year survival outcomes of 63% and 64% (OS and DSS, respectively; median follow-up, 49 months), with pT0N0 and less than or equal to pT1N0 downstaging rates of 38% and 53%, respectively.¹⁶⁴ Bevacizumab had no definitive impact on overall outcomes.

Gemcitabine and cisplatin (GC) has also been evaluated for neoadjuvant therapy of muscle invasive bladder cancer, albeit mainly in smaller phase II or retrospective studies. Overall, these studies showed that GC is effective and well-tolerated when used as neoadjuvant therapy for muscle invasive bladder cancer,¹⁶⁵⁻¹⁶⁹ although some of the studies report lower pathologic response compared to MVAC¹⁶⁸ and lack of a demonstrated OS benefit due to short follow-up or small study size.^{166,167} More recently, the phase II COXEN trial has evaluated ddMVAC and GC as neoadjuvant therapy for muscle invasive bladder cancer with the aim of validating scoring from a coexpression extrapolation algorithm-generated gene expression model.^{170,171} In the ITT population of 227 patients, pT0 rates for ddMVAC and GC were 28% and 30% ($P = .75$) and downstaging was 47% and 40% ($P = .27$), respectively.¹⁷⁰ No significant difference between ddMVAC and GC was reported for OS or event-free survival.¹⁷¹ Dose-dense GC has been evaluated as neoadjuvant therapy in a prospective, phase II trial including 46 evaluable patients.¹⁷² The primary endpoint of this trial was met as 57% of patients had their disease downstaged to NMIBC (less than pT2, N0). Pathologic response also correlated with improved RFS and OS. Thirty-nine percent of patients experienced dose modifications due to treatment toxicity, but no patients were unable to undergo cystectomy due to treatment-related AEs. The most frequent treatment-related AE was anemia (12% grade 3).

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



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

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

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

trial, ddMVAC is the preferred regimen for perioperative treatment of muscle invasive bladder cancer. For patients with borderline renal function or minimal dysfunction, a split-dose administration of cisplatin may be considered (category 2B). Although split-dose is a safer alternative, the relative efficacy remains undefined.

Adjuvant Systemic Therapy

Data are less clear regarding the role of adjuvant systemic therapy in invasive bladder cancer. Studies have shown that adjuvant chemotherapy may delay recurrences and improve OS^{176–178}; however, no randomized comparisons of adequate sample size have definitively shown a survival benefit, in large part due to poor accrual.¹⁷⁹ Clinical trials of adjuvant chemotherapy with cyclophosphamide, doxorubicin, and cisplatin (CAP); MVAC; and methotrexate, vinblastine, epirubicin, and cisplatin (MVEC) regimens have each suggested a survival advantage.^{180–182} However, methodologic issues question the applicability of these studies to all patients with urothelial tumors. In the MVEC trial, patients who experienced relapse in the control arm did not receive chemotherapy, which is not typical of more contemporary treatment approaches. Many of these trials were not randomized, raising the question of selection bias in the analysis of outcomes.

A meta-analysis of 6 trials found a 25% mortality reduction with adjuvant chemotherapy, but the authors pointed out several limitations of the data and concluded that evidence is insufficient for treatment decisions.¹⁸³ Interestingly, the follow-up analysis included 3 more studies for a total of 9 trials (N = 945 patients).¹⁷⁸ A 23% risk reduction for death was observed in the updated analysis (HR, 0.77; 95% CI, 0.59–0.99; $P = .049$) and improved DFS was achieved (HR, 0.66; 95% CI, 0.45–0.91; $P = .014$). Patients with node-positive disease had an even greater DFS benefit.¹⁷⁸ An observational study evaluated 5653 patients of which 23% received adjuvant chemotherapy



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

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

Checkpoint inhibitors have also been investigated in the adjuvant setting, with the phase 3 CheckMate 274 trial of adjuvant nivolumab reporting positive results for its primary endpoints across the entire study population, although the authors note the possibility of a larger effect size for bladder compared to UTUC (see *Adjuvant Treatment and Follow-up* under *UTUC*, below, for more discussion on these data).¹⁸⁵ In the ITT population of 709 patients with muscle invasive urothelial carcinoma treated with radical surgery on CheckMate 274, DFS was 20.8 months with nivolumab compared to 10.8 months with placebo (HR, 0.70; 98.22% CI, 0.55–0.90; $P < .001$). For patients with a programmed death-ligand 1 (PD-L1) expression level of 1% or more, DFS was 74.5% with nivolumab and 55.7% with placebo (HR, 0.55; 98.72% CI, 0.35–0.85; $P < .001$). Importantly, adjuvant nivolumab was tested both in patients who had received neoadjuvant therapy as well as those who did not; 43.4% of the trial participants had received

previous cisplatin-based neoadjuvant therapy. Treatment-related AEs of grade 3 or higher occurred in 17.9% of those treated with nivolumab and 7.2% of those treated with placebo. Further follow-up is ongoing to assess OS outcomes. While atezolizumab has also been tested in the adjuvant setting for patients with high-risk muscle invasive urothelial carcinoma in the phase 3 IMvigor010 study, this study did not meet its primary endpoint of improved DFS with adjuvant atezolizumab compared to observation.¹⁸⁶ Median DFS was 19.4 months with atezolizumab compared to 16.6 months with observation (HR, 0.89; 95% CI, 0.74–1.08; $P = .24$).

The NCCN Guidelines suggest that adjuvant systemic therapy should be discussed with patients with high-risk pathology after cystectomy. If cisplatin-based neoadjuvant therapy was not given and the tumor is found to be pT3, pT4, or pN+ following resection, adjuvant cisplatin-based chemotherapy is the preferred approach, although adjuvant nivolumab may also be considered. If cisplatin-based neoadjuvant therapy was given and the tumor is ypT2–ypT4a or ypN+, nivolumab may be considered, although consideration of this approach should balance its effect at delaying progression of disease with the risk of side effects. A minimum of 3 cycles of a cisplatin-based combination, such as ddMVAC (preferred) or GC, may be used in patients undergoing perioperative chemotherapy. Chemotherapy regimen and dosing recommendations are mainly based on studies in advanced disease.^{153,165,187,188} Carboplatin has not demonstrated a survival benefit and should not be substituted for cisplatin in the perioperative setting. It should be noted that patients with tumors that are pT2 or less and have no nodal involvement or lymphovascular invasion after cystectomy are considered to have lower risk and are not recommended to receive adjuvant therapy.



Adjuvant Radiation

Patients with locally advanced disease (pT3–4) have high rates of pelvic recurrence and poor OS after radical cystectomy, PLND, and perioperative chemotherapy (pelvic failure 20%–45% and survival 10%–50% at 5 years, depending on risk factors).^{189–192} There is an interest in using adjuvant radiation to improve these outcomes, but data are limited and further prospective studies are needed to confirm its benefits. One older randomized study of 236 patients with pT3a to pT4a bladder cancer demonstrated improvement in 5-year DFS and local control compared to surgery alone.¹⁹³ A more recent randomized phase II trial compared adjuvant sequential chemotherapy and radiation versus adjuvant chemotherapy alone in 120 patients with locally advanced disease with one or more risk factors (\geq pT3b, grade 3, or node-positive), in a study population with a high proportion of squamous cell carcinoma. This study demonstrated a significant improvement in local control for chemoradiation (3-year local control of 96% vs. 69%; $P < .01$) and marginal improvements in DFS and OS. Late-grade ≥ 3 gastrointestinal toxicity on the chemoradiation arm was low (7% of patients).¹⁹⁴ A 2019 systematic review evaluating the oncologic efficacy of adjuvant radiation for bladder cancer or UTUC concluded that there was no clear benefit of adjuvant radiation following radical surgery (eg, cystectomy), although the combination of adjuvant radiation with chemotherapy may be beneficial in locally advanced disease.¹⁹⁵

While there are no conclusive data demonstrating improvements in OS, it is reasonable to consider adjuvant radiation in patients with pT3/pT4 urothelial bladder cancer with positive nodes or margins at the time of surgery, although this approach has been evaluated in only a limited number of studies, reflected by the category 2B designation. Patients meeting these characteristics with positive surgical margins and/or lymph nodes identified in the pelvic dissection have especially high pelvic recurrence rates (40%–45% by 5 years), and adjuvant radiation is

reasonably well tolerated and improves local control. Radiation with a dose range of 45 to 50.4 Gy without concurrent chemotherapy may be used. In patients who have not had prior neoadjuvant chemotherapy, it may be reasonable to sandwich adjuvant radiation between cycles of adjuvant chemotherapy.¹⁹⁴ The safety and efficacy of concurrent sensitizing chemotherapy and radiation in the adjuvant setting needs to be further studied.

Bladder Preservation

All bladder-sparing approaches are based on the principle that not all cases require an immediate cystectomy, and the decision to remove the bladder can be deferred until the response to organ-sparing therapy is assessed. In fact, a meta-analysis of 73 studies comprising 9110 patients reported that only 19.2% of patients who initially receive bladder-preserving therapy for muscle invasive bladder cancer eventually require radical cystectomy due to recurrence or lack of response.¹⁹⁶ Another multicenter retrospective analysis of 287 patients with cN+ M0 bladder cancer showed no difference in OS (HR, 0.94; 95% CI, 0.63–1.41; $P = .76$) or PFS (HR, 0.74; 95% CI, 0.50–1.08; $P = .12$) between radical cystectomy versus organ preservation with radical dose radiotherapy.¹⁹⁷ Receiving radical cystectomy or bladder-sparing trimodality therapy was, however, associated with improved OS compared to palliative treatment ($P < .001$).

Bladder-preserving approaches are reasonable alternatives to cystectomy for patients who are medically unfit for surgery and those seeking an alternative to radical cystectomy.^{198,199} Combined modality chemoradiation therapy as an alternative to immediate cystectomy for muscle invasive bladder cancer is endorsed by multiple international organizations that have developed evidence-based consensus guidelines and recommendations, including the International Consultation on Urologic Diseases-European Association of Urology



NCCN Guidelines Version 1.2025

Bladder Cancer

(ICUD-EAU), UK National Institute for Health and Care Excellence (NICE), and the AUA/ASCO/ASTRO/SUO.²⁰⁰⁻²⁰² There is an apparent underutilization of aggressive bladder-preserving therapies for non-cystectomy candidates, especially in patients who are older and Black patients.^{203,204} Between 23% and 50% of patients with muscle invasive bladder cancer who are ≥65 years receive no treatment or non-aggressive therapy, despite prospective, phase II data showing that bladder preservation with trimodality therapy has positive outcomes and an acceptable toxicity profile for patients ≥65 years, with a 2-year OS of 94.4% and 2-year DFS of 72.6%.²⁰⁵ For tools to aid in the optimal assessment and care of older adults with cancer, see the [NCCN Guidelines for Older Adult Oncology](#).

With any of the alternatives to cystectomy, there is concern that bladders that appear to be endoscopically free of tumor based on a clinical assessment (cT0) that includes a repeat TURBT may not be pathologically free of tumor (pT0). Reports have suggested that up to 45% of bladders may be clinically understaged after TURBT.^{204,206,207} Conversely, one series reported that all patients who achieved a complete response after radiotherapy with concurrent cisplatin and fluorouracil (5-FU) were pT0 on immediate cystectomy.²⁰⁸ Although studies report differing frequencies of residual disease after cytotoxic agents (either radiation or chemotherapy), there is consensus that the rate is lower for patients who present with T2 disease than with T3 disease, which should be considered when proposing a bladder-sparing approach.

The decision to use a bladder-preserving approach is partially based on the location of the lesion, depth of invasion, size of the tumor, status of the “uninvolved” urothelium, and status of the patient (eg, bladder capacity, bladder function, comorbidities). Bladder preservation as an alternative to cystectomy is generally reserved for patients with smaller

solitary tumors, negative nodes, no extensive or multifocal CIS, no tumor-related moderate or severe hydronephrosis, and good pre-treatment bladder function. Patients who are medically fit for radical cystectomy but who have hydronephrosis are poor candidates for bladder-sparing procedures.^{209,210} Maximal TURBT with concurrent chemoradiotherapy should be given as primary treatment for these patients, with radiotherapy alone or TURBT alone reserved for select patients (see *TURBT Alone as Primary Treatment for Muscle Invasive Bladder Cancer* below for more information). When possible, bladder-sparing options should be chosen in the context of clinical trials.

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

Several groups have investigated the combination of concurrent or sequential chemotherapy and radiotherapy after TURBT. First, an endoscopic resection that is as complete as possible is performed. Incomplete resection is an unfavorable prognostic factor for the ability to preserve the bladder.²¹¹⁻²¹³

Radiation Therapy Oncology Group (RTOG) protocol 89-03 compared concurrent cisplatin and radiotherapy with or without 2 cycles of induction MCV (methotrexate, cisplatin, and vinblastine) chemotherapy.²¹⁰ No difference in complete clinical response or 5-year OS was observed between the treatment arms. Other studies also reported no significant survival benefit for neoadjuvant chemotherapy before bladder-preserving chemotherapy with radiation therapy (RT).^{212,214}

In the phase 3 RTOG 89-03 trial in which 123 patients with clinical stage T2–T4a were treated with radiotherapy plus concurrent cisplatin, with or without induction MCV chemotherapy, 5-year OS was approximately 49% in both arms.²¹⁰ The subsequent RTOG 95-06 trial treated 34 patients with twice-daily irradiation and concurrent cisplatin and 5-FU



and reported a 3-year OS of 83%.²¹⁵ The RTOG 97-06 trial treated 47 patients with twice-daily irradiation and concurrent cisplatin; patients also received adjuvant chemotherapy with CMV.²¹⁶ Three-year OS was 61%. In the RTOG 99-06 study, 80 patients received twice-daily irradiation plus cisplatin and paclitaxel, followed by adjuvant cisplatin and gemcitabine. Five-year OS was 56%.²¹⁷ In RTOG 0233, 97 patients received twice-daily radiation with concurrent paclitaxel plus cisplatin or 5-FU plus cisplatin. Five-year OS was 73%.²¹⁸ RTOG 0712 investigated 5-FU plus cisplatin with twice-daily radiation or gemcitabine with once-daily radiation, with 33 patients eligible for analysis on each arm. Three-year distant metastasis-free survival rates were 78% and 84%, respectively.²¹⁹ Taken together, the complete response rates ranged from 59% to 88%.

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

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

A meta-analysis of individual patient data from two randomized, phase III studies (BC2001 and BCON) compared two radiotherapy fractionation schedules that are commonly used in treatment of locally advanced bladder cancer, a standard schedule of 64 Gy in 32 fractions

over 6.5 weeks and a hypofractionated schedule of 55 Gy in 20 fractions over 4 weeks.²²² This analysis found that the hypofractionated schedule is noninferior to the standard fractionation schedule for both invasive local control and toxicity and that the hypofractionated schedule is superior regarding invasive local control.

Chemotherapy Following TURBT as Primary Treatment for Muscle Invasive Bladder Cancer

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

Radiotherapy Following TURBT as Primary Treatment for Muscle Invasive Bladder Cancer

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

TURBT Alone as Primary Treatment for Muscle Invasive Bladder Cancer

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



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

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

NCCN Recommendations for Treatment of Muscle Invasive Bladder Cancer

Treatment of Stage II and IIIA Tumors

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

Primary surgical treatment for stage II and IIIA disease is a radical cystectomy and pelvic lymphadenectomy. Neoadjuvant chemotherapy is recommended (category 1). Partial cystectomy along with neoadjuvant cisplatin-based chemotherapy can be considered for stage II (cT2, N0) disease with a single tumor in a suitable location and no presence of CIS. Partial cystectomy is not an option for patients with stage III disease. If cisplatin-based neoadjuvant therapy was not given and the tumor is found to be pT3, pT4, or pN+ following resection, adjuvant cisplatin-based chemotherapy is the preferred approach, although adjuvant nivolumab may also be considered. If cisplatin-based

neoadjuvant therapy was given and the tumor is ypT2–ypT4a or ypN+, nivolumab may be considered. Adjuvant RT is another option for patients with tumors that are pT3–4, with positive nodes or margins, at the time of surgery (category 2B).

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

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

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



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

Treatment of Stage IIIB Tumors

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

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

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

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

Treatment of Stage IVA Tumors

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



NCCN Guidelines Version 1.2025

Bladder Cancer

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

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

Follow-up

Results from a meta-analysis of 13,185 patients who have undergone cystectomy reported a 0.75% to 6.4% prevalence of upper tract recurrence.²²⁸ Surveillance by urine cytology or upper tract imaging detected recurrences in 7% and 30% of cases, respectively.

