

# NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines<sup>®</sup>)

# **Bladder Cancer**

Version 2.2018 — February 7, 2018

NCCN.org



Version 2.2018, 02/07/18 © National Comprehensive Cancer Network, Inc. 2018, All rights reserved. The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.



# NCCN Guidelines Version 2.2018 Panel Members **Bladder Cancer**

NCCN Guidelines Index **Table of Contents** Discussion

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

\*Philippe E. Spiess, MD, MS **v** Vice chair Moffitt Cancer Center

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

**Rick Bangs, MBA** Patient Advocate

Stephen A. Boorjian, MD m **Mayo Clinic Cancer Center** 

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

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

Jason A. Efstathiou, MD, DPhil § Massachusetts General Hospital Cancer Center

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

Richard E. Greenberg, MD a Fox Chase Cancer Center

Khurshid A. Guru, MD σ **Roswell Park Cancer Institute** 

Noah Hahn. MD † The Sidney Kimmel Comprehensive **Cancer Center at Johns Hopkins** 

Harry W. Herr, MD or **Memorial Sloan Kettering Cancer Center** 

#### **NCCN Guidelines Panel Disclosures**

Christopher Hoimes, MD + **Case Comprehensive Cancer Center/** University Hospitals Seidman Cancer Center and Cleveland Clinic Taussig Cancer Institute

Brant A. Inman, MD, MSc or **Duke Cancer Institute** 

Masahito Jimbo, MD, PhD, MPH Þ University of Michigan **Comprehensive Cancer Center** 

A. Karim Kader, MD, PhD or UC San Diego Moores Cancer Center

Subodh M. Lele,  $MD \neq$ Fred & Pamela Buffett Cancer Center

Joshua J. Meeks, MD m **Robert H. Lurie Comprehensive Cancer** Center of Northwestern University

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

Jeffrey S. Montgomery, MD, MHSA to **University of Michigan Comprehensive Cancer Center** 

Lance C. Pagliaro, MD + **Mayo Clinic Cancer Center** 

Sumanta K. Pal, MD † **City of Hope Comprehensive Cancer Center** 



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

Daniel P. Petrylak, MD † Yale Cancer Center/Smilow Cancer Hospital

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

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

Michael P. Porter, MD, MS to Fred Hutchinson Cancer Research Center/ Seattle Cancer Care Alliance

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

Wade J. Sexton, MD  $\varpi$ **Moffitt Cancer Center** 

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

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

Geoffrey Wile, MD db Vanderbilt-Ingram Cancer Center

#### NCCN

ontinue	Mary Dwyer, MS Lisa Gurski, PhD	)
Ununuc	σ Urology	P Internal/Family medicine
	† Medical oncology	ф Diagnostic radiology
	<pre>‡ Hematology/Hematology oncology</pre>	≠ Pathology
	§ Radiotherapy/Radiation oncology	* Discussion writing committee member

Version 2.2018, 02/07/18 © National Comprehensive Cancer Network, Inc. 2018, All rights reserved. The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.



# NCCN Guidelines Version 2.2018 Table of Contents Bladder Cancer

NCCN Guidelines Index Table of Contents Discussion

# NCCN Bladder Cancer Panel Members

Summary of the Guidelines Updates

Bladder Cancer:

- <u>Clinical Presentation and Initial Evaluation (BL-1)</u>
- Noninvasive or Tis, Primary Evaluation/Surgical Treatment (BL-1)
- Secondary Surgical Treatment, Adjuvant Intravesical Treatment, Follow-up (BL-2)
- Posttreatment cTa, cT1, Tis Recurrent or Persistent Disease (BL-3)
- <u>Muscle Invasive or Metastatic, Primary Evaluation/Surgical Treatment, Additional</u> <u>Workup (BL-1)</u>
- <u>cT2 Primary and Adjuvant Treatment (BL-4)</u>
- <u>cT3, cT4a Primary and Adjuvant Treatment (BL-5)</u>
- <u>cT4b Primary and Adjuvant Treatment (BL-6)</u>
- Metastatic Disease, Additional Workup, Primary Treatment (BL-7)
- Follow-up, Recurrent or Persistent Disease (BL-8)
- 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 Variant Histology (BL-D)
- Follow-up (BL-E)
- Principles of Intravesical Treatment (BL-F)
- Principles of Systemic Therapy (BL-G)
- Principles of Radiation Management of Invasive Disease (BL-H)
- Upper 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)

The NCCN Guidelines<sup>®</sup> 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<sup>®</sup> (NCCN<sup>®</sup>) 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<sup>®</sup>. All rights reserved. The NCCN Guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2018.

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

To find clinical trials online at NCCN Member Institutions, <u>click here:</u> <u>nccn.org/clinical\_trials/physician.html</u>.

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

See <u>NCCN Categories of Evidence</u> and <u>Consensus</u>.

# **NCCN Categories of Preference:**

All recommendations are considered appropriate.

See <u>NCCN Categories of Preference</u>

Staging (ST-1)



NCCN Guidelines Index Table of Contents Discussion

Updates in Version 2.2018 of the NCCN Guidelines for Bladder Cancer from Version 1.2018 include:

#### **Upper GU Tract Tumors**

<u>UTT-1</u>

• Footnote f was clarified by adding a link to subsequent therapy options on BL-G 3 of 5. Also for UTT-2.

#### **Urothelial Carcinoma of the Prostate**

<u>UCP-1</u>

• Footnote d was clarified by adding a link to subsequent therapy options on BL-G 3 of 5.

**Continued** 



# **NCCN Guidelines Version 2.2018 Updates Bladder Cancer**

NCCN Guidelines Index **Table of Contents** Discussion

Updates in Version 1.2018 of the NCCN Guidelines for Bladder Cancer from Version 5.2017 include:

#### General

• "Chemotherapy" was replaced by "systemic therapy" as appropriate throughout the guidelines.

# Bladder Cancer

- BL-1
- Primary Evaluation/Surgical Treatment,
- > 4th bullet was revised. "If sessile, suspicious for high grade or Tis, especially in bladder preservation:"

# BL-2

- Secondary Surgical Treatment
- For cT1, high grade, "consider" was added to "cystectomy for high0grade."

# BL-4

- Primary treatment,
- > 2nd option was revised from, "Partial cystectomy (highly selected patients with solitary lesion in a suitable location; no Tis) and neoadjuvant cisplatinbased combination chemotherapy" to "Neoadjuvant cisplatin-based combination systemic therapy followed by partial cystectomy (highly selected patients with solitary lesion in a suitable location; no Tis)."
- + 4th option for non-cystectomy candidates, "TURBT alone" was revised as "TURBT and consider intravesical BCG." Footnote to Principles of Intravesical Therapy was added.
- Adjuvant treatment
- Following partial cystectomy, the patholgoic risk was revised, " (pT3-4,
- positive nodes, or positive margin, or high-grade)."
- > For non-cystectomy candidates, after no tumor, "If prior BCG, maintenance BCG" was added.
- Footnote u was added. "Cystectomy alone is appropriate for those not eligible to receive cisplatin-based chemotherapy." (Also for BL-5)

# BL-6

- For cT4b, cN1-3 nodes, positive nodes on biopsy or CT or MRI, the qualifiers were revised prior to adjuvant treatment
- "No tumor" was changed to "No progression"
- "Tumor present" was changed to "Progression"
- "Adjuvant Treatment" heading was changed to "Subsequent Treatment."
- Footnotes
- Footnote "bb" was added, "Non-bulky disease and no significant clinical progression."
- Footnote "cc" was added, "See Principles of Systemic Therapy (BL-G 3 of 5)."