Follow-up after a cystectomy should include urine cytology, liver function tests, creatinine, and electrolytes. Imaging of the chest, upper tract abdomen, and pelvis should be conducted at intervals based on the risk of recurrence. Patients should be monitored annually for vitamin B₁₂ deficiency if a continent urinary diversion was created. Consider urethral wash cytology for patients with an ileal conduit or continent catheterizable diversion, particularly if CIS was found within the bladder or prostatic urethra. For details of follow-up recommendations, see *Follow-up* in the algorithm.

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

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

Recurrent or Persistent Disease

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

For patients with a preserved bladder, local recurrence or persistent disease should be evaluated as a new cancer. Recurrences are treated based on the extent of disease at relapse, with consideration of prior treatment. As previously discussed, CIS, Ta, or T1 tumors are generally



managed with intravesical therapy, cystectomy, or TURBT. If no response is noted, a cystectomy is advised. Invasive disease is generally managed with radical cystectomy, and a second attempt at bladder preservation is not advisable. Cystectomy may not be possible in a patient who has undergone a full course of EBRT and has bulky residual disease. For these patients, systemic therapy or palliative TURBT and best supportive care is advised.

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

Metastatic (Stage IVB) Urothelial Bladder Cancer

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

Evaluation of Metastatic Disease

If metastasis is suspected, additional workup to evaluate the extent of the disease is necessary. This includes a chest CT and a bone scan if enzyme levels are abnormal or the patient shows signs or symptoms of skeletal involvement. Central nervous system (CNS) imaging should be considered. An estimated GFR should be obtained to assess patient eligibility for cisplatin. For patients with borderline GFR results, a timed or measured urine collection may be considered to more accurately determine cisplatin eligibility.¹³⁰ If the evidence of spread is limited to nodes and biopsy is technically feasible, nodal biopsy should be

considered and patients' disease should be managed as previously outlined for positive nodal disease (stage IIIA, stage IIIB, or stage IVA). Molecular testing should also be performed for patients with metastatic disease (see *Molecular/Genomic Testing*, below).

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

Metastasectomy for Oligometastatic Disease

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

A phase II trial of 11 patients with bladder primary urothelial carcinoma metastatic to the retroperitoneal lymph nodes who underwent complete bilateral retroperitoneal lymph node dissection reported 4-year DSS and RFS rates of 36% and 27%. Patients with viable tumor in no more than two lymph nodes and/or excellent response to presurgical systemic chemotherapy showed the best survival rates indicating that a low burden of disease or good response to presurgical chemotherapy may be important in achieving benefit from metastasectomy.²³⁰ Another phase II trial of 70 patients who underwent complete surgical resection of bladder cancer metastases investigated survival, performance status, and quality of life following surgery. This study reported no survival



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

Beyond these prospective data, several retrospective studies have demonstrated a survival advantage following metastasectomy.²³²⁻²³⁵ A retrospective series of 55 patients with bladder primary urothelial carcinoma metastatic to the pelvic or retroperitoneal lymph nodes, who underwent post-chemotherapy lymph node dissection, reported 5-year DSS and RFS rates of 40% and 39%. The best outcomes were associated with radiologic nodal complete response to preoperative chemotherapy and pN0 versus pN+, but were similar for cN1–3 versus cM1.²³⁶ A systematic review and meta-analysis of available studies, including a total of 412 patients with metastatic urothelial carcinoma, reported an improved OS for patients who underwent metastasectomy compared to non-surgical treatment of metastatic lesions. Five-year survival in these studies ranged from 28% to 72%.²³⁷ Another population-based analysis of 497 patients ≥65 years who had at least one metastasectomy for treatment of urothelial carcinoma found that with careful patient selection, metastasectomy is safe and can be associated with long-term survival in this patient population.²³⁸ Conversely, a study that queried the NCDB database from 2004 to 2016 reported no difference in OS between propensity score-matched patients with urothelial carcinoma who had undergone metastasectomy compared with those who had not (HR, 0.94; 95% CI, 0.83–1.07; $P = .38$).²³⁹ This study found that 7% of metastatic urothelial carcinoma patients were treated with metastasectomy and, on average, patients treated with metastasectomy were younger, had greater than cT3 disease, had radical surgery on the primary tumor, and received systemic therapy.

Due to the limited and somewhat conflicting evidence supporting metastasectomy for bladder cancer, and the often extensive and difficult

nature of the surgery, it is important to carefully select appropriate patients for metastasectomy, including consideration of patient performance status, comorbidities, and overall clinical picture.

Molecular/Genomic Testing

The panel recommends that molecular/genomic testing be performed for stages IVA and IVB bladder cancer and may be considered for stage IIIB. This testing should be performed only in laboratories that are certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA-88) as qualified to perform highly complex molecular pathology testing.²⁴⁰ The NCCN Bladder Cancer Panel recommends that molecular/genomic testing be conducted early, ideally at diagnosis of advanced bladder cancer, to facilitate treatment decision-making and to prevent delays in administering later lines of therapy. In addition to determining eligibility for FDA-approved therapies, molecular/genomic testing may be used to screen for clinical trial eligibility.

Based on the FDA approvals for erdafitinib and fam-trastuzumab deruxtecan, molecular testing should include analysis for *FGFR3* genetic alterations and HER2 overexpression by immunohistochemistry (IHC). For certain patients who are ineligible to receive cisplatin, the checkpoint inhibitor atezolizumab may be considered for first-line therapy based on PD-L1 testing results (see *Checkpoint Inhibitor Monotherapy as First-line Treatment*, below).

Genetic alterations are known to be common in bladder cancer, with data from the Cancer Genome Atlas ranking bladder cancer as the third highest mutated cancer.^{241,242} Supporting this, a study that looked at comprehensive genomic profiling of 295 cases of advanced urothelial carcinoma found that 93% of cases had at least one clinically relevant genetic alteration, with a mean of 2.6 clinically relevant genetic alterations per case. The most commonly identified clinically relevant



genetic alterations were *CDKN2A* (34%), *FGFR3* (21%), *PIK3CA* (20%), and *ERBB2* (17%).²⁴³

First-Line Systemic Therapy for Metastatic Disease

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

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

is advised, considering the patient’s current performance status, extent of disease, and specific prior therapy.

Surgery or radiotherapy may be feasible in highly select metastatic cases for patients who show a major partial response in a previously unresectable primary tumor or who have a solitary site of residual disease that is resectable after chemotherapy. If disease is completely resected, two additional cycles of chemotherapy can be considered, depending on patient tolerance.

Platinum-Based Chemotherapy Regimens (ddMVAC or GC)

GC^{245,246} and ddMVAC^{161,187} are commonly used combination chemotherapy regimens that have shown clinical benefit. A large, international, phase III study randomized 405 patients with locally advanced or metastatic disease to GC or standard (28-day) MVAC.¹⁸⁸ At a median follow-up of 19 months, OS and time to progression were similar in the two arms. Fewer toxic deaths were recorded among patients receiving GC compared to MVAC (1% vs. 3%), although this did not reach statistical significance. A 5-year update analysis confirmed that GC was not superior to MVAC in terms of survival (OS, 13.0% vs. 15.3%; PFS, 9.8% vs. 11.3%, respectively).²⁴⁶ Another large, randomized, phase III trial compared ddMVAC to standard (28-day) MVAC.^{161,187} At a median follow-up of 7.3 years, 24.6% of patients were alive in the ddMVAC cohort compared with 13.2% in the standard MVAC cohort. There was one toxic death in each arm, but less overall toxicity was seen in the dose-dense group. From these data, ddMVAC had improved toxicity and efficacy as compared to standard MVAC; therefore, standard (28-day) MVAC is no longer used. Both GC and ddMVAC with growth factor support are category 1 recommendations for metastatic disease.

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



regimens such as ddMVAC or GC. Regimens with lower toxicity profiles are recommended in patients with compromised liver or renal status or serious comorbid conditions. In patients who are not cisplatin-eligible, carboplatin may be substituted for cisplatin in the metastatic setting for cisplatin-ineligible patients such as those with a GFR less than 60 mL/min. A phase II/III study assessed two carboplatin-containing regimens in medically unfit patients (performance status 2).²⁴⁷ The overall response rate (ORR) was 42% for gemcitabine plus carboplatin and 30% for methotrexate, carboplatin, and vinblastine. However, the response rates dropped to 26% and 20%, respectively, with increased toxicity among patients who were both unfit and had renal impairment (GFR <60 mL/min).

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

Pembrolizumab Plus Enfortumab Vedotin-ejfv

A combination of the immune checkpoint inhibitor, pembrolizumab, with the antibody-drug conjugate, enfortumab vedotin, was initially studied in certain cohorts of the phase Ib/II EV103 study, which included cisplatin-ineligible patients with previously untreated, locally advanced or metastatic urothelial cancer.^{248,249} Forty-five patients within cohort A received the combination of enfortumab vedotin and pembrolizumab.²⁴⁸ After a median of nine treatment cycles, the confirmed ORR was 73.3%, with a complete response rate of 15.6%. The most common treatment-related AEs were peripheral sensory neuropathy (55.6%), fatigue (51.1%), and alopecia (48.9%); 64.4% of patients had grade ≥3 treatment-related AEs and one death was classified as treatment-related. Cohort K randomized patients who were ineligible to receive cisplatin to first-line enfortumab vedotin, alone or in combination with

pembrolizumab.²⁴⁹ The primary endpoint of confirmed ORR was 64.5% (95% CI, 52.7%–75.1%) for the combination compared to 45.2% (95% CI, 33.5%–57.3%) for enfortumab vedotin monotherapy. The median DOR was not reached for the combination and was 13.2 months for the monotherapy.

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

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



Gemcitabine, Cisplatin, and Nivolumab

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

Checkpoint Inhibitor Monotherapy as First-Line Treatment

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

The single-arm, phase II KEYNOTE-052 trial evaluated pembrolizumab as a first-line therapy in 370 patients with advanced urothelial carcinoma who were ineligible for cisplatin-based therapy. Data from this study showed an ORR of 24%, with 5% of patients achieving a complete response. Grade 3 or higher treatment-related AEs occurred in 16% of patients treated with pembrolizumab at the time of data cutoff.²⁵² Long-term outcomes of KEYNOTE-052 were similar to the

initial analysis with an ORR of 28.6% and a median OS of 11.3 months.²⁵³ In May 2018, the FDA issued a safety alert for the use of first-line pembrolizumab and atezolizumab, which warned that early reviews of data from two clinical trials (KEYNOTE-361 and IMvigor130) showed decreased survival for patients receiving pembrolizumab or atezolizumab as first-line monotherapy compared to those receiving cisplatin- or carboplatin-based therapy.²⁵⁴ Based on these data, the pembrolizumab prescribing information was initially amended to restrict first-line use to patients who either 1) are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 as measured by a combined positive score (CPS) of at least 10; or 2) are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.²⁵⁵ Subsequently, the first-line indication was further restricted to only patients who were not eligible for any platinum-containing chemotherapy, removing eligibility for first-line pembrolizumab from the PD-L1-high, platinum-eligible population.²⁵⁶ This amended indication was granted a full (regular) approval by the FDA.

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



Data from the two-cohort, multicenter, phase II IMvigor210 trial evaluated atezolizumab in patients with metastatic disease. In cohort 1, atezolizumab was evaluated as a first-line therapy in 119 patients with locally advanced or metastatic urothelial carcinoma who were ineligible for cisplatin. Data from this study showed an ORR of 23% with 9% of patients showing a complete response. Median OS was 15.9 months. Grade 3 or 4 treatment-related AEs occurred in 16% of patients.²⁵⁸ In May 2018, the FDA issued a safety alert for the use of first-line pembrolizumab and atezolizumab, which warned that early reviews of data from two ongoing clinical trials (KEYNOTE-361 and IMvigor130) showed decreased survival for patients receiving pembrolizumab or atezolizumab as first-line monotherapy compared to those receiving cisplatin- or carboplatin-based therapy.²⁵⁴ Based on these data, the atezolizumab prescribing information was initially amended to restrict first-line use to patients who either 1) are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 as measured by PD-L1–stained tumor-infiltrating immune cells covering at least 5% of the tumor area; or 2) are not eligible for any platinum-containing chemotherapy regardless of the level of tumor PD-L1 expression.²⁵⁹

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

one-sided $P = .027$). For the comparison of group B to group C, the median OS was 15.7 and 13.1 months, respectively.

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

Other Non-Platinum Based Chemotherapy Regimens

Taxanes have been shown to be active as treatment options for urothelial bladder cancer.^{262–265} Based on these results, several groups are exploring two- and three-drug combinations using these agents, with and without cisplatin. A randomized phase III trial was conducted to compare GC and GC plus paclitaxel in 626 patients with locally advanced or metastatic urothelial cancer.²⁶⁶ The addition of paclitaxel to GC resulted in higher response rates and a borderline OS advantage, which was not statistically significant in the ITT analysis. Analysis of eligible patients only (92%) resulted in a small (3.2 months) but statistically significant survival advantage in favor of the three-drug regimen ($P = .03$). There was no difference in PFS. The incidence of neutropenic fever was substantially higher with the three-drug combination (13.2% vs. 4.3%; $P < .001$). Panelists feel that the risk of adding paclitaxel outweighs the limited benefit reported from the trial. The alternative regimens, including cisplatin/paclitaxel,²⁶⁷ gemcitabine/paclitaxel,²⁶⁸ cisplatin/gemcitabine/paclitaxel,²⁶⁹ carboplatin/gemcitabine/paclitaxel,²⁷⁰ and



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

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

Avelumab Maintenance Therapy

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

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

Second-Line and Subsequent Therapy for Metastatic Disease

With the recent changes to first-line treatment options for metastatic disease, many providers are moving towards immune checkpoint inhibitor combinations such as enfortumab vedotin plus pembrolizumab as a first-line treatment option. In this evolving paradigm, there is limited

evidence to guide optimal selection of second- and subsequent-line therapies following these new first-line regimens.

The FDA has approved the PD-L1 inhibitor avelumab as well as the PD-1 inhibitors nivolumab and pembrolizumab for the treatment of locally advanced or metastatic urothelial cell carcinoma that has progressed during or after platinum-based chemotherapy or that has progressed within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy, regardless of PD-L1 expression levels. Pembrolizumab has also been approved in combination with enfortumab vedotin for treatment of adult patients with locally advanced or metastatic urothelial carcinoma and as first-line monotherapy for patients who are ineligible to receive a platinum-containing regimen. Avelumab has also been approved as maintenance treatment for patients with locally advanced or metastatic urothelial carcinoma that has not progressed with first-line platinum-containing chemotherapy. See *First-Line Systemic Therapy for Metastatic Disease*, above, for more discussion of these regimens.

Pembrolizumab Monotherapy

Pembrolizumab is a PD-1 inhibitor that has been evaluated as second-line therapy for patients with bladder cancer who previously received platinum-based therapy and subsequently progressed or metastasized.²⁷³ An open-label, randomized, phase III trial compared pembrolizumab to chemotherapy (paclitaxel, docetaxel, or vinflunine) in 542 patients with advanced urothelial carcinoma that recurred or progressed after platinum-based chemotherapy. Data from this trial showed a longer median OS for patients treated with pembrolizumab compared to chemotherapy (10.3 vs. 7.4 months; $P = .002$). In addition, fewer grade 3, 4, or 5 treatment-related AEs occurred in the pembrolizumab-treated patients compared to those treated with chemotherapy (15.0% vs. 49.4%).²⁷⁴ Long-term results (>2 year follow-



up) from this same phase III trial were consistent with earlier reports, with longer 1- and 2- year OS and PFS results for pembrolizumab compared to chemotherapy.²⁷⁵ The median DOR was not reached for pembrolizumab compared to 4.4 months for chemotherapy. Pembrolizumab also showed lower rates of any grade (62% vs. 90.6%) and grade ≥3 AEs (16.5% vs. 50.2%) compared to chemotherapy. Results from this phase 3 trial have led the NCCN Panel to assign pembrolizumab a category 1 recommendation as a second-line therapy.

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

Nivolumab Monotherapy

Data from a phase II trial in patients with locally advanced or metastatic urothelial carcinoma who progressed after at least one platinum-containing regimen reported an ORR in 52 of 265 patients (19.6%; 95% CI, 15.0–24.9) following treatment with nivolumab that was unaffected by PD-1 tumor status.²⁷⁶ Out of the 270 patients enrolled in the study, grade 3 or 4 treatment-related AEs were reported in 18% of patients. Three patient deaths were the result of treatment.²⁷⁶ The median OS was 8.74 months (95% CI, 6.05–not yet reached). Based on PD-L1 expression of less than 1% and 1% or greater, OS was 5.95 to 11.3 months, respectively. These data are comparable to the phase I/II data that reported an ORR of 24.4% (95% CI, 15.3%–35.4%) that was unaffected by PD-1 tumor status. Of the 78 patients enrolled in this study, two experienced grade 5 treatment-related AEs, and grade 3 or 4 treatment-related AEs were reported in 22% of patients.²⁷⁷ An extended follow-up of this same phase I/II study (minimum follow-up of 37.7 months) reported a similar ORR of 25.6% (95% CI, 16.4%–36.8%) for nivolumab monotherapy, with a median DOR of 30.5 months.²⁷⁸

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

Avelumab

Avelumab is another PD-L1 inhibitor currently in clinical trials to evaluate its activity in the treatment of bladder cancer. Results from the phase 1b trial for 44 patients with platinum-refractory disease demonstrated an ORR of 18.2% that consisted of five complete responses and three partial responses following treatment with avelumab. The median PFS was 11.6 weeks and the median OS was 13.7 months with a 54.3% OS rate at 12 months. Grade 3 or 4 treatment-related AEs occurred in 6.8% of patients treated with avelumab.²⁷⁹ A pooled analysis of two expansion cohorts of the same trial reported results for 249 patients with platinum-refractory metastatic urothelial carcinoma or who were ineligible for cisplatin-based chemotherapy. Of the 161 post-platinum patients with at least 6 months of follow-up, the ORR as determined by independent review was 17%, with 6% reporting complete responses and 11% reporting partial responses. Grade 3 or 4 treatment-related AEs occurred in 8% of patients and, likewise, 8% of patients had a serious AE related to treatment with avelumab.²⁸⁰

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

Erdafitinib

Erdafitinib is a pan-FGFR inhibitor that has been evaluated in a global, open-label, phase II trial of 99 patients with a prespecified *FGFR* alteration who had either previously received chemotherapy or who were cisplatin ineligible, chemotherapy naïve. Of these patients, 12% were chemotherapy naïve and 43% had received two or more prior lines



of therapy. The confirmed ORR was 40% (95% CI, 31%–50%), consisting of 3% complete responses and 37% partial responses. Among patients who had previously received immunotherapy, the confirmed ORR was 59%. Median PFS was 5.5 months and the median OS was 13.8 months. Grade ≥ 3 treatment-related AEs were reported in 46% of patients and 13% of patients discontinued treatment due to AEs.²⁸¹ Upon long-term follow-up (median 24.0 months) of the aforementioned study, the investigator-assessed ORR was 40% (95% CI, 30–49) and the safety profile remained similar to the primary analysis.²⁸²

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

to 4.3 months for erdafitinib. Grade 3–4 AEs were reported in 64.7% of patients treated with erdafitinib versus 50.9% treated with pembrolizumab. AEs led to death in 2.9% of patients treated with erdafitinib and 6.9% of those treated with pembrolizumab.

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

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

Enfortumab Vedotin-ejfv Monotherapy

Enfortumab vedotin is a Nectin-4-directed antibody–drug conjugate that was evaluated in a global, phase II, single-arm EV-201 study of 125 patients with metastatic urothelial carcinoma who had previously received both a platinum-containing chemotherapy regimen and a PD-



1/PD-L1 checkpoint inhibitor. The confirmed ORR was 44% (95% CI, 35.1%–53.2%), including 12% complete responses. Similar response rates were seen in subgroups of patients with liver metastases and in those with no response to prior checkpoint inhibitor therapy. The median DOR was 7.6 months. Grade ≥3 treatment-related AEs were reported in 54% of patients and treatment-related AEs led to dose reductions or discontinuation of therapy in 32% and 12% of patients, respectively.²⁸⁶ Subsequently, an open-label, phase III trial of enfortumab vedotin (EV-301) evaluated the therapy in 608 patients with advanced urothelial carcinoma who had previously received both a platinum-containing regimen as well as a checkpoint inhibitor.²⁸⁷ Patients were randomized 1:1 to either enfortumab vedotin or the investigator's choice of chemotherapy (docetaxel, paclitaxel, or vinflunine). After a median follow-up of 11.1 months, OS was longer with enfortumab vedotin than with chemotherapy (12.88 vs. 8.97 months; HR, 0.70; 95% CI, 0.56–0.89; $P = .001$). Median PFS was also longer for enfortumab vedotin (5.55 vs. 3.71 months; HR, 0.62; 95% CI, 0.51–0.75; $P < .001$). The incidence of grade 3 or greater AEs was similar in both groups, 51.4% with enfortumab vedotin compared to 49.8% with chemotherapy.

Enfortumab vedotin has also been evaluated as a second-line treatment option. Cohort 2 of the phase II EV-201 study enrolled 91 patients who had previously been treated with a PD-1 or PD-L1 checkpoint inhibitor therapy and were ineligible for a cisplatin-containing regimen.²⁸⁸ Of the 89 patients who received treatment with enfortumab vedotin, the confirmed ORR was 52% (95% CI, 41%–62%) with 20% of patients having a complete response. Fifty-five percent of patients had grade 3 or higher AEs, with neutropenia, maculopapular rash, and fatigue being the most common. Four deaths were considered to be related to treatment, caused by acute kidney injury, metabolic acidosis, multiple organ dysfunction, and pneumonitis. Data supporting second-line use of

enfortumab vedotin post-platinum or other non-platinum chemotherapy are more limited than post-checkpoint inhibitor, although the phase I EV-101 dose escalation/expansion study included patients with pretreated metastatic urothelial carcinoma who had not previously received a checkpoint inhibitor.²⁸⁹ Of the 23 patients in this category, 43.5% showed a clinical response to enfortumab vedotin treatment. Furthermore, the FDA indication for second-line enfortumab vedotin specifies that the therapy is “indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer who are ineligible for cisplatin-containing chemotherapy and have previously received one or more prior lines of therapy.”²⁹⁰

Sacituzumab Govitecan-hziy

Sacituzumab govitecan is another antibody–drug conjugate composed of an anti-Trop-2 humanized monoclonal antibody coupled to SN-38, the active metabolite of the topoisomerase 1 inhibitor, irinotecan. Sacituzumab govitecan has been evaluated in cohort 1 of TROPY-U-01, a phase II open-label study with 113 patients in cohort 1.²⁹¹ Patients within this cohort had locally advanced, unresectable, or metastatic urothelial carcinoma that had progressed following prior platinum-based and PD-1/PD-L1 checkpoint inhibitor therapy and were treated with sacituzumab govitecan. At a median follow-up of 9.1 months, ORR was 27% (95% CI, 19.5%–36.6%) and 77% of participants showed a decrease in measurable disease. The median DOR was 7.2 months (95% CI, 4.7–8.6 months), median PFS was 5.4 months (95% CI, 3.5–7.2 months), and median OS was 10.9 months (95% CI, 9.0–13.8 months). Key grade greater than or equal to three treatment-related AEs were neutropenia (35%), leukopenia (18%), anemia (14%), diarrhea (10%), and febrile neutropenia (10%). Six percent of patients in the study discontinued treatment as a result of treatment-related AEs.



Fam-trastuzumab deruxtecan-nxki (T-DXd)

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

NCCN Recommendations for Systemic Therapy of Metastatic Disease

Based on the available data, the NCCN Panel recommends that patients with metastatic urothelial carcinoma who are eligible for a cisplatin-containing regimen receive either a cisplatin-based regimen or pembrolizumab in combination with enfortumab vedotin as first-line therapy, with pembrolizumab plus enfortumab vedotin being the preferred option. First-line cisplatin-based regimens include GC, ddMVAC with growth factor support, or gemcitabine-cisplatin plus

nivolumab. All four of these regimens are supported by category 1 data. A patient who is ineligible for cisplatin, but eligible for carboplatin, may receive gemcitabine in combination with carboplatin first-line, although pembrolizumab plus enfortumab vedotin is the preferred option regardless of cisplatin-eligibility. If there is no progression on a first-line platinum-containing chemotherapy, avelumab maintenance therapy is preferred (category 1), unless nivolumab was included in the first-line regimen, in which case nivolumab maintenance therapy should be used.

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

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



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

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

Targeted Therapies Not Recommended

Early results from a phase I/II multicenter study of durvalumab for 61 patients with PD-L1–positive inoperable or metastatic urothelial bladder cancer that progressed following a platinum-based regimen showed that 46.4% of patients who were PD-L1 positive had disease that responded to treatment; no response was seen in patients who were PD-L1 negative.²⁹⁶ A 2017 update on this study (N = 191) showed an ORR of 17.8% and a median OS of 18.2 months, with 55% of patients surviving at 1 year.²⁹⁷ In May 2017, the FDA granted accelerated approval to durvalumab based on these initial results. Subsequently, in February 2021, the makers of durvalumab voluntarily withdrew this indication

based on negative results from the phase III DANUBE trial.²⁹⁸ DANUBE evaluated the use of durvalumab, with or without tremelimumab, compared to chemotherapy for first-line treatment of advanced urothelial carcinoma.²⁹⁹ The trial did not meet its primary endpoints as both durvalumab alone and in combination with tremelimumab failed to improve OS compared to chemotherapy.

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

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

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



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

Non-Urothelial Carcinomas of the Bladder

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

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

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

histology with localized disease regardless of stage.³⁰⁷⁻³¹¹ In addition, a retrospective analysis has shown that neoadjuvant chemotherapy may have a modest benefit for other variant histologies.³¹² In patients with non-urothelial carcinomas of any stage, no data support the use of adjuvant chemotherapy, although the risk for relapse may be high. Some of the general principles of management applicable to urothelial carcinomas are appropriate with minor variations.

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

Upper Tract Urothelial Carcinoma

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



Renal Pelvis Tumors

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

Workup

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

Primary Treatment

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

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

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



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

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

Endoscopic Management of UTUC

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

Mitomycin for pyelocalyceal solution (also called UGN-101 or mitomycin gel) has been FDA-approved for treatment of adult patients with low-grade UTUC.³³⁰ This approval was based on OLYMPUS, a single-arm, multicenter, phase 3 trial of patients with treatment-naïve or recurrent

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

Adjuvant Treatment and Follow-up

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



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

Based on these data, adjuvant therapy should be discussed for patients with pT3–4 or nodal disease. If no platinum-based neoadjuvant treatment was given, adjuvant treatment with a platinum-based regimen should be discussed. Alternatively, adjuvant nivolumab may be considered (category 2B). If platinum-based neoadjuvant therapy was given and the disease was determined to be ypT2–4 or ypN+ after surgery, adjuvant nivolumab may be considered, although adjuvant therapy would be most appropriate for patients who value the

opportunity to delay recurrence, and who accept the risk of side effects, even if the chance for cure was not improved in this situation. Follow-up should be the same as pT0/pT1 disease with the addition of chest imaging and a stronger recommendation for cytology.

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

Urothelial Carcinoma of the Ureter

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



Workup

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

Primary Treatment

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

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

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

lymphadenectomy. Neoadjuvant chemotherapy can be considered in select patients.

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

Follow-up

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

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

Urothelial Carcinomas of the Prostate

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



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

Workup

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

Primary Treatment

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

patients with only ductal and acini invasion. Local recurrences in patients undergoing TURP and BCG therapy are treated with cystoprostatectomy with or without urethrectomy.

Primary Carcinoma of the Urethra

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

Workup

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

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

Treatment

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



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

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

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

receiving chemoradiation alone (54%). If systemic therapy is used, the choice of regimen should be based on histology.

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

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

Summary

Urothelial tumors represent a spectrum of diseases with a range of prognoses. After a tumor is diagnosed anywhere within the urothelial tract, the patient remains at risk for developing a new lesion at the same or a different location and with a similar or more advanced stage. For patients with non-muscle invasive disease, continued monitoring for recurrence is an essential part of management, because most



recurrences are non-muscle invasive and can be treated endoscopically. Within each category of disease, more refined methods to determine prognosis and guide management, based on molecular staging, are under development with the goal of optimizing each patient's likelihood of cure and chance for organ preservation.

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

Within the category of metastatic disease, several new agents and combination regimens have been studied and seem to be superior to those that were previously considered standard therapies. In particular, immune checkpoint inhibitors, antibody-drug conjugates, and targeted therapies have emerged as new options for the treatment of metastatic bladder cancer. Experts surmise that the treatment of urothelial tumors will evolve rapidly over the next few years, with improved outcomes across all disease stages.

Discussion
Update in
progress

**References**

1. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. *CA Cancer J Clin* 2024;74:12-49. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/38230766>.
2. Cancer Stat Facts: Bladder Cancer. NIH NCI: Surveillance, Epidemiology, and End Results Program; 2023. Available at: <https://seer.cancer.gov/statfacts/html/urinb.html>. Accessed February 8, 2024.
3. DeGeorge KC, Holt HR, Hodges SC. Bladder cancer: Diagnosis and treatment. *Am Fam Physician* 2017;96:507-514. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29094888>.
4. Xu Y, Huo R, Chen X, Yu X. Diabetes mellitus and the risk of bladder cancer: A PRISMA-compliant meta-analysis of cohort studies. *Medicine (Baltimore)* 2017;96:e8588. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29145273>.
5. Antoni S, Ferlay J, Soerjomataram I, et al. Bladder cancer incidence and mortality: A global overview and recent trends. *Eur Urol* 2017;71:96-108. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27370177>.
6. Kiriluk KJ, Prasad SM, Patel AR, et al. Bladder cancer risk from occupational and environmental exposures. *Urol Oncol* 2012;30:199-211. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22385990>.
7. Hu J, Chen JB, Cui Y, et al. Association of metformin intake with bladder cancer risk and oncologic outcomes in type 2 diabetes mellitus patients: A systematic review and meta-analysis. *Medicine (Baltimore)* 2018;97:e11596. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30045293>.
8. Carlo MI, Ravichandran V, Srinivasan P, et al. Cancer susceptibility mutations in patients with urothelial malignancies. *J Clin Oncol* 2020;38:406-414. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31794323>.
9. PubMed Overview. Available at: <https://pubmed.ncbi.nlm.nih.gov/about/>. Accessed April 29, 2024.
10. Freedman-Cass DA, Fischer T, Alpert AB, et al. The value and process of inclusion: Using sensitive, respectful, and inclusive language and images in NCCN content. *J Natl Compr Canc Netw* 2023;21:434-441. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/37156485>.
11. Welty CJ, Wright JL, Hotaling JM, et al. Persistence of urothelial carcinoma of the bladder risk among former smokers: results from a contemporary, prospective cohort study. *Urol Oncol* 2014;32:25 e21-25. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23506963>.
12. van der Post RS, Kiemeny LA, Ligtenberg MJ, et al. Risk of urothelial bladder cancer in Lynch syndrome is increased, in particular among MSH2 mutation carriers. *J Med Genet* 2010;47:464-470. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20591884>.
13. Messing EM, Tangen CM, Lerner SP, et al. Effect of intravesical instillation of gemcitabine vs saline immediately following resection of suspected low-grade non-muscle-invasive bladder cancer on tumor recurrence: SWOG S0337 randomized clinical trial. *JAMA* 2018;319:1880-1888. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29801011>.
14. Bosschiet J, Nieuwenhuijzen JA, van Ginkel T, et al. Value of an immediate intravesical instillation of mitomycin C in patients with non-muscle-invasive bladder cancer: A prospective multicentre randomised study in 2243 patients. *Eur Urol* 2018;73:226-232. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28705539>.
15. Sylvester RJ, Oosterlinck W, Holmang S, et al. Systematic review and individual patient data meta-analysis of randomized trials comparing a single immediate instillation of chemotherapy after transurethral resection with transurethral resection alone in patients with stage pTa-pT1 urothelial carcinoma of the bladder: Which patients benefit from the instillation? *Eur Urol* 2016;69:231-244. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26091833>.



16. Fujimoto N, Harada S, Terado M, et al. Multiple biopsies of normal-looking urothelium in patients with superficial bladder cancer: Are they necessary? *Int J Urol* 2003;10:631-635. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/14633065>.

17. Gudjonsson S, Blackberg M, Chebil G, et al. The value of bladder mapping and prostatic urethra biopsies for detection of carcinoma in situ (CIS). *BJU Int* 2012;110:E41-45. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22035276>.

18. Herr HW, Al-Ahmadie H, Dalbagni G, Reuter VE. Bladder cancer in cystoscopically normal-appearing mucosa: a case of mistaken identity? *BJU Int* 2010;106:1499-1501. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20346034>.

19. Matsushima M, Kikuchi E, Hasegawa M, et al. Clinical impact of bladder biopsies with TUR-BT according to cytology results in patients with bladder cancer: a case control study. *BMC Urol* 2010;10:12. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20591189>.

20. Amin MB, Edge SB, Greene F, et al., eds. *AJCC Cancer Staging Manual*, 8th ed. New York: Springer International Publishing; 2017.