## **BL-A 1 of 5**

- Principles of Imaging for Bladder/Urothelial Cancer, Non-muscle invasive
- Abdominal and pelvic imaging, Staging, 3rd bullet was revised, "Renal ultrasound (US) or CT without contrast may be utilized in conjunction with retrograde evaluation ureteropyelography..." Also ureteropyelography was added to retrograde for 1st sub-bullet under Follow-up.

# **BL-A 3 of 5**

- Principles of Imaging for Bladder/Urothelial Cancer, Muscle invasive
- Abdominal and pelvic imaging, 4th sub-bullet was revised, "Ureteroscopy if suspected upper tract lesions."
- Suspected bone metastasis, bullet was revised by adding, "MRI" as an option.
- Neurologic/Brain Imaging, 1st sub-bullet was revised, "Brain MRI without and with IV contrast recommended only in symptomatic or selected 'high-risk' (eg, small cell histology) patients."

# **BL-B1 of 4**

- Principles of Surgical Management
- TURBT for Staging
  - ◊ 1st bullet, 3rd sub-bullet, the following sub-bullet was revised, "Large (≥3 cm) or multi-focal lesions."
  - ◊ 2nd bullet was revised, "Enhanced (blue light and narrow banding) cystoscopy may be helpful in identifying lesions not visible using white light cystoscopy."
- TURBT/Maximal TURBT for Treatment
  - O Bullet was removed, "Primary treatment option for cT2, cT3, and cT4a disease."
  - ♦ 1st bullet was revised, "Bladder preservation with maximally complete and safe TURBT and concurrent chemoradiotherapy is generally reserved for patients with smaller most suitable for *patients with* solitary tumors, negative nodes, no carcinoma in situ, no tumor-related hydronephrosis, and good pre-treatment bladder function."
  - 3rd bullet was revised, "A visually and microscopically complete TURBT is associated with improved patient outcomes in nonmetastatic settings."

# BL-B 4 of 4

- Principles of Surgical Management
- Endoscopic Management of Upper Tract Urothelial Cancer (UTUC) was added. Continued



# **NCCN Guidelines Version 2.2018 Updates Bladder Cancer**

NCCN Guidelines Index Table of Contents Discussion

Updates in Version 1.2018 of the NCCN Guidelines for Bladder Cancer from Version 5.2017 include: BL-E

• A link to the NCCN Guidelines for Survivorship was added.

#### **BL-G 1 of 5**

- Principles of Systemic Therapy
- The NCCN Categories of Preference has been applied to all of the suggested treatment regimens.
- Perioperative chemotherapy (neoadjuvant or adjuvant) options are listed under two groups, "Preferred regimens" and "Other recommended regimens."
- > 5th bullet was revised, "DDMVAC is preferred over standard MVAC based on category 1 evidence for metastatic disease showing DDMVAC ... "
- > 6th bullet was revised, "Perioperative gemcitabine and cisplatin is a reasonable alternative to DDMVAC based on category 1 evidence for metastatic disease ... "

#### **BL-G 2 of 5**

- Principles of Systemic Therapy
- Heading was revised by adding, "First-line chemotherapy systemic therapy for locally advanced or metastatic disease (Stage IV)."
- > The regimen options are listed under three groups, "Preferred regimens," "Other recommended regimens," and "Useful under certain circumstances."
- > 1st bullet was revised, "The presence of both visceral non-nodal metastases and ECOG performance score  $\geq 2$  strongly predict poor outcome with chemotherapy. Patients without these adverse prognostic factors have the greatest benefit from chemotherapy. The impact of these factors in relation to immune checkpoint inhibition is not fully defined, but they remain poor prognostic indicators in general."

#### **BL-G 3 of 5**

- Subsequent systemic therapy was separated into two groups and revised as,
- Subsequent systemic therapy for locally advanced or metastatic disease (Stage) IV) (post-platinum)
  - ♦ The regimen options are listed under four groups, "Preferred regimen," "Alternate preferred regimens," "Other recommended regimens," and "Useful under certain circumstances based on prior medical therapy."
  - ♦ Footnote "b" was added, "If platinum (eg, cisplatin or carboplatin) more than 12 months ago, consider re-treatment with platinum if the patient is still platinum eligible."
- Subsequent systemic therapy for locally advanced or metastatic disease (Stage) IV) (post-checkpoint inhibitor)
  - **O** The regimen options are listed under four groups, "Preferred regimen for cisplatin ineligible, chemotherapy naïve," "Preferred regimens for cisplatin eligible, chemotherapy naïve," "Other recommended regimens" and "Useful under certain circumstances based on prior medical therapy."

# BL-G 4 of 5

- Header was clarified from, "Radiosensitizing chemotherapy regimens for bladder-preserving chemoradiation following a maximal TURBT" to "Radiosensitizing chemotherapy regimens for organ-preserving chemoradiation."
- > The regimen options are listed under two groups, "Preferred regimens" and "Other recommended regimen."
- The statement in parentheses next to preferred regimens was revised, "doublet chemotherapy is preferred when feasible."
- Header was clarified from "Radiosensitizing chemotherapy given concurrently with conventionally fractionated radiation for palliation of metastases or for pelvic recurrence after cystectomy" to "Radiosensitizing chemotherapy given concurrently with conventionally fractionated radiation for palliation of metastases or recurrence."
- > The regimen options are listed under two groups, "Preferred regimen" and "Other recommended regimens"

# BL-H 1 of 3

- Principles of Radiation Management of Invasive Disease,
- A statement was added to the page, "Unless otherwise stated, doses are 1.8–2.0 daily fractionation." (Also for BL-H 2 of 3.)

## BL-H 2 of 3

• A sub-bullet for recurrent disease was added, "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."

# **Upper GU Tract Tumors**

## UTT-1

 Primary treatment for non-metastatic was revised by adding "± perioperative intravesical chemotherapy" to both Low grade and High grade, large, or parenchymal invasion. Footnote to Principles of Intravesical Therapy was added.

# Continued

		National Comprehensive	NCCN Guidelines Version 2 2018 Undates	NCCN Guidelines Index
N	CCN	Cancer Network <sup>®</sup>	Bladder Cancer	<u>Table of Contents</u> <u>Discussion</u>

Updates in Version 1.2018 of the NCCN Guidelines for Bladder Cancer from Version 5.2017 include:

#### **Urothelial Carcinoma of the Prostate**

#### UCP-1

• Pathology, "prostatic urethra" was clarified by adding, "Mucosal."