21. Pasin E, Josephson DY, Mitra AP, et al. Superficial bladder cancer: an update on etiology, molecular development, classification, and natural history. *Rev Urol* 2008;10:31-43. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18470273>.

22. Brimo F, Wu C, Zeizafoun N, et al. Prognostic factors in T1 bladder urothelial carcinoma: the value of recording millimetric depth of invasion, diameter of invasive carcinoma, and muscularis mucosa invasion. *Hum Pathol* 2013;44:95-102. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22939956>.

23. Hu Z, Mudaliar K, Quek ML, et al. Measuring the dimension of invasive component in pT1 urothelial carcinoma in transurethral resection specimens can predict time to recurrence. *Ann Diagn Pathol* 2014;18:49-52. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24370460>.

24. van Rhijn BW, van der Kwast TH, Alkhateeb SS, et al. A new and highly prognostic system to discern T1 bladder cancer substage. *Eur Urol* 2012;61:378-384. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22036775>.

25. Sylvester RJ, van der Meijden AP, Oosterlinck W, et al. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. *Eur Urol* 2006;49:466-465; discussion 475-467. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16442208>.

26. Edge SB, Byrd DR, Compton CC, et al. *AJCC Cancer Staging Manual*, 7th ed. New York: Springer; 2010:1-646.

27. Schmidbauer J, Witjes F, Schmeller N, et al. Improved detection of urothelial carcinoma in situ with hexaminolevulinate fluorescence cystoscopy. *J Urol* 2004;171:135-138. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/14665861>.

28. Jocham D, Witjes F, Wagner S, et al. Improved detection and treatment of bladder cancer using hexaminolevulinate imaging: a prospective, phase III multicenter study. *J Urol* 2005;174:862-866; discussion 866. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16093971>.

29. Grossman HB, Gomella L, Fradet Y, et al. A phase III, multicenter comparison of hexaminolevulinate fluorescence cystoscopy and white light cystoscopy for the detection of superficial papillary lesions in patients with bladder cancer. *J Urol* 2007;178:62-67. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17499283>.

30. Fradet Y, Grossman HB, Gomella L, et al. A comparison of hexaminolevulinate fluorescence cystoscopy and white light cystoscopy for the detection of carcinoma in situ in patients with bladder cancer: a phase III, multicenter study. *J Urol* 2007;178:68-73; discussion 73. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17499291>.



31. Stenzl A, Burger M, Fradet Y, et al. Hexaminolevulinate guided fluorescence cystoscopy reduces recurrence in patients with nonmuscle invasive bladder cancer. *J Urol* 2010;184:1907-1913. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20850152>.
32. Hermann GG, Mogensen K, Carlsson S, et al. Fluorescence-guided transurethral resection of bladder tumours reduces bladder tumour recurrence due to less residual tumour tissue in Ta/T1 patients: a randomized two-centre study. *BJU Int* 2011;108:E297-303. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21414125>.
33. Yuan H, Qiu J, Liu L, et al. Therapeutic outcome of fluorescence cystoscopy guided transurethral resection in patients with non-muscle invasive bladder cancer: a meta-analysis of randomized controlled trials. *PLoS One* 2013;8:e74142. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24058522>.
34. Burger M, Grossman HB, Droller M, et al. Photodynamic diagnosis of non-muscle-invasive bladder cancer with hexaminolevulinate cystoscopy: a meta-analysis of detection and recurrence based on raw data. *Eur Urol* 2013;64:846-854. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23602406>.
35. Rink M, Babjuk M, Catto JW, et al. Hexyl aminolevulinate-guided fluorescence cystoscopy in the diagnosis and follow-up of patients with non-muscle-invasive bladder cancer: a critical review of the current literature. *Eur Urol* 2013;64:624-638. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23906669>.
36. Kamat AM, Cookson M, Witjes JA, et al. The impact of blue light cystoscopy with hexaminolevulinate (HAL) on progression of bladder cancer - A new analysis. *Bladder Cancer* 2016;2:273-278. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27376146>.
37. Cauberg EC, Kloen S, Visser M, et al. Narrow band imaging cystoscopy improves the detection of non-muscle-invasive bladder cancer. *Urology* 2010;76:658-663. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20223505>.
38. Chen G, Wang B, Li H, et al. Applying narrow-band imaging in complement with white-light imaging cystoscopy in the detection of urothelial carcinoma of the bladder. *Urol Oncol* 2013;31:475-479. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22079940>.
39. Geavlete B, Jecu M, Multescu R, Geavlete P. Narrow-band imaging cystoscopy in non-muscle-invasive bladder cancer: a prospective comparison to the standard approach. *Ther Adv Urol* 2012;4:211-217. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23024703>.
40. Shen YJ, Zhu YP, Ye DW, et al. Narrow-band imaging flexible cystoscopy in the detection of primary non-muscle invasive bladder cancer: a "second look" matters? *Int Urol Nephrol* 2012;44:451-457. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21792663>.
41. Tatsugami K, Kuroiwa K, Kamoto T, et al. Evaluation of narrow-band imaging as a complementary method for the detection of bladder cancer. *J Endourol* 2010;24:1807-1811. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20707727>.
42. Naselli A, Introini C, Timossi L, et al. A randomized prospective trial to assess the impact of transurethral resection in narrow band imaging modality on non-muscle-invasive bladder cancer recurrence. *Eur Urol* 2012;61:908-913. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22280855>.
43. Naito S, Algaba F, Babjuk M, et al. The Clinical Research Office of the Endourological Society (CROES) multicentre randomised trial of narrow band imaging-assisted transurethral resection of bladder tumour (TURBT) versus conventional white light imaging-assisted TURBT in primary non-muscle-invasive bladder cancer patients: Trial protocol and 1-year results. *Eur Urol* 2016;70:506-515. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27117749>.
44. Xiong Y, Li J, Ma S, et al. A meta-analysis of narrow band imaging for the diagnosis and therapeutic outcome of non-muscle invasive bladder cancer. *PLoS One* 2017;12:e0170819. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28192481>.



45. Kang W, Cui Z, Chen Q, et al. Narrow band imaging-assisted transurethral resection reduces the recurrence risk of non-muscle invasive bladder cancer: A systematic review and meta-analysis. *Oncotarget* 2017;8:23880-23890. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27823975>.
46. Herr HW, Donat SM. A comparison of white-light cystoscopy and narrow-band imaging cystoscopy to detect bladder tumour recurrences. *BJU Int* 2008;102:1111-1114. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18778359>.
47. Raspollini MR, Comperat EM, Lopez-Beltran A, et al. News in the classification of WHO 2022 bladder tumors. *Pathologica* 2022;115:32-40. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/36704871>.
48. Moch H, Amin MB, Berney DM, et al. The 2022 World Health Organization Classification of Tumours of the Urinary System and Male Genital Organs-Part A: Renal, Penile, and Testicular Tumours. *Eur Urol* 2022;82:458-468. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35853783>.
49. Netto GJ, Amin MB, Berney DM, et al. The 2022 World Health Organization Classification of Tumors of the Urinary System and Male Genital Organs-Part B: Prostate and Urinary Tract Tumors. *Eur Urol* 2022;82:469-482. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35965208>.
50. Kardoust Parizi M, Margulis V, Compe Rat E, Shariat SF. The value and limitations of urothelial bladder carcinoma molecular classifications to predict oncological outcomes and cancer treatment response: A systematic review and meta-analysis. *Urol Oncol* 2021;39:15-33. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32900624>.
51. Mori K, Abufaraj M, Mostafaei H, et al. A systematic review and meta-analysis of variant histology in urothelial carcinoma of the bladder treated with radical cystectomy. *J Urol* 2020;204:1129-1140. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32716694>.
52. Veskimäe E, Espinos EL, Bruins HM, et al. What is the prognostic and clinical importance of urothelial and nonurothelial histological variants of bladder cancer in predicting oncological outcomes in patients with muscle-invasive and metastatic bladder cancer? A european association of urology muscle invasive and metastatic bladder cancer guidelines panel systematic review. *Eur Urol Oncol* 2019;2:625-642. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31601522>.
53. Chalasani V, Chin JL, Izawa JI. Histologic variants of urothelial bladder cancer and nonurothelial histology in bladder cancer. *Can Urol Assoc J* 2009;3:S193-198. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20019984>.
54. Siefker-Radtke A. Urachal adenocarcinoma: a clinician's guide for treatment. *Semin Oncol* 2012;39:619-624. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23040259>.
55. Jones G, Cleves A, Wilt TJ, et al. Intravesical gemcitabine for non-muscle invasive bladder cancer. *Cochrane Database Syst Rev* 2012;1:CD009294. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22259002>.
56. Sylvester RJ, van der Meijden AP, Witjes JA, Kurth K. Bacillus calmette-guerin versus chemotherapy for the intravesical treatment of patients with carcinoma in situ of the bladder: a meta-analysis of the published results of randomized clinical trials. *J Urol* 2005;174:86-91; discussion 91-82. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15947584>.
57. Han MA, Maisch P, Jung JH, et al. Intravesical gemcitabine for non-muscle invasive bladder cancer. *Cochrane Database Syst Rev* 2021;6:CD009294. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34125951>.
58. Li R, Li Y, Song J, et al. Intravesical gemcitabine versus mitomycin for non-muscle invasive bladder cancer: a systematic review and meta-analysis of randomized controlled trial. *BMC Urol* 2020;20:97. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32660456>.



59. Morales A, Eidinger D, Bruce AW. Intracavitary Bacillus Calmette-Guerin in the treatment of superficial bladder tumors. *J Urol* 1976;116:180-183. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/820877>.
60. Bohle A, Jocham D, Bock PR. Intravesical bacillus Calmette-Guerin versus mitomycin C for superficial bladder cancer: a formal meta-analysis of comparative studies on recurrence and toxicity. *J Urol* 2003;169:90-95. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12478111>.
61. Han RF, Pan JG. Can intravesical bacillus Calmette-Guerin reduce recurrence in patients with superficial bladder cancer? A meta-analysis of randomized trials. *Urology* 2006;67:1216-1223. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16765182>.
62. Shelley MD, Kynaston H, Court J, et al. A systematic review of intravesical bacillus Calmette-Guerin plus transurethral resection vs transurethral resection alone in Ta and T1 bladder cancer. *BJU Int* 2001;88:209-216. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11488731>.
63. Shelley MD, Wilt TJ, Court J, et al. Intravesical bacillus Calmette-Guerin is superior to mitomycin C in reducing tumour recurrence in high-risk superficial bladder cancer: a meta-analysis of randomized trials. *BJU Int* 2004;93:485-490. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15008714>.
64. Malmstrom PU, Sylvester RJ, Crawford DE, et al. An individual patient data meta-analysis of the long-term outcome of randomised studies comparing intravesical mitomycin C versus bacillus Calmette-Guerin for non-muscle-invasive bladder cancer. *Eur Urol* 2009;56:247-256. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19409692>.
65. Spencer BA, McBride RB, Hershman DL, et al. Adjuvant intravesical bacillus calmette-guerin therapy and survival among elderly patients with non-muscle-invasive bladder cancer. *J Oncol Pract* 2013;9:92-98. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23814517>.
66. Jarvinen R, Kaasinen E, Sankila A, et al. Long-term efficacy of maintenance bacillus Calmette-Guerin versus maintenance mitomycin C instillation therapy in frequently recurrent TaT1 tumours without carcinoma in situ: a subgroup analysis of the prospective, randomised FinnBladder I study with a 20-year follow-up. *Eur Urol* 2009;56:260-265. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19395154>.
67. Schmidt S, Kunath F, Coles B, et al. Intravesical Bacillus Calmette-Guerin versus mitomycin C for Ta and T1 bladder cancer. *Cochrane Database Syst Rev* 2020;1:CD011935. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31912907>.
68. Gontero P, Oderda M, Mehnert A, et al. The impact of intravesical gemcitabine and 1/3 dose Bacillus Calmette-Guerin instillation therapy on the quality of life in patients with nonmuscle invasive bladder cancer: results of a prospective, randomized, phase II trial. *J Urol* 2013;190:857-862. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23545101>.
69. Sylvester RJ, Brausi MA, Kirkels WJ, et al. Long-term efficacy results of EORTC genito-urinary group randomized phase 3 study 30911 comparing intravesical instillations of epirubicin, bacillus Calmette-Guerin, and bacillus Calmette-Guerin plus isoniazid in patients with intermediate- and high-risk stage Ta T1 urothelial carcinoma of the bladder. *Eur Urol* 2010;57:766-773. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20034729>.
70. Duchek M, Johansson R, Jahnson S, et al. Bacillus Calmette-Guerin is superior to a combination of epirubicin and interferon-alpha2b in the intravesical treatment of patients with stage T1 urinary bladder cancer. A prospective, randomized, Nordic study. *Eur Urol* 2010;57:25-31. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19819617>.
71. Lamm DL, Blumenstein BA, Crissman JD, et al. Maintenance bacillus Calmette-Guerin immunotherapy for recurrent TA, T1 and carcinoma in situ transitional cell carcinoma of the bladder: a randomized Southwest Oncology Group Study. *J Urol* 2000;163:1124-1129. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10737480>.



72. Ehdaie B, Sylvester R, Herr HW. Maintenance bacillus Calmette-Guerin treatment of non-muscle-invasive bladder cancer: a critical evaluation of the evidence. *Eur Urol* 2013;64:579-585. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23711538>.

73. Oddens J, Brausi M, Sylvester R, et al. Final results of an EORTC-GU cancers group randomized study of maintenance bacillus Calmette-Guerin in intermediate- and high-risk Ta, T1 papillary carcinoma of the urinary bladder: one-third dose versus full dose and 1 year versus 3 years of maintenance. *Eur Urol* 2013;63:462-472. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23141049>.

74. Bohle A, Bock PR. Intravesical bacille Calmette-Guerin versus mitomycin C in superficial bladder cancer: formal meta-analysis of comparative studies on tumor progression. *Urology* 2004;63:682-686; discussion 686-687. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15072879>.

75. Sylvester RJ, van der MA, Lamm DL. Intravesical bacillus Calmette-Guerin reduces the risk of progression in patients with superficial bladder cancer: a meta-analysis of the published results of randomized clinical trials. *J Urol* 2002;168:1964-1970. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12394686>.

76. U.S. Food and Drug Administration. Prescribing Information. BCG live, for intravesical use. 2009. Available at: <http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM163039.pdf>. Accessed February 8, 2024.

77. van der Meijden AP, Sylvester RJ, Oosterlinck W, et al. Maintenance Bacillus Calmette-Guerin for Ta T1 bladder tumors is not associated with increased toxicity: results from a European Organisation for Research and Treatment of Cancer Genito-Urinary Group Phase III Trial. *Eur Urol* 2003;44:429-434. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/14499676>.

78. Colombel M, Saint F, Chopin D, et al. The effect of ofloxacin on bacillus calmette-guerin induced toxicity in patients with superficial bladder cancer: results of a randomized, prospective, double-blind,

placebo controlled, multicenter study. *J Urol* 2006;176:935-939. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16890660>.

79. Damiano R, De Sio M, Quarto G, et al. Short-term administration of prulifloxacin in patients with nonmuscle-invasive bladder cancer: an effective option for the prevention of bacillus Calmette-Guerin-induced toxicity? *BJU Int* 2009;104:633-639. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19298412>.

80. Brausi M, Oddens J, Sylvester R, et al. Side effects of Bacillus Calmette-Guerin (BCG) in the treatment of intermediate- and high-risk Ta, T1 papillary carcinoma of the bladder: results of the EORTC genito-urinary cancers group randomised phase 3 study comparing one-third dose with full dose and 1 year with 3 years of maintenance BCG. *Eur Urol* 2014;65:69-76. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23910233>.

81. Lebre T, Bohin D, Kassardjian Z, et al. Recurrence, progression and success in stage Ta grade 3 bladder tumors treated with low dose bacillus Calmette-Guerin instillations. *J Urol* 2000;163:63-67. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10604315>.

82. Martinez-Pineiro JA, Martinez-Pineiro L, Solsona E, et al. Has a 3-fold decreased dose of bacillus Calmette-Guerin the same efficacy against recurrences and progression of T1G3 and Tis bladder tumors than the standard dose? Results of a prospective randomized trial. *J Urol* 2005;174:1242-1247. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16145378>.

83. Mugiya S, Ozono S, Nagata M, et al. Long-term outcome of a low-dose intravesical bacillus Calmette-Guerin therapy for carcinoma in situ of the bladder: results after six successive instillations of 40 mg BCG. *Jpn J Clin Oncol* 2005;35:395-399. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15976065>.

84. Grimm MO, van der Heijden AG, Colombel M, et al. Treatment of high-grade non-muscle-invasive bladder carcinoma by standard number and dose of BCG instillations versus reduced number and standard dose of BCG instillations: Results of the European Association of



Urology Research Foundation randomised phase III clinical trial "NIMBUS". Eur Urol 2020;78:690-698. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32446864>.

85. Bandari J, Maganty A, MacLeod LC, Davies BJ. Manufacturing and the market: Rationalizing the shortage of bacillus Calmette-Guerin. Eur Urol Focus 2018;4:481-484. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30005997>.

86. BCG Shortage Notice. 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); 2019. Available at: <https://www.auanet.org/bcg-shortage-notice>. Accessed February 8, 2024.

87. Di Lorenzo G, Perdona S, Damiano R, et al. Gemcitabine versus bacille Calmette-Guerin after initial bacille Calmette-Guerin failure in non-muscle-invasive bladder cancer: a multicenter prospective randomized trial. Cancer 2010;116:1893-1900. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20162706>.

88. Friedrich MG, Pichlmeier U, Schwaibold H, et al. Long-term intravesical adjuvant chemotherapy further reduces recurrence rate compared with short-term intravesical chemotherapy and short-term therapy with Bacillus Calmette-Guerin (BCG) in patients with non-muscle-invasive bladder carcinoma. Eur Urol 2007;52:1123-1129. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17383080>.

89. Chou R, Selph S, Buckley DI, et al. Intravesical therapy for the treatment of nonmuscle invasive bladder cancer: A systematic review and meta-analysis. J Urol 2017;197:1189-1199. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28027868>.

90. van der Meijden AP, Brausi M, Zambon V, et al. Intravesical instillation of epirubicin, bacillus Calmette-Guerin and bacillus Calmette-Guerin plus isoniazid for intermediate and high risk Ta, T1 papillary carcinoma of the bladder: a European Organization for Research and

Treatment of Cancer genito-urinary group randomized phase III trial. J Urol 2001;166:476-481. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11458050>.

91. Steinberg G, Bahnson R, Brosman S, et al. Efficacy and safety of valrubicin for the treatment of Bacillus Calmette-Guerin refractory carcinoma in situ of the bladder. The Valrubicin Study Group. J Urol 2000;163:761-767. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10687972>.

92. Barlow LJ, McKiernan JM, Benson MC. The novel use of intravesical docetaxel for the treatment of non-muscle invasive bladder cancer refractory to BCG therapy: a single institution experience. World J Urol 2009;27:331-335. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19214528>.

93. Milbar N, Kates M, Chappidi MR, et al. Oncological outcomes of sequential intravesical gemcitabine and docetaxel in patients with non-muscle invasive bladder cancer. Bladder Cancer 2017;3:293-303. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29152553>.

94. Breyer BN, Whitson JM, Carroll PR, Konety BR. Sequential intravesical gemcitabine and mitomycin C chemotherapy regimen in patients with non-muscle invasive bladder cancer. Urol Oncol 2010;28:510-514. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19171491>.

95. Klaassen Z, Kamat AM, Kassouf W, et al. Treatment Strategy for Newly Diagnosed T1 High-grade Bladder Urothelial Carcinoma: New Insights and Updated Recommendations. Eur Urol 2018;74:597-608. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30017405>.

96. Pfister C, Kerkeni W, Rigaud J, et al. Efficacy and tolerance of one-third full dose bacillus Calmette-Guerin maintenance therapy every 3 months or 6 months: two-year results of URO-BCG-4 multicenter study. Int J Urol 2015;22:53-60. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25256813>.



NCCN Guidelines Version 1.2025

Bladder Cancer

97. Yokomizo A, Kanimoto Y, Okamura T, et al. Randomized controlled study of the efficacy, safety and quality of life with low dose bacillus Calmette-Guerin instillation therapy for nonmuscle invasive bladder cancer. *J Urol* 2016;195:41-46. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26307162>.

98. Boorjian SA, Alemozaffar M, Konety BR, et al. Intravesical nadofaragene firadenovec gene therapy for BCG-unresponsive non-muscle-invasive bladder cancer: a single-arm, open-label, repeat-dose clinical trial. *Lancet Oncol* 2021;22:107-117. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33253641>.

99. Schuckman AK, Lotan Y, Boorjian SA, et al. Efficacy of intravesical nadofaragene firadenovec for patients with carcinoma in situ (CIS), BCG-unresponsive non-muscle invasive bladder cancer (NMIBC): Longer-term follow-up from the phase III trial [abstract]. *Journal of Urology* 2021;206:e296-e296. Available at: <https://www.auajournals.org/doi/abs/10.1097/JU.0000000000002001.01>.

100. Lotan Y, Schuckman AK, Boorjian SA, et al. Phase III trial of intravesical nadofaragene firadenovec in patients with high-grade, BCG-unresponsive, non-muscle invasive bladder cancer: Two year follow-up in the Ta/T1 cohort [abstract]. *Journal of Urology* 2021;206:e296-e296. Available at: <https://www.auajournals.org/doi/abs/10.1097/JU.0000000000002001.02>.

101. Chamie K, Chang SS, Kramolowsky E, et al. IL-15 superagonist NAI in BCG-unresponsive non-muscle-invasive bladder cancer. *NEJM Evid* 2023;2:EVIDo2200167. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/38320011>.

102. Chamie K, Chang SS, Kramolowsky EV, et al. Quality of life in the phase 2/3 trial of N-803 plus bacillus Calmette-Guerin in bacillus Calmette-Guerin-unresponsive nonmuscle-invasive bladder cancer. *Urol Pract* 2024;11:367-375. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/38226931>.

103. Balar AV, Kamat AM, Kulkarni GS, et al. Pembrolizumab monotherapy for the treatment of high-risk non-muscle-invasive bladder cancer unresponsive to BCG (KEYNOTE-057): an open-label, single-arm, multicentre, phase 2 study. *Lancet Oncol* 2021;22:919-930. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34051177>.

104. Necchi A, Roumigué M, Esen AA, et al. Pembrolizumab (pembro) monotherapy for patients (pts) with high-risk non-muscle-invasive bladder cancer (HR NMIBC) unresponsive to bacillus Calmette-Guérin (BCG): Results from cohort B of the phase 2 KEYNOTE-057 trial [abstract]. *Journal of Clinical Oncology* 2023;41:LBA442-LBA442. Available at: https://ascopubs.org/doi/abs/10.1200/JCO.2023.41.6_suppl.LBA442.

105. Chang SS, Boorjian SA, Chou R, et al. Diagnosis and treatment of non-muscle invasive bladder cancer: AUA/suo guideline. *J Urol* 2016;196:1021-1029. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27317986>.

106. Ritch CR, Velasquez MC, Kwon D, et al. Use and validation of the AUA/SUO risk grouping for nonmuscle invasive bladder cancer in a contemporary cohort. *J Urol* 2020;203:505-511. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31609178>.

107. Ramirez-Backhaus M, Dominguez-Escrig J, Collado A, et al. Restaging transurethral resection of bladder tumor for high-risk stage Ta and T1 bladder cancer. *Curr Urol Rep* 2012;13:109-114. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22367558>.

108. Divrik RT, Yildirim U, Zorlu F, Ozen H. The effect of repeat transurethral resection on recurrence and progression rates in patients with T1 tumors of the bladder who received intravesical mitomycin: a prospective, randomized clinical trial. *J Urol* 2006;175:1641-1644. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16600720>.

109. Eroglu A, Ekin RG, Koc G, Divrik RT. The prognostic value of routine second transurethral resection in patients with newly diagnosed stage pT1 non-muscle-invasive bladder cancer: results from



randomized 10-year extension trial. *Int J Clin Oncol* 2020;25:698-704. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31760524>.

110. Grimm MO, Steinhoff C, Simon X, et al. Effect of routine repeat transurethral resection for superficial bladder cancer: a long-term observational study. *J Urol* 2003;170:433-437. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12853793>.

111. Herr HW. The value of a second transurethral resection in evaluating patients with bladder tumors. *J Urol* 1999;162:74-76. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10379743>.

112. Petrelli F, Giannatempo P, Maccagnano C, et al. Active surveillance for non-muscle invasive bladder cancer: A systematic review and pooled-analysis. *Cancer Treat Res Commun* 2021;27:100369. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33838570>.

113. Laukhtina E, Abufaraj M, Al-Ani A, et al. Intravesical therapy in patients with intermediate-risk non-muscle-invasive bladder cancer: A systematic review and network meta-analysis of disease recurrence. *Eur Urol Focus* 2021. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33762203>.

114. Huncharek M, McGarry R, Kupelnick B. Impact of intravesical chemotherapy on recurrence rate of recurrent superficial transitional cell carcinoma of the bladder: results of a meta-analysis. *Anticancer Res* 2001;21:765-769. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11299841>.

115. Huncharek M, Geschwind JF, Witherspoon B, et al. Intravesical chemotherapy prophylaxis in primary superficial bladder cancer: a meta-analysis of 3703 patients from 11 randomized trials. *J Clin Epidemiol* 2000;53:676-680. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10941943>.

116. Mirabal JR, Taylor JA, Lerner SP. CIS of the bladder: Significance and implications for therapy. *Bladder Cancer* 2019;5:193-204. Available at: <https://content.iospress.com/articles/bladder-cancer/blc190236>.

117. Herr HW, Sogani PC. Does early cystectomy improve the survival of patients with high risk superficial bladder tumors? *J Urol* 2001;166:1296-1299. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11547061>.

118. Mari A, Kimura S, Foerster B, et al. A systematic review and meta-analysis of the impact of lymphovascular invasion in bladder cancer transurethral resection specimens. *BJU Int* 2019;123:11-21. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29807387>.

119. Catto JWF, Gordon K, Collinson M, et al. Radical cystectomy against intravesical BCG for high-risk high-grade nonmuscle invasive bladder cancer: Results from the randomized controlled BRAVO-Feasibility study. *J Clin Oncol* 2021;39:202-214. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33332191>.

120. Chou R, Gore JL, Buckley D, et al. Urinary Biomarkers for diagnosis of bladder cancer: A systematic review and meta-analysis. *Ann Intern Med* 2015;163:922-931. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26501851>.

121. Aoun F, Kourie HR, El Rassy E, van Velthoven R. Bladder and vaginal transitional cell carcinoma: A case report. *Oncol Lett* 2016;12:2181-2183. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27602160>.

122. Koyanagi Y, Kubo C, Nagata S, et al. Detection of pagetoid urothelial intraepithelial neoplasia extending to the vagina by cervical screening cytology: a case report with renewed immunochemical summary. *Diagn Pathol* 2019;14:9. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30711015>.

123. Reyes MC, Park KJ, Lin O, et al. Urothelial carcinoma involving the gynecologic tract: a morphologic and immunohistochemical study of 6 cases. *Am J Surg Pathol* 2012;36:1058-1065. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22510759>.



NCCN Guidelines Version 1.2025

Bladder Cancer

124. Schwalb DM, Herr HW, Fair WR. The management of clinically unconfirmed positive urinary cytology. *J Urol* 1993;150:1751-1756. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/8230495>.

125. Skinner EC, Goldman B, Sakr WA, et al. SWOG S0353: Phase II trial of intravesical gemcitabine in patients with nonmuscle invasive bladder cancer and recurrence after 2 prior courses of intravesical bacillus Calmette-Guerin. *J Urol* 2013;190:1200-1204. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23597452>.

126. Raj GV, Herr H, Serio AM, et al. Treatment paradigm shift may improve survival of patients with high risk superficial bladder cancer. *J Urol* 2007;177:1283-1286; discussion 1286. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17382713>.

127. Gofrit ON, Pode D, Lazar A, et al. Watchful waiting policy in recurrent Ta G1 bladder tumors. *Eur Urol* 2006;49:303-306; discussion 306-307. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16413659>.

128. Soloway MS, Bruck DS, Kim SS. Expectant management of small, recurrent, noninvasive papillary bladder tumors. *J Urol* 2003;170:438-441. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12853794>.

129. Li R, Sundi D, Zhang J, et al. Systematic review of the therapeutic efficacy of bladder-preserving treatments for non-muscle-invasive bladder cancer following intravesical bacillus Calmette-Guerin. *Eur Urol* 2020;78:387-399. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32143924>.

130. Raj GV, Iasonos A, Herr H, Donat SM. Formulas calculating creatinine clearance are inadequate for determining eligibility for Cisplatin-based chemotherapy in bladder cancer. *J Clin Oncol* 2006;24:3095-3100. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16809735>.

131. Kang EY, Staples CA, McGuinness G, et al. Detection and differential diagnosis of pulmonary infections and tumors in patients with AIDS: value of chest radiography versus CT. *AJR Am J Roentgenol*

1996;166:15-19. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/8571866>.

132. Ebner L, Butikofer Y, Ott D, et al. Lung nodule detection by microdose CT versus chest radiography (standard and dual-energy subtracted). *AJR Am J Roentgenol* 2015;204:727-735. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25794062>.

133. Verma S, Rajesh A, Prasad SR, et al. Urinary bladder cancer: role of MR imaging. *Radiographics* 2012;32:371-387. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22411938>.

134. Ha HK, Koo PJ, Kim SJ. Diagnostic accuracy of F-18 FDG PET/CT for preoperative lymph node staging in newly diagnosed bladder cancer patients: A systematic review and meta-analysis. *Oncology* 2018;95:31-38. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29847834>.

135. Huang L, Kong Q, Liu Z, et al. The diagnostic value of MR imaging in differentiating T staging of bladder cancer: A meta-analysis. *Radiology* 2018;286:502-511. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29206594>.

136. Woo S, Suh CH, Kim SY, et al. Diagnostic performance of MRI for prediction of muscle-invasiveness of bladder cancer: A systematic review and meta-analysis. *Eur J Radiol* 2017;95:46-55. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28987698>.

137. Solsona E, Iborra I, Collado A, et al. Feasibility of radical transurethral resection as monotherapy for selected patients with muscle invasive bladder cancer. *J Urol* 2010;184:475-480. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20620402>.

138. Leibovici D, Kassouf W, Pisters LL, et al. Organ preservation for muscle-invasive bladder cancer by transurethral resection. *Urology* 2007;70:473-476. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17905099>.

139. Koie T, Hatakeyama S, Yoneyama T, et al. Uterus-, fallopian tube-, ovary-, and vagina-sparing cystectomy followed by U-shaped ileal



NCCN Guidelines Version 1.2025

Bladder Cancer

neobladder construction for female bladder cancer patients: oncological and functional outcomes. *Urology* 2010;75:1499-1503. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19969331>.

140. Game X, Mallet R, Guillotreau J, et al. Uterus, fallopian tube, ovary and vagina-sparing laparoscopic cystectomy: technical description and results. *Eur Urol* 2007;51:441-446; discussion 446. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16939698>.

141. Parekh DJ, Reis IM, Castle EP, et al. Robot-assisted radical cystectomy versus open radical cystectomy in patients with bladder cancer (RAZOR): an open-label, randomised, phase 3, non-inferiority trial. *Lancet* 2018;391:2525-2536. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29976469>.

142. Rai BP, Bondad J, Vasdev N, et al. Robotic versus open radical cystectomy for bladder cancer in adults. *Cochrane Database Syst Rev* 2019;4:CD011903. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31016718>.

143. Bochner BH, Dalbagni G, Marzouk KH, et al. Randomized trial comparing open radical cystectomy and robot-assisted laparoscopic radical cystectomy: Oncologic outcomes. *Eur Urol* 2018;74:465-471. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29784190>.

144. Venkatramani V, Reis IM, Castle EP, et al. Predictors of recurrence, and progression-free and overall survival following open versus robotic radical cystectomy: Analysis from the RAZOR trial with a 3-year followup. *J Urol* 2020;203:522-529. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31549935>.

145. Shariat SF, Palapattu GS, Karakiewicz PI, et al. Discrepancy between clinical and pathologic stage: impact on prognosis after radical cystectomy. *Eur Urol* 2007;51:137-149; discussion 149-151. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16793197>.

146. Leissner J, Hohenfellner R, Thuroff JW, Wolf HK. Lymphadenectomy in patients with transitional cell carcinoma of the urinary bladder; significance for staging and prognosis. *BJU Int*

2000;85:817-823. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10792159>.

147. Herr HW, Bochner BH, Dalbagni G, et al. Impact of the number of lymph nodes retrieved on outcome in patients with muscle invasive bladder cancer. *J Urol* 2002;167:1295-1298. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11832716>.

148. Herr HW, Faulkner JR, Grossman HB, et al. Surgical factors influence bladder cancer outcomes: a cooperative group report. *J Clin Oncol* 2004;22:2781-2789. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15199091>.