#### **Primary Carcinoma of the Urethra**

#### PCU-2

#### Footnotes

- > Footnote "e" was added, "See Principles of Intravesical Treatment (BL-F)."
- ▶ Footnote "i" was added, "See Principles of Systemic Therapy (BL-G 1 of 5)." (Also for PCU-3)
- ▶ Footnote "I" was added, "See Principles of Systemic Therapy (BL-G 2 of 5)." (Also for PCU-3)
- ▶ Footnote "m" was added, "See Principles of Systemic Therapy (BL-G 3 of 5)." (Also for PCU-3)

#### PCU-3

- Primary treatment for T3, T4 and palpable inguinal lymph nodes,
- For cN0, "± consolidative surgery" was added to "Chemoradiotherapy (preferred)."
- For cN1/cN2, "Chemoradiotherapy followed by consideration of consolidative surgery" was revised as, "Chemoradiotherapy ± consolidative surgery."
- · After primary treatment for distant metastasis, "systemic therapy or chemoradiotherapy" was removed and replaced with a link to "See Metastatic Disease (BL-7)."

#### ST-1

• Staging was updated to reflect changes in the AJCC Cancer Staging Manual, Eighth Edition, 2017.



<sup>a</sup>See Principles of Imaging for Bladder/Urothelial Cancer (BL-A).

<sup>b</sup>See Principles of Surgical Management (BL-B).

<sup>c</sup>Immediate intravesical chemotherapy, not immunotherapy, has been shown to decrease recurrence in select subgroups of patients.

<sup>d</sup>Although there is no standard for immediate perioperative intravesical chemotherapy, mitomycin is most commonly used.

<sup>e</sup>The modifier "c" refers to clinical staging based on bimanual examination under anesthesia, endoscopic surgery (biopsy or transurethral resection), and imaging studies. The modifier "p" refers to pathologic staging based on cystectomy and lymph node dissection.

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













<sup>a</sup>See Principles of Imaging for Bladder/Urothelial Cancer (BL-A).

<sup>e</sup>The modifier "c" refers to clinical staging based on bimanual examination under anesthesia, endoscopic surgery (biopsy or transurethral resection), and imaging studies. The modifier "p" refers to pathologic staging based on cystectomy and lymph node dissection. <sup>z</sup>If technically possible.

<sup>aa</sup>See Principles of Systemic Therapy (BL-G 2 of 5).

<sup>dd</sup>Consider molecular testing in a CLIA-approved laboratory. <u>See Discussion</u>.

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



<sup>a</sup>See Principles of Imaging for Bladder/Urothelial Cancer (BL-A). <sup>b</sup>See Principles of Surgical Management (BL-B). <sup>h</sup>See Follow-Up (BL-E). <sup>j</sup>See Principles of Intravesical Treatment (BL-F). <sup>j</sup>See Principles of Systemic Therapy (BL-G 3 of 5). <sup>c</sup>See Principles of Systemic Therapy (BL-G 3 of 5). <sup>cef</sup> not a cystectomy candidate, consider concurrent chemoradiotherapy (<u>See BL-G 4 of 5</u>). <sup>(if no prior RT)</sup>, change in intravesical agent, or a clinical trial.

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

Version 2.2018, 02/07/18 © National Comprehensive Cancer Network, Inc. 2018, All rights reserved. The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.



NCCN Guidelines Version 2.2018 Bladder Cancer

NCCN Guidelines Index Table of Contents Discussion

# 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.<sup>7</sup>

# Abdominal and Pelvic Imaging

Staging:

- > CT urography (CTU) (CT of the abdomen and pelvis without and with IV contrast with excretory imaging).
- MR urography (MRU) may be appropriate in patients with poor renal function or iodinated contrast allergy but with GFR
   30 and no acute renal failure. May be performed without gadolinium-based contrast utilizing T2 imaging and native image contrast to evaluate upper tracts. Will have decreased sensitivity to plaque-like or non-obstructive lesions and metastasis.
- Renal ultrasound (US) or CT without contrast may be utilized in conjunction with retrograde ureteropyelography in patients who cannot receive either iodinated or gadolinium-based contrast material.
- Ureteroscopy

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.
- Or 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.<sup>8,9</sup>
- Follow-up of NMIBC: (See BL-E)
- Upper tract (CTU, MRU, or retrograde ureteropyelography with CT or US) and abdominal/pelvic imaging at baseline. For high-risk patients, UT imaging also performed at 12 mo and every 1–2 years thereafter up to 10 years.

# **Evaluation for Suspected Bone Metastasis**

- Bone imaging not generally recommended as bone metastasis is unlikely. Neurologic/Brain Imaging<sup>1,11</sup>
- Staging
   Brain MRI not generally recommended.
   Brain MRI not generally recommended.
   References on BL-A 5 of 5
   Note: All recommendations are category 2A unless otherwise indicated.
   Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



NCCN Guidelines Version 2.2018 Bladder Cancer

NCCN Guidelines Index Table of Contents Discussion

# PRINCIPLES OF IMAGING FOR BLADDER/UROTHELIAL CANCER

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

Muscle Invasive Bladder Cancer

**Chest Imaging** 

- Chest imaging may be performed with plain film radiography with posteroanterior (PA) and lateral views in early-stage disease. If an abnormality is seen, then CT of the chest may then be performed.
- Staging:<sup>1</sup>
- ▶ PA and lateral chest x-ray, or
- CT of the chest without contrast when the chest x-ray is equivocal or there is an abnormality identified on chest x-ray or in selected high-risk patients. Chest CT with IV contrast could be considered in patients undergoing concurrent imaging of the abdomen and pelvis.<sup>2</sup>
- ▶ PET/CT (category 2B) may be beneficial in selected patients with T2 (muscle-invasive disease) and in patients with ≥cT3 disease. Will also include abdomen and pelvis if performed.<sup>3-6</sup> PET/CT should not be used to delineate the anatomy of the upper urinary tract.
- Follow-up with or without cystectomy: (See BL-E)
- ▶ PA and lateral chest x-ray, or
- Chest CT with IV contrast when the chest x-ray is equivocal or there is an abnormality identified on chest x-ray.
  - **O May be performed without contrast if IV contrast cannot be given.**
  - ♦ Consider performing with the abdomen and pelvis for a single exam in patients who also need imaging of the abdomen and pelvis.
- PET/CT (category 2B) may be performed if not previously done or if metastasis is suspected in selected patients. This examination will also include abdomen and pelvis. PET/CT should not be used to delineate the anatomy of the upper urinary tract.
- Follow-up of cT4b (<u>See BL-E</u>) and metastatic disease:
- ▶ PA and lateral chest x-ray, or
- Chest CT with IV contrast (preferred) or when the chest x-ray is equivocal or there is an abnormality identified on chest x-ray.
  - **O May be performed without contrast if IV contrast cannot be given.**
  - **Orginal Consider** Consider performing with the abdomen and pelvis for a single exam in patients who also need imaging of the abdomen and pelvis.
- PET/CT (category 2B) may be performed if not previously done or in high-risk patients in whom metastatic disease is suspected. Could also be used to guide biopsy in certain patients. PET/CT should not be used to delineate the anatomy of the upper urinary tract.

<u>Continued on</u> <u>next page</u> <u>References on</u> <u>BL-A 5 of 5</u>

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



# NCCN Guidelines Version 2.2018 **Bladder Cancer**

NCCN Guidelines Index Table of Contents Discussion

# PRINCIPLES OF IMAGING FOR BLADDER/UROTHELIAL CANCER

Muscle Invasive Bladder Cancer (Continued)

# Abdominal and Pelvic Imaging

- Staging:
- CTU (CT of the abdomen and pelvis without and with IV contrast with excretory imaging).<sup>10</sup>
- > MRU may be appropriate in patients with poor renal function or iodinated contrast allergy but with GFR >30 and no acute renal failure.
- > Renal US and CT without contrast (particularly when PET/CT is not utilized) may be utilized in conjunction with retrograde evaluation in patients who cannot receive either iodinated or gadolinium-based contrast material.
- Ureteroscopy if suspected upper tract lesions
- ▶ PET/CT (category 2B) may be useful in selected patients with ≥cT2 disease and may change management in patients with ≥cT3 disease.<sup>7</sup> 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.<sup>7</sup>
- Follow-up (See BL-E):
- > Upper tract and abdominal/pelvic imaging as defined previously at 3- to 6-month intervals for 2 years. Then abdominal/pelvic imaging annually up to 5 y and as indicated thereafter.
- > PET/CT (category 2B) may be performed if not previously done or in high-risk patients in whom metastatic disease is suspected. Could also be used to guide biopsy in certain patients. PET/CT should not be used to delineate the anatomy of the upper urinary tract.

# **Evaluation for Suspected Bone Metastasis**

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

# Neurologic/Brain Imaging<sup>1,11</sup>

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

	National
	Comprehensive
NCCN	Cancer
	Network®

# NCCN Guidelines Version 2.2018 Bladder Cancer

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

Upper Tract (renal pelvis and urothelial carcinoma of the ureter<sup>12</sup>

- Staging and follow-up of ≤T1 disease (see recommendations for NMIBC bladder cancer).
- Staging and follow-up of ≥T2 disease (see recommendations for MIBC bladder cancer).

# Urothelial Carcinoma of the Prostate/Primary Carcinoma of the Urethra

- Staging:
- ▶ PA and lateral chest x-ray.
- ▶ Chest CT may be performed if chest x-ray equivocal or "high-risk" patients ≥T1 disease.
- Consider abdominal CT or MRI in high-risk T1 disease or patients with ≥T2 disease.<sup>13</sup>
- MRI of the pelvis without and with IV contrast for local staging.
- Additional staging if urothelial carcinoma of prostate:
- Imaging of upper tracts and collecting system.
- CTU (CT of the abdomen and pelvis without and with IV contrast with excretory imaging).
- MRU may be appropriate in patients with poor renal function or iodinated contrast allergy but with GFR >30 and no acute renal failure.
   Ureteroscopy
- Renal US or CT without contrast may be utilized in conjunction with retrograde evaluation in patients who cannot receive either iodinated or gadolinium-based contrast material.
- Additional staging if primary carcinoma of non-prostatic male urethra or female urethra:
- In the setting of palpable inguinal lymph nodes.
  - $\diamond$  Biopsy of palpable nodes.
  - $\diamond$  CT of the chest, abdomen, and pelvis for additional staging, if not yet performed.

# • Follow-up:

- Low-risk T1 or <T1 disease</p>
  - ◊ 1- to 2-year follow-up.
  - MRI or CT of pelvis with and without IV contrast.

# High-risk T1 or ≥T2:

- **A 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.

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

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

# References on BL-A 5 of 5

	National
	Comprehensive
NCCN	Cancer
	Network®

# NCCN Guidelines Version 2.2018 Bladder Cancer

# PRINCIPLES OF IMAGING FOR BLADDER/UROTHELIAL CANCER REFERENCES

- <sup>1</sup>Shinagare 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.
- <sup>2</sup>Witjes 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.
- <sup>3</sup>Kollberg 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.
- <sup>4</sup>Goodfellow H, Viney Z, Hughes P, et al. Role of fluorodeoxyglucose positron emission tomography (FDG PET)-computed tomography (CT) in the staging of bladder cancer. BJU Int 2014;114:389-395.
- <sup>5</sup>Lu 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.
- <sup>6</sup>Kibel 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.
- <sup>7</sup>Leyendecker 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.
- <sup>8</sup>Tekes A, Kamel I, Imam K, et al. Dynamic MRI of bladder cancer: evaluation of staging accuracy. AJR Am J Roentgenol 2005;184:121–127.
   <sup>9</sup>Wu 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.
- <sup>10</sup>Zhang J, Gerst S, Lefkowitz RA, et al. Imaging of bladder cancer. Radiol Clin North Am 2007;45:183-205.
- <sup>11</sup>Anderson TS, Regine WF, Kryscio R, et al. Neurologic complications of bladder carcinoma: A review of 359 cases. Cancer 2003;97:2267-2272.
- <sup>12</sup>Rouprêt M, Babjuk M, Compérat E, et al. European guidelines on upper tract urothelial carcinomas: 2013 update. Eur Urol 2013;63:1059-1071.
- <sup>13</sup>Gakis G, Witjes JA, Compérat E, et al. EAU guidelines on primary urethral carcinoma. Eur Urol 2013;64:823-830.



# NCCN Guidelines Version 2.2018 Bladder Cancer

NCCN Guidelines Index Table of Contents Discussion

#### PRINCIPLES OF SURGICAL MANAGEMENT

- Transurethral Resection of the Bladder Tumor (TURBT) for Staging
- Adequate resection with muscle in specimen
- Muscle may be omitted in cases of documented low-grade Ta disease
- In cases of suspected or known carcinoma in situ
  - **OBIOPSY adjacent to papillary tumor**
  - Onsider prostate urethral biopsy
- > Papillary Appearing Tumor (likely non-muscle invasive)
  - **◊ Early repeat TURBT (within 6 weeks) if** 
    - Incomplete initial resection
    - No muscle in original specimen for high-grade disease
    - Large (≥3 cm) or multi-focal lesions
    - Any T1 lesion
- > Transurethral Resection for Sessile or Invasive Appearing Tumor (likely muscle invasive)
  - Or Repeat TURBT if
    - Prior resection did not include muscle in the setting of high grade disease
    - Any T1 lesion
    - First resection does not allow adequate staging/attribution of risk for treatment selection
    - Incomplete resection and considering tri-modality bladder preservation therapy
- Enhanced (blue light and narrow band imaging) cystoscopy may be helpful in identifying lesions not visible using white light cystoscopy
- Immediate postoperative intravesical chemotherapy within 24 hours if NMIBC and if no concern for bladder perforation
- > The most commonly used option for intravesical chemotherapy is mitomycin.

# **TURBT/Maximal TURBT for Treatment**

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

# Continued on next page



NCCN Guidelines Version 2.2018 Bladder Cancer

NCCN Guidelines Index Table of Contents Discussion

#### PRINCIPLES OF SURGICAL MANAGEMENT

# Transurethral Resection of the Prostate (TURP)

- Primary treatment option for urothelial carcinoma of the prostate with ductal/acini or prostatic urethral pathology.
- Postsurgical intravesical BCG is recommended (see Principles of Intravesical Therapy).