149. Konety BR, Joslyn SA, O'Donnell MA. Extent of pelvic lymphadenectomy and its impact on outcome in patients diagnosed with bladder cancer: analysis of data from the Surveillance, Epidemiology and End Results Program data base. *J Urol* 2003;169:946-950. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12576819>.

150. Wright JL, Lin DW, Porter MP. The association between extent of lymphadenectomy and survival among patients with lymph node metastases undergoing radical cystectomy. *Cancer* 2008;112:2401-2408. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18383515>.

151. Gschwend JE, Heck MM, Lehmann J, et al. Extended versus limited lymph node dissection in bladder cancer patients undergoing radical cystectomy: Survival results from a prospective, randomized trial. *Eur Urol* 2019;75:604-611. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30337060>.

152. Mulwijk T, Akand M, Gevaert T, Joniau S. No survival difference between super extended and standard lymph node dissection at radical cystectomy: what can we learn from the first prospective randomized phase III trial? *Transl Androl Urol* 2019;8:S112-S115. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31143684>.

153. Grossman HB, Natale RB, Tangen CM, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for



locally advanced bladder cancer. N Engl J Med 2003;349:859-866. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12944571>.

154. Sherif A, Holmberg L, Rintala E, et al. Neoadjuvant cisplatin-based combination chemotherapy in patients with invasive bladder cancer: a combined analysis of two Nordic studies. Eur Urol 2004;45:297-303. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15036674>.

155. Winkler E, Kirchner TS, Segal R, et al. Neoadjuvant chemotherapy for transitional cell carcinoma of the bladder: a systematic review and meta-analysis. J Urol 2004;171:561-569. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/14713760>.

156. Vashistha V, Quinn DI, Dorff TB, Daneshmand S. Current and recent clinical trials for perioperative systemic therapy for muscle invasive bladder cancer: a systematic review. BMC Cancer 2014;14:966. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25515347>.

157. Advanced Bladder Cancer Meta-analysis C. Neoadjuvant chemotherapy in invasive bladder cancer: update of a systematic review and meta-analysis of individual patient data advanced bladder cancer (ABC) meta-analysis collaboration. Eur Urol 2005;48:202-205; discussion 205-206. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15939524>.

158. Trialists ICo, Party MRCABCW, European Organisation for R, et al. International phase III trial assessing neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: long-term results of the BA06 30894 trial. J Clin Oncol 2011;29:2171-2177. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21502557>.

159. Kitamura H, Hinotsu S, Tsukamoto T, et al. Effect of neoadjuvant chemotherapy on health-related quality of life in patients with muscle-invasive bladder cancer: results from JCOG0209, a randomized phase III study. Jpn J Clin Oncol 2020;50:1464-1469. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32699909>.

160. Audenet F, Sfakianos JP, Waingankar N, et al. A delay ≥8 weeks to neoadjuvant chemotherapy before radical cystectomy increases the risk of upstaging. Urol Oncol 2019;37:116-122. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30509868>.

161. Sternberg CN, de Mulder P, Schornagel JH, et al. Seven year update of an EORTC phase III trial of high-dose intensity M-VAC chemotherapy and G-CSF versus classic M-VAC in advanced urothelial tract tumours. Eur J Cancer 2006;42:50-54. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16330205>.

162. Plimack ER, Hoffman-Censits JH, Viterbo R, et al. Accelerated methotrexate, vinblastine, doxorubicin, and cisplatin is safe, effective, and efficient neoadjuvant treatment for muscle-invasive bladder cancer: results of a multicenter phase II study with molecular correlates of response and toxicity. J Clin Oncol 2014;32:1895-1901. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24821881>.

163. Choueiri TK, Jacobus S, Bellmunt J, et al. Neoadjuvant dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin with pegfilgrastim support in muscle-invasive urothelial cancer: pathologic, radiologic, and biomarker correlates. J Clin Oncol 2014;32:1889-1894. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24821883>.

164. McConkey DJ, Choi W, Shen Y, et al. A prognostic gene expression signature in the molecular classification of chemotherapy-naïve urothelial cancer is predictive of clinical outcomes from neoadjuvant chemotherapy: A phase 2 trial of dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin with bevacizumab in urothelial cancer. Eur Urol 2016;69:855-862. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26343003>.

165. Dash A, Pettus JAt, Herr HW, et al. A role for neoadjuvant gemcitabine plus cisplatin in muscle-invasive urothelial carcinoma of the bladder: a retrospective experience. Cancer 2008;113:2471-2477. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18823036>.

166. Herchenhorn D, Dienstmann R, Peixoto FA, et al. Phase II trial of neoadjuvant gemcitabine and cisplatin in patients with resectable



NCCN Guidelines Version 1.2025

Bladder Cancer

bladder carcinoma. Int Braz J Urol 2007;33:630-638; discussion 638. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17980060>.

167. Khaled HM, Shafik HE, Zabhloul MS, et al. Gemcitabine and cisplatin as neoadjuvant chemotherapy for invasive transitional and squamous cell carcinoma of the bladder: effect on survival and bladder preservation. Clin Genitourin Cancer 2014;12:e233-240. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24889794>.

168. Niedersuss-Beke D, Puntus T, Kunit T, et al. Neoadjuvant Chemotherapy with Gemcitabine plus Cisplatin in Patients with Locally Advanced Bladder Cancer. Oncology 2017;93:36-42. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28399521>.

169. Yuh BE, Ruel N, Wilson TG, et al. Pooled analysis of clinical outcomes with neoadjuvant cisplatin and gemcitabine chemotherapy for muscle invasive bladder cancer. J Urol 2013;189:1682-1686. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23123547>.

170. Flaig TW, Tangen CM, Daneshmand S, et al. A randomized phase II study of coexpression extrapolation (COXEN) with neoadjuvant chemotherapy for bladder cancer (SWOG S1314; NCT02177695). Clin Cancer Res 2021;27:2435-2441. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33568346>.

171. Flaig TW, Tangen CM, Daneshmand S, et al. Long-term outcomes from a phase 2 study of neoadjuvant chemotherapy for muscle-invasive bladder cancer (SWOG S1314; NCT02177695). Eur Urol 2023;84:341-347. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/37414705>.

172. Iyer G, Balar AV, Milowsky MI, et al. Multicenter prospective phase II trial of neoadjuvant dose-dense gemcitabine plus cisplatin in patients with muscle-invasive bladder cancer. J Clin Oncol 2018;36:1949-1956. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29742009>.

173. Pfister C, Gravis G, Flechon A, et al. Dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin or gemcitabine and cisplatin as perioperative chemotherapy for patients with nonmetastatic muscle-invasive bladder cancer: Results of the GETUG-AFU V05 VESPER trial.

J Clin Oncol 2022;JCO2102051. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35254888>.

174. Pfister C, Gravis G, Flechon A, et al. Randomized phase III trial of dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin, or gemcitabine and cisplatin as perioperative chemotherapy for patients with muscle-invasive bladder cancer. Analysis of the GETUG-AFU V05 VESPER trial secondary endpoints: Chemotherapy toxicity and pathological responses. Eur Urol 2021;79:214-221. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32868138>.

175. Chung DY, Kang DH, Kim JW, et al. Comparison of oncologic outcomes of dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin (ddMVAC) with gemcitabine and cisplatin (GC) as neoadjuvant chemotherapy for muscle-invasive bladder cancer: Systematic review and meta-analysis. Cancers (Basel) 2021;13. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34199565>.

176. Millikan R, Dinney C, Swanson D, et al. Integrated therapy for locally advanced bladder cancer: final report of a randomized trial of cystectomy plus adjuvant M-VAC versus cystectomy with both preoperative and postoperative M-VAC. J Clin Oncol 2001;19:4005-4013. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11600601>.

177. Galsky MD, Stensland KD, Moshier E, et al. Effectiveness of adjuvant chemotherapy for locally advanced bladder cancer. J Clin Oncol 2016;34:825-832. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26786930>.

178. Leow JJ, Martin-Doyle W, Rajagopal PS, et al. Adjuvant chemotherapy for invasive bladder cancer: a 2013 updated systematic review and meta-analysis of randomized trials. Eur Urol 2014;66:42-54. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24018020>.

179. Hussain MH, Wood DP, Bajorin DF, et al. Bladder cancer: narrowing the gap between evidence and practice. J Clin Oncol 2009;27:5680-5684. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19858384>.



180. Lehmann J, Franzaring L, Thuroff J, et al. Complete long-term survival data from a trial of adjuvant chemotherapy vs control after radical cystectomy for locally advanced bladder cancer. *BJU Int* 2006;97:42-47. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/16336326>.

181. Stockle M, Wellek S, Meyenburg W, et al. Radical cystectomy with or without adjuvant polychemotherapy for non-organ-confined transitional cell carcinoma of the urinary bladder: prognostic impact of lymph node involvement. *Urology* 1996;48:868-875. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/8973669>.

182. Skinner DG, Daniels JR, Russell CA, et al. The role of adjuvant chemotherapy following cystectomy for invasive bladder cancer: a prospective comparative trial. *J Urol* 1991;145:459-464; discussion 464-457. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/1997689>.

183. Advanced Bladder Cancer Meta-analysis C. Adjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis of individual patient data Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. *Eur Urol* 2005;48:189-199; discussion 199-201. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/15939530>.

184. Krajewski W, Nowak L, Moschini M, et al. Impact of adjuvant chemotherapy on survival of patients with advanced residual disease at radical cystectomy following neoadjuvant chemotherapy: Systematic review and meta-analysis. *J Clin Med* 2021;10. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/33567656>.

185. Bajorin DF, Witjes JA, Gschwend JE, et al. Adjuvant nivolumab versus placebo in muscle-invasive urothelial carcinoma. *N Engl J Med* 2021;384:2102-2114. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/34077643>.

186. Bellmunt J, Hussain M, Gschwend JE, et al. Adjuvant atezolizumab versus observation in muscle-invasive urothelial carcinoma (IMvigor010): a multicentre, open-label, randomised, phase 3

trial. *Lancet Oncol* 2021;22:525-537. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/33721560>.

187. Sternberg CN, de Mulder PH, Schornagel JH, et al. Randomized phase III trial of high-dose-intensity methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) chemotherapy and recombinant human granulocyte colony-stimulating factor versus classic MVAC in advanced urothelial tract tumors: European Organization for Research and Treatment of Cancer Protocol no. 30924. *J Clin Oncol* 2001;19:2638-2646. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/11352955>.

188. von der Maase H, Hansen SW, Roberts JT, et al. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. *J Clin Oncol* 2000;18:3068-3077. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11001674>.

189. Novotny V, Froehner M, May M, et al. Risk stratification for locoregional recurrence after radical cystectomy for urothelial carcinoma of the bladder. *World J Urol* 2015;33:1753-1761. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/25663359>.

190. Ku JH, Kim M, Jeong CW, et al. Risk prediction models of locoregional failure after radical cystectomy for urothelial carcinoma: external validation in a cohort of korean patients. *Int J Radiat Oncol Biol Phys* 2014;89:1032-1037. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/25035206>.

191. Christodouleas JP, Baumann BC, He J, et al. Optimizing bladder cancer locoregional failure risk stratification after radical cystectomy using SWOG 8710. *Cancer* 2014;120:1272-1280. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/24390799>.

192. Sargos P, Baumann BC, Eapen L, et al. Risk factors for locoregional recurrence after radical cystectomy of muscle-invasive bladder cancer: A systematic-review and framework for adjuvant radiotherapy. *Cancer Treat Rev* 2018;70:88-97. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/30125800>.



193. Zaghloul MS, Awwad HK, Akoush HH, et al. Postoperative radiotherapy of carcinoma in bilharzial bladder: improved disease free survival through improving local control. *Int J Radiat Oncol Biol Phys* 1992;23:511-517. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/1612951>.

194. Zaghloul MS, Christodouleas JP, Smith A, et al. Adjuvant sandwich chemotherapy plus radiotherapy vs adjuvant chemotherapy alone for locally advanced bladder cancer after radical cystectomy: A randomized phase 2 trial. *JAMA Surg* 2018;153:e174591. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29188298>.

195. Iwata T, Kimura S, Abufaraj M, et al. The role of adjuvant radiotherapy after surgery for upper and lower urinary tract urothelial carcinoma: A systematic review. *Urol Oncol* 2019;37:659-671. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31255542>.

196. Schuettfort VM, Pradere B, Quhal F, et al. Incidence and outcome of salvage cystectomy after bladder sparing therapy for muscle invasive bladder cancer: a systematic review and meta-analysis. *World J Urol* 2021;39:1757-1768. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32995918>.

197. Swinton M, Mariam NGB, Tan JL, et al. Bladder-sparing treatment with radical dose radiotherapy is an effective alternative to radical cystectomy in patients with clinically node-positive nonmetastatic bladder cancer. *J Clin Oncol* 2023;41:4406-4415. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/37478391>.

198. Garcia-Perdomo HA, Montes-Cardona CE, Guacheta M, et al. Muscle-invasive bladder cancer organ-preserving therapy: systematic review and meta-analysis. *World J Urol* 2018;36:1997-2008. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29943218>.

199. Royce TJ, Feldman AS, Mossanen M, et al. Comparative effectiveness of bladder-preserving tri-modality therapy versus radical cystectomy for muscle-invasive bladder cancer. *Clin Genitourin Cancer* 2019;17:23-31.e23. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30482661>.

200. Gakis G, Efstathiou J, Lerner SP, et al. ICUD-EAU International Consultation on Bladder Cancer 2012: Radical cystectomy and bladder preservation for muscle-invasive urothelial carcinoma of the bladder. *Eur Urol* 2013;63:45-57. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22917985>.

201. Bladder cancer: diagnosis and management. National Institute for Health and Care Excellence (NICE); 2015. Available at: <https://www.nice.org.uk/guidance/ng2>. Accessed April 29, 2024.

202. Chang SS, Bochner BH, Chou R, et al. Treatment of non-metastatic muscle-invasive bladder cancer: Aua/asco/astro/suo guideline. *J Urol* 2017;198:552-559. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28456635>.

203. Fedeli U, Fedewa SA, Ward EM. Treatment of muscle invasive bladder cancer: evidence from the National Cancer Database, 2003 to 2007. *J Urol* 2011;185:72-78. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21074192>.

204. Gray PJ, Fedewa SA, Shipley WU, et al. Use of potentially curative therapies for muscle-invasive bladder cancer in the United States: results from the National Cancer Data Base. *Eur Urol* 2013;63:823-829. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23200811>.

205. Mohamed HAH, Salem MA, Elnaggar MS, et al. Trimodalities for bladder cancer in elderly: Transurethral resection, hypofractionated radiotherapy and gemcitabine. *Cancer Radiother* 2018;22:236-240. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29678595>.

206. Herr HW, Bajorin DF, Scher HI. Neoadjuvant chemotherapy and bladder-sparing surgery for invasive bladder cancer: ten-year outcome. *J Clin Oncol* 1998;16:1298-1301. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/9552029>.

207. Splinter T, Denis L. Restaging procedures, criteria of response, and relationship between pathological response and survival. *Semin Oncol* 1990;17:606-612. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/2218573>.



208. Housset M, Maulard C, Chretien Y, et al. Combined radiation and chemotherapy for invasive transitional-cell carcinoma of the bladder: a prospective study. *J Clin Oncol* 1993;11:2150-2157. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/8229129>.

209. Shipley WU, Kaufman DS, Zehr E, et al. Selective bladder preservation by combined modality protocol treatment: long-term outcomes of 190 patients with invasive bladder cancer. *Urology* 2002;60:62-67; discussion 67-68. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12100923>.

210. Shipley WU, Winter KA, Kaufman DS, et al. Phase III trial of neoadjuvant chemotherapy in patients with invasive bladder cancer treated with selective bladder preservation by combined radiation therapy and chemotherapy: initial results of Radiation Therapy Oncology Group 89-03. *J Clin Oncol* 1998;16:3576-3583. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/9817278>.

211. Rodel C, Grabenbauer GG, Kuhn R, et al. Combined-modality treatment and selective organ preservation in invasive bladder cancer: long-term results. *J Clin Oncol* 2002;20:3061-3071. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12118019>.

212. Efstathiou JA, Spiegel DY, Shipley WU, et al. Long-term outcomes of selective bladder preservation by combined-modality therapy for invasive bladder cancer: the MGH experience. *Eur Urol* 2012;61:705-711. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22101114>.

213. Giacalone NJ, Shipley WU, Clayman RH, et al. Long-term outcomes after bladder-preserving tri-modality therapy for patients with muscle-invasive bladder cancer: An updated analysis of the Massachusetts General Hospital experience. *Eur Urol* 2017;71:952-960. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28081860>.

214. Zapatero A, Martin De Vidales C, Arellano R, et al. Long-term results of two prospective bladder-sparing trimodality approaches for invasive bladder cancer: neoadjuvant chemotherapy and concurrent radio-chemotherapy. *Urology* 2012;80:1056-1062. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22999456>.

215. Kaufman DS, Winter KA, Shipley WU, et al. The initial results in muscle-invasive bladder cancer of RTOG 95-06: phase I/II trial of transurethral surgery plus radiation therapy with concurrent cisplatin and 5-fluorouracil followed by selective bladder preservation or cystectomy depending on the initial response. *Oncologist* 2000;5:471-476. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11110598>.

216. Hagan MP, Winter KA, Kaufman DS, et al. RTOG 97-06: initial report of a phase I-II trial of selective bladder conservation using TURBT, twice-daily accelerated irradiation sensitized with cisplatin, and adjuvant MCV combination chemotherapy. *Int J Radiat Oncol Biol Phys* 2003;57:665-672. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/14529770>.

217. Kaufman DS, Winter KA, Shipley WU, et al. Phase I-II RTOG study (99-06) of patients with muscle-invasive bladder cancer undergoing transurethral surgery, paclitaxel, cisplatin, and twice-daily radiotherapy followed by selective bladder preservation or radical cystectomy and adjuvant chemotherapy. *Urology* 2009;73:833-837. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19100600>.

218. Mitin T, Hunt D, Shipley WU, et al. Transurethral surgery and twice-daily radiation plus paclitaxel-cisplatin or fluorouracil-cisplatin with selective bladder preservation and adjuvant chemotherapy for patients with muscle invasive bladder cancer (RTOG 0233): a randomised multicentre phase 2 trial. *Lancet Oncol* 2013;14:863-872. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23823157>.

219. Coen JJ, Zhang P, Saylor PJ, et al. Bladder preservation with twice-a-day radiation plus fluorouracil/cisplatin or once daily radiation plus gemcitabine for muscle-invasive bladder cancer: NRG/RTOG 0712-A randomized phase II trial. *J Clin Oncol* 2019;37:44-51. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30433852>.

220. Efstathiou JA, Bae K, Shipley WU, et al. Late pelvic toxicity after bladder-sparing therapy in patients with invasive bladder cancer: RTOG 89-03, 95-06, 97-06, 99-06. *J Clin Oncol* 2009;27:4055-4061. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19636019>.



NCCN Guidelines Version 1.2025

Bladder Cancer

221. James ND, Hussain SA, Hall E, et al. Radiotherapy with or without chemotherapy in muscle-invasive bladder cancer. *N Engl J Med* 2012;366:1477-1488. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22512481>.
222. Choudhury A, Porta N, Hall E, et al. Hypofractionated radiotherapy in locally advanced bladder cancer: an individual patient data meta-analysis of the BC2001 and BCON trials. *Lancet Oncol* 2021;22:246-255. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33539743>.
223. Coppin CM, Gospodarowicz MK, James K, et al. Improved local control of invasive bladder cancer by concurrent cisplatin and preoperative or definitive radiation. The National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 1996;14:2901-2907. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/8918486>.
224. Herr HW. Conservative management of muscle-infiltrating bladder cancer: prospective experience. *J Urol* 1987;138:1162-1163. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/3669160>.
225. Mak RH, Zietman AL, Heney NM, et al. Bladder preservation: optimizing radiotherapy and integrated treatment strategies. *BJU Int* 2008;102:1345-1353. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19035903>.
226. Haque W, Verma V, Butler EB, Teh BS. Chemotherapy versus chemoradiation for node-positive bladder cancer: Practice patterns and outcomes from the National Cancer Data Base. *Bladder Cancer* 2017;3:283-291. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29152552>.
227. Hermans TJ, Fransen van de Putte EE, Horenblas S, et al. Pathological downstaging and survival after induction chemotherapy and radical cystectomy for clinically node-positive bladder cancer-Results of a nationwide population-based study. *Eur J Cancer* 2016;69:1-8. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27814469>.
228. Picozzi S, Ricci C, Gaeta M, et al. Upper urinary tract recurrence following radical cystectomy for bladder cancer: a meta-analysis on 13,185 patients. *J Urol* 2012;188:2046-2054. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23083867>.
229. Tey J, Ho F, Koh WY, et al. Palliative radiotherapy for bladder cancer: a systematic review and meta-analysis. *Acta Oncol* 2021;60:635-644. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33591843>.
230. Sweeney P, Millikan R, Donat M, et al. Is there a therapeutic role for post-chemotherapy retroperitoneal lymph node dissection in metastatic transitional cell carcinoma of the bladder? *J Urol* 2003;169:2113-2117. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12771730>.
231. Otto T, Krege S, Suhr J, Rubben H. Impact of surgical resection of bladder cancer metastases refractory to systemic therapy on performance score: a phase II trial. *Urology* 2001;57:55-59. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11164143>.
232. Siefker-Radtke AO, Walsh GL, Pisters LL, et al. Is there a role for surgery in the management of metastatic urothelial cancer? The M. D. Anderson experience. *J Urol* 2004;171:145-148. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/14665863>.
233. Lehmann J, Suttman H, Albers P, et al. Surgery for metastatic urothelial carcinoma with curative intent: the German experience (AUO AB 30/05). *Eur Urol* 2009;55:1293-1299. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19058907>.
234. Dodd PM, McCaffrey JA, Herr H, et al. Outcome of postchemotherapy surgery after treatment with methotrexate, vinblastine, doxorubicin, and cisplatin in patients with unresectable or metastatic transitional cell carcinoma. *J Clin Oncol* 1999;17:2546-2552. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10561321>.
235. Abe T, Shinohara N, Harabayashi T, et al. Impact of multimodal treatment on survival in patients with metastatic urothelial cancer. *Eur*



Urol 2007;52:1106-1113. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/17367917>.

236. Ho PL, Willis DL, Patil J, et al. Outcome of patients with clinically node-positive bladder cancer undergoing consolidative surgery after preoperative chemotherapy: The M.D. Anderson Cancer Center Experience. Urol Oncol 2016;34:59.e51-58. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/26421586>.

237. Patel V, Collazo Lorduy A, Stern A, et al. Survival after metastasectomy for metastatic urothelial carcinoma: A systematic review and meta-analysis. Bladder Cancer 2017;3:121-132. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28516157>.

238. Faltas BM, Gennarelli RL, Elkin E, et al. Metastasectomy in older adults with urothelial carcinoma: Population-based analysis of use and outcomes. Urol Oncol 2018;36:9 e11-19 e17. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/28988653>.

239. Dursun F, Mackay A, Guzman JCA, et al. Utilization and outcomes of metastasectomy for patients with metastatic urothelial cancer: An analysis of the national cancer database. Urol Oncol 2021. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34348861>.

240. Centers for Medicare & Medicaid Services. Clinical Laboratory Improvement Amendments (CLIA). 2024. Available at: <https://www.cms.gov/medicare/quality/clinical-laboratory-improvement-amendments>. Accessed April 29, 2024.

241. Alexandrov LB, Nik-Zainal S, Wedge DC, et al. Signatures of mutational processes in human cancer. Nature 2013;500:415-421. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23945592>.

242. Cancer Genome Atlas Research N. Comprehensive molecular characterization of urothelial bladder carcinoma. Nature 2014;507:315-322. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24476821>.

243. Ross JS, Wang K, Khaira D, et al. Comprehensive genomic profiling of 295 cases of clinically advanced urothelial carcinoma of the

urinary bladder reveals a high frequency of clinically relevant genomic alterations. Cancer 2016;122:702-711. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/26651075>.

244. Gupta S, Sonpavde G, Grivas P, et al. Defining “platinum-ineligible” patients with metastatic urothelial cancer (mUC) [abstract]. Journal of Clinical Oncology 2019;37:451-451. Available at: https://ascopubs.org/doi/abs/10.1200/JCO.2019.37.7_suppl.451.

245. Kaufman D, Raghavan D, Carducci M, et al. Phase II trial of gemcitabine plus cisplatin in patients with metastatic urothelial cancer. J Clin Oncol 2000;18:1921-1927. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10784633>.

246. von der Maase H, Sengelov L, Roberts JT, et al. Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. J Clin Oncol 2005;23:4602-4608. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16034041>.

247. De Santis M, Bellmunt J, Mead G, et al. Randomized phase II/III trial assessing gemcitabine/ carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer “unfit” for cisplatin-based chemotherapy: phase II—results of EORTC study 30986. J Clin Oncol 2009;27:5634-5639. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19786668>.

248. Hoimes CJ, Flaig TW, Milowsky MI, et al. Enfortumab vedotin plus pembrolizumab in previously untreated advanced urothelial cancer. J Clin Oncol 2023;41:22-31. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/36041086>.

249. O'Donnell PH, Milowsky MI, Petrylak DP, et al. Enfortumab vedotin with or without pembrolizumab in cisplatin-ineligible patients with previously untreated locally advanced or metastatic urothelial cancer. J Clin Oncol 2023;41:4107-4117. Available at:

250. Powles T, Valderrama BP, Gupta S, et al. Enfortumab vedotin and pembrolizumab in untreated advanced urothelial cancer. N Engl J Med



NCCN Guidelines Version 1.2025

Bladder Cancer

2024;390:875-888. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/38446675>.

251. van der Heijden MS, Sonpavde G, Powles T, et al. Nivolumab plus gemcitabine-cisplatin in advanced urothelial carcinoma. *N Engl J Med* 2023;389:1778-1789. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/37870949>.

252. Balar AV, Castellano D, O'Donnell PH, et al. First-line pembrolizumab in cisplatin-ineligible patients with locally advanced and unresectable or metastatic urothelial cancer (KEYNOTE-052): a multicentre, single-arm, phase 2 study. *Lancet Oncol* 2017;18:1483-1492. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28967485>.

253. Vuky J, Balar AV, Castellano D, et al. Long-term outcomes in KEYNOTE-052: Phase II study investigating first-line pembrolizumab in cisplatin-ineligible patients with locally advanced or metastatic urothelial cancer. *J Clin Oncol* 2020;38:2658-2666. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/32552471>.

254. U. S. Food and Drug Administration. FDA Alerts Health Care Professionals and Oncology Clinical Investigators about an Efficacy Issue Identified in Clinical Trials for Some Patients Taking pembrolizumab or atezolizumab as Monotherapy to Treat Urothelial Cancer with Low Expression of PD-L1. 2018. Available at: <https://www.fda.gov/Drugs/DrugSafety/ucm608075.htm>. Accessed April 29, 2024.

255. U. S. Food and Drug Administration. Prescribing Information. Pembrolizumab injection, for intravenous use. 2024. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/125514s160lbl.pdf. Accessed April 29, 2024.

256. ASCO Post. FDA Revises Label for Pembrolizumab in Patients With Advanced Urothelial Carcinoma. 2021. Available at: <https://ascopost.com/issues/september-25-2021/fda-revises-label-for-pembrolizumab-in-patients-with-advanced-urothelial-carcinoma/>. Accessed April 29, 2024.

257. Powles T, Csoszi T, Ozguroglu M, et al. Pembrolizumab alone or combined with chemotherapy versus chemotherapy as first-line therapy for advanced urothelial carcinoma (KEYNOTE-361): a randomised, open-label, phase 3 trial. *Lancet Oncol* 2021;22:931-945. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34051178>.

258. Balar AV, Galsky MD, Rosenberg JE, et al. Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial. *Lancet* 2017;389:67-76. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27939400>.

259. U. S. Food and Drug Administration. Prescribing Information. Atezolizumab injection, for intravenous use. 2024. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761034s053lbl.pdf. Accessed April 29, 2024.

260. Galsky MD, Ariba JAA, Bamias A, et al. Atezolizumab with or without chemotherapy in metastatic urothelial cancer (IMvigor130): a multicentre, randomised, placebo-controlled phase 3 trial. *Lancet* 2020;395:1547-1557. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32416780>.

261. Medscape. Atezolizumab Bladder Cancer Indication Withdrawn in US. 2022. Available at: <https://www.medscape.com/viewarticle/984722>. Accessed April 29, 2024.

262. Vaughn DJ, Broome CM, Hussain M, et al. Phase II trial of weekly paclitaxel in patients with previously treated advanced urothelial cancer. *J Clin Oncol* 2002;20:937-940. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11844814>.

263. Sideris S, Aoun F, Zanaty M, et al. Efficacy of weekly paclitaxel treatment as a single agent chemotherapy following first-line cisplatin treatment in urothelial bladder cancer. *Mol Clin Oncol* 2016;4:1063-1067. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27284445>.

264. Papamichael D, Gallagher CJ, Oliver RT, et al. Phase II study of paclitaxel in pretreated patients with locally advanced/metastatic cancer



NCCN Guidelines Version 1.2025

Bladder Cancer

of the bladder and ureter. Br J Cancer 1997;75:606-607. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/9052419>.

265. McCaffrey JA, Hilton S, Mazumdar M, et al. Phase II trial of docetaxel in patients with advanced or metastatic transitional-cell carcinoma. J Clin Oncol 1997;15:1853-1857. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/9164195>.

266. Bellmunt J, von der Maase H, Mead GM, et al. Randomized phase III study comparing paclitaxel/cisplatin/gemcitabine and gemcitabine/cisplatin in patients with locally advanced or metastatic urothelial cancer without prior systemic therapy: EORTC Intergroup Study 30987. J Clin Oncol 2012;30:1107-1113. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22370319>.

267. Burch PA, Richardson RL, Cha SS, et al. Phase II study of paclitaxel and cisplatin for advanced urothelial cancer. J Urol 2000;164:1538-1542. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11025699>.

268. Meluch AA, Greco FA, Burris HA, 3rd, et al. Paclitaxel and gemcitabine chemotherapy for advanced transitional-cell carcinoma of the urothelial tract: a phase II trial of the Minnie pearl cancer research network. J Clin Oncol 2001;19:3018-3024. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11408496>.

269. Bellmunt J, Guillem V, Paz-Ares L, et al. Phase I-II study of paclitaxel, cisplatin, and gemcitabine in advanced transitional-cell carcinoma of the urothelium. Spanish Oncology Genitourinary Group. J Clin Oncol 2000;18:3247-3255. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10986057>.

270. Hussain M, Vaishampayan U, Du W, et al. Combination paclitaxel, carboplatin, and gemcitabine is an active treatment for advanced urothelial cancer. J Clin Oncol 2001;19:2527-2533. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11331332>.

271. Pectasides D, Glotsos J, Bountouroglou N, et al. Weekly chemotherapy with docetaxel, gemcitabine and cisplatin in advanced

transitional cell urothelial cancer: a phase II trial. Ann Oncol 2002;13:243-250. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11886001>.

272. Powles T, Park SH, Voog E, et al. Avelumab maintenance therapy for advanced or metastatic urothelial carcinoma. N Engl J Med 2020;383:1218-1230. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32945632>.

273. Plimack ER, Bellmunt J, Gupta S, et al. Safety and activity of pembrolizumab in patients with locally advanced or metastatic urothelial cancer (KEYNOTE-012): a non-randomised, open-label, phase 1b study. Lancet Oncol 2017;18:212-220. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28081914>.

274. Bellmunt J, de Wit R, Vaughn DJ, et al. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. N Engl J Med 2017;376:1015-1026. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28212060>.

275. Fradet Y, Bellmunt J, Vaughn DJ, et al. Randomized phase III KEYNOTE-045 trial of pembrolizumab versus paclitaxel, docetaxel, or vinflunine in recurrent advanced urothelial cancer: results of >2 years of follow-up. Ann Oncol 2019;30:970-976. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31050707>.

276. Sharma P, Retz M, Siefker-Radtke A, et al. Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial. Lancet Oncol 2017;18:312-322. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28131785>.

277. Sharma P, Callahan MK, Bono P, et al. Nivolumab monotherapy in recurrent metastatic urothelial carcinoma (CheckMate 032): a multicentre, open-label, two-stage, multi-arm, phase 1/2 trial. Lancet Oncol 2016;17:1590-1598. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27733243>.



278. Sharma P, Siefker-Radtke A, de Braud F, et al. Nivolumab alone and with ipilimumab in previously treated metastatic urothelial carcinoma: CheckMate 032 nivolumab 1 mg/kg plus ipilimumab 3 mg/kg expansion cohort results. *J Clin Oncol* 2019;37:1608-1616. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31100038>.

279. Apolo AB, Infante JR, Balmanoukian A, et al. Avelumab, an anti-programmed death-ligand 1 antibody, in patients with refractory metastatic urothelial carcinoma: Results from a multicenter, phase Ib study. *J Clin Oncol* 2017;35:2117-2124. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28375787>.