# Transurethral Resection (TUR) of the Urethral Tumor

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

#### Partial Cystectomy

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

# Radical Cystectomy/Cystoprostatectomy

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

## Radical Nephroureterectomy with Cuff of Bladder

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

## Continued on next page

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



NCCN Guidelines Version 2.2018 Bladder Cancer

#### PRINCIPLES OF SURGICAL MANAGEMENT

## **Urethrectomy**

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

# Regional Lymphadenectomy

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

# Pelvic Exenteration (category 2B)

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

# Continued on next page



# NCCN Guidelines Version 2.2018 Bladder Cancer

NCCN Guidelines Index Table of Contents Discussion

## 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</p>
- Unifocal tumor
- For favorable tumors ureteroscopic and percutaneous management provide similar survival outcomes compared to nephroureterectomy
- Less favorable clinical and pathologic criteria for nephron preservation:
- Multifocal tumors
- Flat or sessile tumor architecture
- ▶ Tumor size >1.5 cm
- ► High-grade tumors
- ▶ cT2-T4 tumors
- Mid and proximal ureteral tumor due to technical challenges
- Tumor crossing in fundibulum or ureteropelvic junction
- Imperative indications for conservative therapy of UTUC
- Bilateral renal pelvis and/or urothelial carcinoma of the ureter
- Solitary or solitary functioning kidney
- Chronic kidney disease/renal insufficiency
- Hereditary predisposition (eg, hereditary nonpolyposis colon cancer [HNPCC])
- Percutaneous or ureteroscopic surgical procedures
- Tumor fulguration/cautery
- > Tumor resection incorporating electrical energy, baskets, or cold cup devices with fulguration of the tumor bed
- Laser therapies (Nd:YAG penetration 4–6 mm, Ho:YAG shallow penetration <0.5 mm)</p>
- Extirpative surgical procedures
- Segmental ureterectomy ± ureteral reimplantation for distal ureteral tumors
- Complete ureterectomy with ileal ureter replacement (proximal/mid ureteral tumors)
- Topical immunotherapy and chemotherapy management
- ▶ BCG, mitomycin
- ▶ Route of administration might include percutaneous antegrade (preferred) or retrograde ureteral catheters
- Induction and maintenance therapy regimens, similar to intravesical therapy, can be used
- Patients with renal pelvis and urothelial carcinoma of the ureter managed with nephron-preserving procedures and adjunctive therapies require long-term surveillance, including cross-sectional urography or endoscopic visualization. Treatment can be associated with patient anxiety, tumor seeding, and the need for multiple procedures and ultimate nephroureterectomy with bladder cuff. Clinical/pathologic understaging is problematic. Recurrence or tumor persistence might be life-threatening due to disease progression.

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

Printed by Anton Kat	oakov on 3/5/2018 6:44:07 AM.	For personal use only. Not approved for distribution. Copyright $@$ 2018 Nationa	I Comprehensive Cancer Network, Inc., All Rights Reserved.
NCCN	National Comprehensive Cancer Network®	NCCN Guidelines Version 2 Bladder Cancer	.2018 <u>NCCN Guidelines Index</u> <u>Table of Contents</u> <u>Discussion</u>
		PRINCIPLES OF PATHOLOG	GY MANAGEMENT
<ul> <li>Classifica</li> <li>Flat uro</li> <li>Uroth</li> <li>Papillar</li> <li>Uroth</li> <li>Papill</li> <li>Urothe</li> <li>Urothelia similarly</li> </ul>	ation of Urothelial N thelial neoplastic le elial carcinoma in s y urothelial neoplas ary urothelial neoplas ary urothelial carci ology report on bio ularis propria (detru- this structure is in ce or absence of lar ce or absence of su tumors with an inv to the WHO/ISUP (2)	leoplasia (WHO/ISUP Consensus 2004): esion: situ stic lesions: lasm of low malignant potential noma, low-grade noma, high-grade psy/TURBT specimens should specify: usor muscle) is present and, if present, vaded by tumor nina propria invasion nphovascular space invasion bjacent carcinoma in situ verted growth pattern should be graded 2004) system for exophytic tumors as detailed	<ul> <li>Variant histology should be stated if present:</li> <li>Urothelial carcinoma with divergent differentiation (squamous/glandular).</li> <li>Percentage of divergent differentiation may be stated. Eg, "urothelial carcinoma with glandular (35%) differentiation."</li> <li>Micropapillary variant of urothelial carcinoma.</li> <li>Percentage of micropapillary component should be stated. However, no percentage limitation is required for diagnosis.</li> <li>Nested variant of urothelial carcinoma.</li> <li>Lymphoepithelioma-like carcinoma.</li> <li>Sarcomatoid carcinoma.</li> <li>Undifferentiated carcinoma with trophoblastic giant cells.</li> <li>Undifferentiated carcinoma (including giant cell carcinoma)</li> <li>Squamous cell carcinoma (comprised almost entirely of keratin-forming squamous carcinoma)</li> </ul>

- ♦ Squamous cell carcinoma (non-verrucous and nonschistosomal)
- **◊ Verrucous squamous carcinoma**
- Squamous cell carcinoma, associated with precedent or concurrent infection with schistosomal species.
- Adenocarcinoma
  - Orimary adenocarcinoma
    - Enteric pattern (acinar, villous, cribriform, or solid)
    - Mucinous or colloid carcinoma
  - Signet-ring cell carcinoma
  - Mixed pattern
  - Our Urachal carcinoma (majority are adenocarcinoma)
    - Clear cell adenocarcinoma
- Neuroendocrine carcinoma
  - ◊ Small cell carcinoma
  - Large cell neuroendocrine carcinoma
  - **Mixed patterns**

Amin MB, McKenney JK, Paner GP, et al, International Consultation on Urologic Disease-European Association of Urology Consultation on Bladder Cancer 2012. ICUD-EAU International Consultation on Bladder Cancer 2012: Pathology. Eur Urol 2013;63:16-35. Epstein, JI. Diagnosis and classification of flat, papillary, and invasive urothelial carcinoma: the WHO/ISUP consensus. Int J Surg Path 2010;18(3 Suppl):106S-111S.

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

	National
	Comprehensive
NCCN	Cancer
	Network®

# NCCN Guidelines Version 2.2018 Bladder Cancer

NCCN Guidelines Index Table of Contents Discussion

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

#### Mixed Histology:

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

#### Pure Squamous:

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

# Pure Adenocarcinoma Including Urachal:

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

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

Any Small-Cell Component (or neuroendocrine features):

- Neoadjuvant chemotherapy followed by local treatment (cystectomy or radiotherapy) is recommended for any patient with small-cell component histology with localized disease regardless of stage.
- Neoadjuvant chemotherapy
- > Standard cisplatin eligible
  - ♦ Etoposide + cisplatin<sup>7</sup>
  - ◊ Alternating ifosfamide + doxorubicin with etoposide + cisplatin<sup>8-10</sup>
- Standard cisplatin ineligible
   Etoposide + carboplatin<sup>11</sup>
- Metastatic chemotherapy
- Standard cisplatin eligible
   Etoposide + cisplatin<sup>7</sup>
- Standard cisplatin ineligible

   Etoposide + carboplatin<sup>11</sup>
- Alternate regimen for select patients
  - ◊ Alternating ifosfamide + doxorubicin with etoposide + cisplatin<sup>8-10</sup>

#### Primary Bladder Sarcoma:

• Treatment as per <u>NCCN Guidelines for Soft Tissue Sarcoma</u>.