280. Patel MR, Ellerton J, Infante JR, et al. Avelumab in metastatic urothelial carcinoma after platinum failure (JAVELIN Solid Tumor): pooled results from two expansion cohorts of an open-label, phase 1 trial. *Lancet Oncol* 2018;19:51-64. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29217288>.

281. Loriot Y, Necchi A, Park SH, et al. Erdafitinib in locally advanced or metastatic urothelial carcinoma. *N Engl J Med* 2019;381:338-348. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31340094>.

282. Siefker-Radtke AO, Necchi A, Park SH, et al. Efficacy and safety of erdafitinib in patients with locally advanced or metastatic urothelial carcinoma: long-term follow-up of a phase 2 study. *Lancet Oncol* 2022;23:248-258. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35030333>.

283. Loriot Y, Matsubara N, Park SH, et al. Erdafitinib or chemotherapy in advanced or metastatic urothelial carcinoma. *N Engl J Med* 2023;389:1961-1971. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/37870920>.

284. Siefker-Radtke AO, Matsubara N, Park SH, et al. Erdafitinib versus pembrolizumab in pretreated patients with advanced or metastatic urothelial cancer with select FGFR alterations: cohort 2 of the randomized phase III THOR trial. *Ann Oncol* 2024;35:107-117. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/37871702>.

285. U.S. Food & Drug Administration. FDA approves erdafitinib for locally advanced or metastatic urothelial carcinoma. 2024. Available at: <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-erdafitinib-locally-advanced-or-metastatic-urothelial-carcinoma>. Accessed February 6, 2024.

286. Rosenberg JE, O'Donnell PH, Balar AV, et al. Pivotal trial of enfortumab vedotin in urothelial carcinoma after platinum and anti-programmed death 1/programmed death ligand 1 therapy. *J Clin Oncol* 2019;37:2592-2600. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31356140>.

287. Powles T, Rosenberg JE, Sonpavde GP, et al. Enfortumab vedotin in previously treated advanced urothelial carcinoma. *N Engl J Med* 2021;384:1125-1135. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33577729>.

288. Yu EY, Petrylak DP, O'Donnell PH, et al. Enfortumab vedotin after PD-1 or PD-L1 inhibitors in cisplatin-ineligible patients with advanced urothelial carcinoma (EV-201): a multicentre, single-arm, phase 2 trial. *Lancet Oncol* 2021;22:872-882. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33991512>.

289. Rosenberg J, Sridhar SS, Zhang J, et al. EV-101: A phase I study of single-agent enfortumab vedotin in patients with nectin-4-positive solid tumors, including metastatic urothelial carcinoma. *J Clin Oncol* 2020;38:1041-1049. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32031899>.

290. U.S. Food & Drug Administration. Prescribing Information. Enfortumab vedotin-ejfv for injection, for intravenous use. 2023. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761137s00_6s008lbl.pdf. Accessed April 29, 2024.

291. Tagawa ST, Balar AV, Petrylak DP, et al. TROPY-U-01: A phase II open-label study of sacituzumab govitecan in patients with metastatic urothelial carcinoma progressing after platinum-based chemotherapy



and checkpoint inhibitors. J Clin Oncol 2021;39:2474-2485. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33929895>.

292. U.S. Food & Drug Administration. Prescribing information. Fam-trastuzumab deruxtecan-nxki for injection, for intravenous use. 2024. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761139s02/8lbl.pdf. Accessed April 29, 2024.

293. Meric-Bernstam F, Makker V, Oaknin A, et al. Efficacy and Safety of Trastuzumab Deruxtecan in Patients With HER2-Expressing Solid Tumors: Primary Results From the DESTINY-PanTumor02 Phase II Trial. J Clin Oncol 2024;42:47-58. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/37870536>.

294. Wong RL, Ferris LA, Do OA, et al. Efficacy of platinum rechallenge in metastatic urothelial carcinoma after previous platinum-based chemotherapy for metastatic disease. Oncologist 2021. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34355457>.

295. Taguchi S, Kawai T, Ambe Y, et al. Enfortumab vedotin versus platinum rechallenge in post-platinum, post-pembrolizumab advanced urothelial carcinoma: A multicenter propensity score-matched study. Int J Urol 2023. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/37740409>.

296. Massard C, Gordon MS, Sharma S, et al. Safety and efficacy of durvalumab (MEDI4736), an anti-programmed cell death ligand-1 immune checkpoint inhibitor, in patients with advanced urothelial bladder cancer. J Clin Oncol 2016;34:3119-3125. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27269937>.

297. Powles T, O'Donnell PH, Massard C, et al. Efficacy and safety of durvalumab in locally advanced or metastatic urothelial carcinoma: Updated results from a phase 1/2 open-label study. JAMA Oncol 2017;3:e172411. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28817753>.

298. Urology Times. Durvalumab FDA indication for bladder cancer voluntarily withdrawn. 2021. Available at: <https://www.urologytimes.com/view/durvalumab-fda-indication-for-bladder-cancer-voluntarily-withdrawn>. Accessed April 29, 2024.

299. Powles T, van der Heijden MS, Castellano D, et al. Durvalumab alone and durvalumab plus tremelimumab versus chemotherapy in previously untreated patients with unresectable, locally advanced or metastatic urothelial carcinoma (DANUBE): a randomised, open-label, multicentre, phase 3 trial. Lancet Oncol 2020;21:1574-1588. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32971005>.

300. Rosenberg JE, Hoffman-Censits J, Powles T, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet 2016;387:1909-1920. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26952546>.

301. Necchi A, Joseph RW, Loriot Y, et al. Atezolizumab in platinum-treated locally advanced or metastatic urothelial carcinoma: post-progression outcomes from the phase II IMvigor210 study. Ann Oncol 2017;28:3044-3050. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28950298>.

302. Powles T, Duran I, van der Heijden MS, et al. Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): a multicentre, open-label, phase 3 randomised controlled trial. Lancet 2018;391:748-757. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29268948>.

303. Sternberg CN, Loriot Y, James N, et al. Primary results from SAUL, a multinational single-arm safety study of atezolizumab therapy for locally advanced or metastatic urothelial or nonurothelial carcinoma of the urinary tract. Eur Urol 2019;76:73-81. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30910346>.

304. Pal SK, Hoffman-Censits J, Zheng H, et al. Atezolizumab in platinum-treated locally advanced or metastatic urothelial carcinoma:



NCCN Guidelines Version 1.2025

Bladder Cancer

Clinical experience from an expanded access study in the United States. *Eur Urol* 2018;73:800-806. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29478735>.

305. Merseburger AS, Castellano D, Powles T, et al. Safety and efficacy of atezolizumab in understudied populations with pretreated urinary tract carcinoma: Subgroup analyses of the SAUL study in real-world practice. *J Urol* 2021;206:240-251. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33835866>.

306. ASCO Post. Atezolizumab's Indication in Previously Treated Metastatic Bladder Cancer Is Withdrawn. 2021. Available at: <https://ascopost.com/news/march-2021/atezolizumab-s-indication-in-previously-treated-metastatic-bladder-cancer-is-withdrawn/>. Accessed April 29, 2024.

307. Ismaili N. A rare bladder cancer--small cell carcinoma: review and update. *Orphanet J Rare Dis* 2011;6:75. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22078012>.

308. Siefker-Radtke AO, Dinney CP, Abrahams NA, et al. Evidence supporting preoperative chemotherapy for small cell carcinoma of the bladder: a retrospective review of the M. D. Anderson cancer experience. *J Urol* 2004;172:481-484. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15247709>.

309. Siefker-Radtke AO, Kamat AM, Grossman HB, et al. Phase II clinical trial of neoadjuvant alternating doublet chemotherapy with ifosfamide/doxorubicin and etoposide/cisplatin in small-cell urothelial cancer. *J Clin Oncol* 2009;27:2592-2597. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19414678>.

310. Kaushik D, Frank I, Boorjian SA, et al. Long-term results of radical cystectomy and role of adjuvant chemotherapy for small cell carcinoma of the bladder. *Int J Urol* 2015;22:549-554. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25761779>.

311. Lynch SP, Shen Y, Kamat A, et al. Neoadjuvant chemotherapy in small cell urothelial cancer improves pathologic downstaging and long-

term outcomes: results from a retrospective study at the MD Anderson Cancer Center. *Eur Urol* 2013;64:307-313. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22564397>.

312. Vetterlein MW, Wankowicz SAM, Seisen T, et al. Neoadjuvant chemotherapy prior to radical cystectomy for muscle-invasive bladder cancer with variant histology. *Cancer* 2017;123:4346-4355. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28743155>.

313. Chau C, Rimmer Frcr Y, Choudhury Ph DA, et al. Treatment outcomes for small cell carcinoma of the bladder: Results from a UK patient retrospective cohort study. *Int J Radiat Oncol Biol Phys* 2021;110:1143-1150. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33561506>.

314. McGregor BA, Campbell MT, Xie W, et al. Results of a multicenter, phase 2 study of nivolumab and ipilimumab for patients with advanced rare genitourinary malignancies. *Cancer* 2021;127:840-849. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33216356>.

315. Bryant CM, Dang LH, Stechmiller BK, et al. Treatment of small cell carcinoma of the bladder with chemotherapy and radiation after transurethral resection of a bladder tumor. *Am J Clin Oncol* 2016;39:69-75. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24517956>.

316. Roupert M, Babjuk M, Comperat E, et al. European Association of Urology Guidelines on Upper Urinary Tract Urothelial Carcinoma: 2017 Update. *Eur Urol* 2018;73:111-122. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28867446>.

317. Metcalfe MJ, Petros FG, Rao P, et al. Universal point of care testing for Lynch Ssyndrome in patients with upper tract urothelial carcinoma. *J Urol* 2018;199:60-65. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28797715>.

318. O'Brien T, Ray E, Singh R, et al. Prevention of bladder tumours after nephroureterectomy for primary upper urinary tract urothelial carcinoma: a prospective, multicentre, randomised clinical trial of a single postoperative intravesical dose of mitomycin C (the ODMIT-C



Trial). Eur Urol 2011;60:703-710. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/21684068>.

319. Ito A, Shintaku I, Satoh M, et al. Prospective randomized phase II trial of a single early intravesical instillation of pirarubicin (THP) in the prevention of bladder recurrence after nephroureterectomy for upper urinary tract urothelial carcinoma: the THP Monotherapy Study Group Trial. J Clin Oncol 2013;31:1422-1427. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/23460707>.

320. Miyamoto K, Ito A, Wakabayashi M, et al. A Phase III trial of a single early intravesical instillation of pirarubicin to prevent bladder recurrence after radical nephroureterectomy for upper tract urothelial carcinoma (JCOG1403, UTUC THP Phase III). Jpn J Clin Oncol 2018;48:94-97. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/29136187>.

321. Margulis V, Puligandla M, Trabulsi EJ, et al. Phase II trial of neoadjuvant systemic chemotherapy followed by extirpative surgery in patients with high grade upper tract urothelial carcinoma. J Urol 2020;203:690-698. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/31702432>.

322. Kim DK, Lee JY, Kim JW, et al. Effect of neoadjuvant chemotherapy on locally advanced upper tract urothelial carcinoma: A systematic review and meta-analysis. Crit Rev Oncol Hematol 2019;135:59-65. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/30819447>.

323. Qiu D, Hu J, He T, et al. Effect of neoadjuvant chemotherapy on locally advanced upper tract urothelial carcinoma: a pooled analysis. Transl Androl Urol 2020;9:2094-2106. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/33209672>.

324. Chen L, Ou Z, Wang R, et al. Neoadjuvant chemotherapy benefits survival in high-grade upper tract urothelial carcinoma: A propensity score-based analysis. Ann Surg Oncol 2020;27:1297-1303. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31853757>.

325. Leow JJ, Chong YL, Chang SL, et al. Neoadjuvant and adjuvant chemotherapy for upper tract urothelial carcinoma: A 2020 systematic review and meta-analysis, and future perspectives on systemic therapy. Eur Urol 2021;79:635-654. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/32798146>.

326. Mandalapu RS, Remzi M, de Reijke TM, et al. Update of the ICUD-SIU consultation on upper tract urothelial carcinoma 2016: treatment of low-risk upper tract urothelial carcinoma. World J Urol 2017;35:355-365. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27233780>.

327. Seisen T, Peyronnet B, Dominguez-Escrig JL, et al. Oncologic outcomes of kidney-sparing surgery versus radical nephroureterectomy for upper tract urothelial carcinoma: A systematic review by the EAU Non-muscle Invasive Bladder Cancer Guidelines Panel. Eur Urol 2016;70:1052-1068. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/27477528>.

328. Yakoubi R, Colin P, Seisen T, et al. Radical nephroureterectomy versus endoscopic procedures for the treatment of localised upper tract urothelial carcinoma: a meta-analysis and a systematic review of current evidence from comparative studies. Eur J Surg Oncol 2014;40:1629-1634. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/25108813>.

329. Gakis G, Schubert T, Alemozaffar M, et al. Update of the ICUD-SIU consultation on upper tract urothelial carcinoma 2016: treatment of localized high-risk disease. World J Urol 2017;35:327-335. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/27043218>.

330. U.S. Food and Drug Administration. Prescribing information. Mitomycin for pyelocalyceal solution. 2021. Available at:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/211728s002lbl.pdf. Accessed April 29, 2024.

331. Kleinmann N, Matin SF, Pierorazio PM, et al. Primary chemoablation of low-grade upper tract urothelial carcinoma using UGN-101, a mitomycin-containing reverse thermal gel (OLYMPUS): an open-label, single-arm, phase 3 trial. The Lancet Oncology



2020;21:776-785. Available at:
<https://pubmed.ncbi.nlm.nih.gov/32631491/>.

332. Matin SF, Pierorazio PM, Kleinmann N, et al. Durability of response to primary chemoablation of low-grade upper tract urothelial carcinoma using UGN-101, a mitomycin-containing reverse thermal gel: OLYMPUS trial final report. *J Urol* 2022;207:779-788. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/34915741>.

333. Necchi A, Lo Vullo S, Mariani L, et al. Adjuvant chemotherapy after radical nephroureterectomy does not improve survival in patients with upper tract urothelial carcinoma: a joint study by the European Association of Urology-Young Academic Urologists and the Upper Tract Urothelial Carcinoma Collaboration. *BJU Int* 2018;121:252-259. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28940605>.

334. Birtle A, Johnson M, Chester J, et al. Adjuvant chemotherapy in upper tract urothelial carcinoma (the POUT trial): a phase 3, open-label, randomised controlled trial. *Lancet* 2020;395:1268-1277. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/32145825>.

335. Li X, Cui M, Gu X, et al. Pattern and risk factors of local recurrence after nephroureterectomy for upper tract urothelial carcinoma. *World J Surg Oncol* 2020;18:114. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/32473636>.

336. Huang YC, Chang YH, Chiu KH, et al. Adjuvant radiotherapy for locally advanced upper tract urothelial carcinoma. *Sci Rep* 2016;6:38175. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/27910890>.

337. Czito B, Zietman A, Kaufman D, et al. Adjuvant radiotherapy with and without concurrent chemotherapy for locally advanced transitional cell carcinoma of the renal pelvis and ureter. *J Urol* 2004;172:1271-1275. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15371822>.

338. Audenet F, Yates DR, Cussenot O, Roupret M. The role of chemotherapy in the treatment of urothelial cell carcinoma of the upper

urinary tract (UUT-UCC). *Urol Oncol* 2013;31:407-413. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/20884249>.

339. Kokorovic A, Westerman ME, Krause K, et al. Revisiting an old conundrum: A systematic review and meta-analysis of intravesical therapy for treatment of urothelial carcinoma of the prostate. *Bladder Cancer* 2021;7:243-252. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/34195319>.

340. Dayyani F, Hoffman K, Eifel P, et al. Management of advanced primary urethral carcinomas. *BJU Int* 2014;114:25-31. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/24447439>.

341. Dalbagni G, Zhang ZF, Lacombe L, Herr HW. Male urethral carcinoma: analysis of treatment outcome. *Urology* 1999;53:1126-1132. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10367840>.

342. Grigsby PW. Carcinoma of the urethra in women. *Int J Radiat Oncol Biol Phys* 1998;41:535-541. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/9635699>.

343. Dimarco DS, Dimarco CS, Zincke H, et al. Surgical treatment for local control of female urethral carcinoma. *Urol Oncol* 2004;22:404-409. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15464921>.

344. Dayyani F, Pettaway CA, Kamat AM, 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. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/22534087>.

345. Cohen MS, Triaca V, Billmeyer B, et al. Coordinated chemoradiation therapy with genital preservation for the treatment of primary invasive carcinoma of the male urethra. *J Urol* 2008;179:536-541; discussion 541. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/18076921>.