## References on BL-D 2 of 2



NCCN Guidelines Version 2.2018 Bladder Cancer

NCCN Guidelines Index Table of Contents Discussion

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

#### REFERENCES

<sup>1</sup>Meeks JJ, et al. Pathological response to neoadjuvant chemotherapy for muscle-invasive micropapillary bladder cancer. BJU Int 2013;111:E325-30. <sup>2</sup>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.

<sup>3</sup>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.

<sup>4</sup>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.

<sup>5</sup>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.

<sup>6</sup>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.

<sup>7</sup>Roth BJ, Johnson DH, Einhorn LH, et al. Randomized study of cyclophosphamide, doxorubicin, and vincristine versus etoposide and cisplatin versus alternation of these two regimens in extensive small-cell lung cancer: a phase III trial of the Southeastern Cancer Study Group. J Clin Oncol 1992;10:282-291.

<sup>8</sup>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.

<sup>9</sup>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.

<sup>10</sup>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.

<sup>11</sup>Okamoto H, Watanabe K, Nishiwaki Y, et al. Phase II study of area under the plasma-concentration-versus-time curve-based carboplatin plus standard-dose intravenous etoposide in elderly patients with small-cell lung cancer. J Clin Oncol 1999;17:3540-3545.

NCCN	National Comprehensive Cancer Network <sup>®</sup>	NCCN Guidelines Version 2.2018 Bladder Cancer
------	---	--

## FOLLOW-UP

No single follow-up plan is appropriate for all patients. The follow-up tables are to provide guidance, and should be modified for the individual patient based on sites of disease, biology of disease, and length of time on treatment. Reassessment of disease activity should be performed in patients with new or worsening signs or symptoms of disease, regardless of the time interval from previous studies. Further study is required to define optimal follow-up duration. **Table 1: Non-Muscle Invasive Bladder Cancer** 

Category       1       2       3       4       5       5-10       >10         Cystoscopy       Low risk       3, 12       Annually       As clinically indicated         Intermediate risk       3, 6, 12       Every 6 mo       Annually       As clinically indicated         High risk       Every 3 mo       Every 6 mo       Annually       As clinically indicated         maging       Low risk       UT baseline AP baseline       As clinically indicated       As clinically indicated         Intermediate risk       UT baseline AP baseline       As clinically indicated       As clinically indicated         High risk       Consider: UT baseline, 12 AP baseline       UT every 1–2 y       As clinically indicated         Hood tests       Low risk Intermediate risk High risk       N/A       N/A         Irine Tests       Low risk Intermediate risk       UC as (6, 12 Mo       UC every 6 Mo       Annually       As clinically indicated         High risk       UC every 3 mo Consider urinary urothelial tumor markers (category 2B)       UC every 6 mo       Annually       As clinically indicated         Table Legend on BL-E 4 of 4       See Recurrent or Persistent Disease (BL-8)       See Post-Cystectomy or Post-Bladder Sparing (BL-E See NCCN Guideli for Survivorship       See NCCN Guideli         te: All recommendations are category	<u>Test</u>	AUA Risk		Year (at month intervals)							
Low risk       3, 12       Annually       As clinically indicated         Intermediate risk       3, 6, 12       Every 6 mo       Annually       As clinically indicated         High risk       Every 3 mo       Every 6 mo       Annually       As clinically indicated         maging       Low risk       UT baseline AP baseline       As clinically indicated AP baseline       As clinically indicated         High risk       Consider: UT baseline, 12 AP baseline       UT every 1–2 y       As clinically indicated         High risk       Low risk Intermediate risk High risk       VI baseline, 12 AP baseline       VI every 1–2 y       As clinically indicated         Intermediate risk       UT baseline, 12 AP baseline       VI baseline, 12 AP baseline       VI every 1–2 y       As clinically indicated         Intermediate risk       UC as 6, 12       UC every 6 Mood tests       N/A       N/A         Intermediate risk       UC 3, 6, 12       UC every 6 Mood       Annually       As clinically indicated         Intermediate risk       UC 3, 6, 12       UC every 6 Moo       Annually       As clinically indicated         Intermediate risk       UC 3, 6, 12       UC every 6 Moo       Annually       As clinically indicated         Intermediate risk       UC every 3 mo       UC every 6 mo       Annually       As		Category	1	2 3 4 5 5-1					>10		
Intermediate risk       3, 6, 12       Every 6 mo       Annually       As clinically indicated         High risk       Every 3 mo       Every 6 mo       Annually       As clinically indicated         maging       Low risk       UT baseline AP baseline Paseline Intermediate risk       UT baseline AP baseline Intermediate risk       As clinically indicated         High risk       Consider: UT baseline, 12 AP baseline       UT every 1–2 y       As clinically indicated         High risk       Low risk Intermediate risk High risk       N/A       As clinically indicated         Intermediate risk High risk       UC 3, 6, 12       UC every 6 Mo       Annually       As clinically indicated Annually         Intermediate risk High risk       UC every 3 mo Consider urinary urothelial tumor markers (category 2B)       UC every 6 mo Consider urinary urothelial tumor markers (category 2B)       As clinically indicated       As clinically indicated         Table Legend on BL-E 4 of 4       See Recurrent or Persistent Disease (BL-8)       See Post-Cystectomy or Post-Bladder Sparing (BL-E See NCCN Guideli for Survivorship       See NCCN Guideli for Survivorship	Cystoscopy	Low risk	3, 12		Ann	ually		As clin	nically indicated		
High risk     Every 3 mo     Every 6 mo     Annually     As clinically indicated       maging     Low risk     UT baseline AP baseline High risk     UT baseline AP baseline 12 AP baseline     As clinically indicated As clinically indicated       High risk     Consider: UT baseline, 12 AP baseline     UT every 1–2 y     As clinically indicated       Ilood tests     Low risk Intermediate risk High risk     N/A       Irine Tests     Low risk     N/A       Intermediate risk, UC 3, 6, 12 High risk     UC every 6 mo     N/A       Intermediate risk, UC 3, 6, 12 High risk     UC every 6 mo     Annually       Intermediate risk, UC a, 6, 12 High risk     UC every 6 mo     Annually       As clinically indicated     See Post-Cystectomy or Post-Bladder Sparing (BL-E See NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.		Intermediate risk	3, 6, 12	Every 6 mo		Annually		As clin	ically indicated		
Low risk       UT baseline AP baseline       As clinically indicated         Intermediate risk       UT baseline AP baseline       As clinically indicated         High risk       Consider: UT baseline, 12 AP baseline       UT every 1–2 y       As clinically indicated         N/A       12 AP baseline       N/A         Intermediate risk       Intermediate risk       N/A         High risk       UC a, 6, 12       UC every 6 mo       Annually         Intermediate risk       UC avery 3 mo Consider urinary urothelial tumor markers (category 28)       UC every 6 mo       Annually         Table Legend on BL-E 4 of 4       See Recurrent or Persistent Disease (BL-8)       See Post-Cystectomy or Post-Bladder Sparing (BL-E See NCCN Guideli for Survivorship       See NCCN Guideli for Survivorship		High risk	Every	3 mo		Every 6 mo		Annually	As clinically indicated		
AP baseline       As clinically indicated         Intermediate risk       UT baseline, AP baseline       As clinically indicated         High risk       Consider: UT baseline, 12 AP baseline       UT every 1–2 y       As clinically indicated         Blood tests       Low risk       Table baseline       N/A         Intermediate risk       High risk       N/A         Intermediate risk       Intermediate risk       N/A         Irine Tests       Low risk       UC 3, 6, 12       UC every 6 mo       Annually       As clinically indicated         High risk       UC every 3 mo Consider urinary urothelial tumor markers (category 2B)       UC every 6 mo       Annually       As clinically indicated         Table Legend on BL-E 4 of 4       See Recurrent or Persistent Disease (BL-8)       See Post-Cystectomy or Post-Bladder Sparing (BL-E See NCCN Guideli for Survivorship       See NCCN Guideli for Survivorship	Imaging	Low risk	UT baseline			As clinic	ally indicated				
Intermediate risk         UT baseline AP baseline         As clinically indicated           High risk         Consider: UT baseline, 12 AP baseline         UT every 1–2 y         As clinically indicated           Blood tests         Low risk Intermediate risk High risk         N/A           Frine Tests         Low risk         UC 3, 6, 12         UC every 6 mo         Annually         As clinically indicated           High risk         UC every 3 mo Consider urinary urothelial tumor markers (category 2B)         UC every 6 mo         Annually         As clinically indicated           Table Legend on BL-E 4 of 4         See Recurrent or Persistent Disease (BL-8)         See Post-Cystectomy or Post-Bladder Sparing (BL-E See NCCN Guideli for Survivorship         See NCCN Guideli for Survivorship	55		AP baseline	seline							
High risk       Consider: UT baseline, 12 AP baseline       UT every 1–2 y       As clinically indicated         Blood tests       Low risk       N/A         Intermediate risk       N/A         Intermediate risk       N/A         Frine Tests       Low risk         Intermediate risk       UC 3, 6, 12         UC every 6       Annually         High risk       UC every 3 mo Consider urinary urothelial tumor markers (category 2B)         Table Legend on BL-E 4 of 4       See Recurrent or Persistent Disease (BL-8)         See Post-Cystectomy or Post-Bladder Sparing (BL-E See NCCN Guideli for Survivorship		Intermediate risk	UT baseline AP baseline	As clinically indicated As clinically indicated							
Blood tests       Low risk       N/A         Intermediate risk       High risk         Irine Tests       Low risk         Intermediate risk       UC 3, 6, 12         UC every 6       Annually         High risk       UC every 3 mo         UC every 6 mo       Annually         As clinically indicated         Table Legend on BL-E 4 of 4       See Recurrent or Persistent Disease (BL-8)         See Post-Cystectomy or Post-Bladder Sparing (BL-E         See NCCN Guidelin         Inical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.		High risk	Consider: UT baseline, 12 AP baseline	UT every 1–2 y As clinically indicated							
Intermediate risk       Intermediate risk         High risk       Low risk       N/A         Irine Tests       Low risk       UC 3, 6, 12       UC every 6         Intermediate risk       UC 3, 6, 12       UC every 6       Annually         High risk       UC every 3 mo       UC every 6 mo       Annually         High risk       UC every 3 mo       UC every 6 mo       Annually         Table Legend on BL-E 4 of 4       See Recurrent or Persistent Disease (BL-8)       See Post-Cystectomy or Post-Bladder Sparing (BL-E         >te: All recommendations are category 2A unless otherwise indicated. Inical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.       See NCCN Guideling for Survivorship	Blood tests	Low risk				N/A					
High risk       N/A         Irine Tests       Low risk       UC 3, 6, 12       UC every 6 mo       Annually       As clinically indicated         High risk       UC every 3 mo Consider urinary urothelial tumor markers (category 2B)       UC every 6 mo       Annually       As clinically indicated         Table Legend on BL-E 4 of 4       See Recurrent or Persistent Disease (BL-8)       See Post-Cystectomy or Post-Bladder Sparing (BL-E See NCCN Guideling for Survivorship         ve: All recommendations are category 2A unless otherwise indicated. Inical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.       See NCCN Guideling for Survivorship		Intermediate risk									
Low risk       Low risk       N/A         Intermediate risk       UC 3, 6, 12       UC every 6 mo       Annually       As clinically indicated         High risk       UC every 3 mo Consider urinary urothelial tumor markers (category 2B)       UC every 6 mo       Annually       As clinically indicated         Table Legend on BL-E 4 of 4       See Recurrent or Persistent Disease (BL-8)       See Post-Cystectomy or Post-Bladder Sparing (BL-E See NCCN Guideli for Survivorship         ve: All recommendations are category 2A unless otherwise indicated. inical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.       See Number See See See See See See See See See S		High risk									
Low risk       Low risk       N/A         Intermediate risk       UC 3, 6, 12       UC every 6 mo       Annually       As clinically indicated         High risk       UC every 3 mo Consider urinary urothelial tumor markers (category 2B)       UC every 6 mo       Annually       As clinically indicated         Table Legend on BL-E 4 of 4       See Recurrent or Persistent Disease (BL-8)       See Post-Cystectomy or Post-Bladder Sparing (BL-E See NCCN Guidelii for Survivorship         >te: All recommendations are category 2A unless otherwise indicated. inical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.											
Intermediate risk       UC 3, 6, 12       UC every 6 mo       Annually       As clinically indicated         High risk       UC every 3 mo Consider urinary urothelial tumor markers (category 2B)       UC every 6 mo Consider urinary urothelial tumor markers (category 2B)       As clinically indicated         Table Legend on BL-E 4 of 4       See Recurrent or Persistent Disease (BL-8)       See Post-Cystectomy or Post-Bladder Sparing (BL-E See NCCN Guideling for Survivorship         >te: All recommendations are category 2A unless otherwise indicated. inical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.       See NCCN Guideling for Survivorship	Urine Tests	Low risk				N/A					
High risk       UC every 3 mo Consider urinary urothelial tumor markers (category 2B)       UC every 6 mo       Annually       As clinically indicated         • Table Legend on BL-E 4 of 4       See Recurrent or Persistent Disease (BL-8)       See Post-Cystectomy or Post-Bladder Sparing (BL-E See NCCN Guideling         • Det: All recommendations are category 2A unless otherwise indicated. inical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.       See NCCN Guideling		Intermediate risk	UC 3, 6, 12	UC every 6 mo	Annually		As clinically indicated				
Table Legend on BL-E 4 of 4       See Recurrent or Persistent Disease (BL-8)       See Post-Cystectomy or Post-Bladder Sparing (BL-E         Dete: All recommendations are category 2A unless otherwise indicated.       See NCCN Guideli         inical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.       See NCCN Guideli		High risk	UC every 3 mo Consider urinar tumor markers	o UC every 6 mo Annually ary urothelial 's (category 2B)					As clinically indicated		
ote: All recommendations are category 2A unless otherwise indicated. inical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.	e Table Lege	end on BL-E 4 of 4	See Recu	irrent or Persis	tent Disease (I	<u>BL-8)</u> <u>See Po</u>	ost-Cystectom	y or Post-Bla	dder Sparing (BL-E 2		
Vinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.		nondations are estagen	24 unloss otherwise	indicated				]	<u>See NCCN Guidelin</u>		
	Clinical Trials: N	CCN believes that the be	st management of any	y patient with cance	r is in a clinical trial.	Participation in clin	ical trials is especi	ally encouraged.			

Comprehensive Cancer	NCCN Guidelines Version 2.2018 Bladder Cancer	NCCN Guidelines Index Table of Contents Discussion
	Comprehensive Cancer Network <sup>®</sup>	Comprehensive Cancer Network® NCCN Guidelines Version 2.2018 Bladder Cancer

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

Test	Risk Category	Year (at month intervals)									
		1	2	3	4	5	5–10	>10			
Cystoscopy	Post-cystectomy NMIBC		N/A								
	Post-cystectomy MIBC										
	Post-bladder sparing (ie, partial cystectomy or chemoradiation)	Every	3 mo	Every	Every 6 mo An		nually	As clinically indicated			
Imaging	Post-cystectomy NMIBC	AP/UT 3, 12	AP/UT Annually				R annually	As clinically indicated			
	Post-cystectomy MIBC	AP/UT ever C every 3	y 3–6 mo 3–6 mo		AP annually C annually		R annually	As clinically indicated			
	Post-bladder sparing (ie, partial cystectomy or chemoradiation)	AP/UT every 3– MIB C every 3–6 mo	-6 months for C nths for MIBC		AP annually C annually		As clinically indicated				

See Table Legend on BL-E 4 of 4

See Recurrent or Persistent Disease (BL-8)

Table 2 continued on next page

#### See NCCN Guidelines for Survivorship

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

	National		
	Comprehensive	NCCN Guidelines Version 2.2018	NCCN Guidelines Index
NCCN	Cancer	Bladder Cancer	Table of Contents Discussion
	Network®		

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

Test	Risk Category	Year (at month intervals)								
		1	2	3	4	5	5–10	>10		
Blood tests	Post-cystectomy NMIBC or Post-cystectomy MIBC	<ul> <li>R every 3–6 mo</li> <li>LFT every 3–6 mo</li> <li>CBC, CMP every 3–6 mo if received chemotherapy</li> </ul>		• R an • LFT a • B12 a	nually nnually nnually		As clinical	ly indicated		
	Post-bladder sparing (ie, partial cystectomy or chemoradiation)	<ul> <li>R every 3–6 mo</li> <li>LFT every 3–6 mo</li> <li>CBC, CMP every 3–6 mo if received chemotherapy</li> </ul>								
Urine Tests	Post-cystectomy NMIBC or Post-cystectomy MIBC	UC every 6 Consider UW ev	–12 mo ery 6–12 mo*		UC UW	as clinically ind as clinically ind	dicated dicated			
	Post-bladder sparing (ie, partial cystectomy or chemoradiation)	UC every 6	6–12 mo UC as clinically i			as clinically ind	dicated			

	National	
	Comprehensive	Ν
NCCN	Cancer	D
	Network®	D

NCCN Guidelines Version 2.2018 Bladder Cancer

NCCN Guidelines Index Table of Contents Discussion

FOLLOW-UP

# Table Legend

Imaging studies:

UT = upper tract imaging: CT urography, MR urography, intravenous pyelogram (IVP), retrograde pyelography, or ureteroscopy

AP = abdominal-pelvic imaging: CT, MRI, or PET/CT (PET/CT not recommended for NMIBC)

AP/UT = CT urography or MR urography (image upper tracts + axial imaging of abdomen/pelvis)

R = renal imaging to look for hydronephrosis: renal ultrasound

C = chest imaging: Chest x-ray (preferred), CT chest, or PET/CT

# Blood tests:

B = bone testing: calcium, magnesium, phosphate, alkaline phosphatase

CMP = complete metabolic panel

LFT = liver function testing: AST, ALT, bilirubin, alkaline phosphatase

R = renal function testing: electrolytes, creatinine

Urine tests:

UC = urine cytology, done at time of cystoscopy if bladder in situ

UW = urethral wash cytology, reserved for high-risk patients: positive urethral margin, multifocal CIS, prostatic urethral invasion



# NCCN Guidelines Version 2.2018 Bladder Cancer

NCCN Guidelines Index Table of Contents Discussion

# PRINCIPLES OF INTRAVESICAL TREATMENT

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

## **Intravesical Therapy for Bladder Cancer**

Immediate Postoperative Intravesical Chemotherapy

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

# Induction (Adjuvant) Intravesical Chemotherapy or BCG

- Treatment option for NMIBC (See BL-2, BL-3, and BL-8).
- The most commonly used agents are BCG, mitomycin, and gemcitabine.
- Initiated 3–4 weeks after TURBT with or without maintenance.
- Weekly instillations during induction are given for approximately 6 weeks.
- Maximum of 2 consecutive 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.<sup>1</sup>
- 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.<sup>1</sup>

#### **Continued on next page**

# References on BL-F 3 of 3

	National	
	Comprehensive	NCCN (
NCCN	Cancer	Bladdo
	Network®	Diauue

## PRINCIPLES OF INTRAVESICAL TREATMENT

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

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

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

Postsurgical Intraprostatic BCG for Urothelial Carcinoma of the Prostate

- Treatment for patients with ductal + acini, or prostatic urethra involvement. See Urothelial Carcinoma of the Prostate (UCP-1)
- Initiated 3-4 weeks after TURP
- Induction (adjuvant) BCG should be followed with maintenance BCG
- Data indicate a reduction in recurrence in the prostate in patients with superficial disease<sup>2-8</sup>

Postsurgical Intraurethral Therapy for Primary Carcinoma of the Urethra

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

Postsurgical Intrapelvic Therapy for Upper Tract Tumors

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

References on BL-F 3 of 3

	National	
	Comprehensive	NCC
NCCN	Cancer	Blad
	Network®	Diau

NCCN Guidelines Version 2.2018 Bladder Cancer

#### PRINCIPLES OF INTRAVESICAL TREATMENT

#### REFERENCES

- <sup>1</sup>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.
- <sup>2</sup>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.
- <sup>3</sup>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.
- <sup>4</sup>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.
- <sup>5</sup>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.
- <sup>6</sup>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.
- <sup>7</sup>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.
- <sup>8</sup>Solsona E, Iborra I, Ricos JV, et al. Recurrence of superficial bladder tumors in prostatic urethra. Eur Urol 1991;19:89-92.
- <sup>9</sup>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.
- <sup>10</sup>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.
- <sup>11</sup>Audenet F, Traxer O, Bensalah K, Roupret 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.



# NCCN Guidelines Version 2.2018 Bladder Cancer

#### PRINCIPLES OF SYSTEMIC THERAPY

#### Perioperative chemotherapy (neoadjuvant or adjuvant)

#### Preferred regimens

• DDMVAC (dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin) with growth factor support for 3 or 4 cycles<sup>1,2</sup>

• Gemcitabine and cisplatin for 4 cycles<sup>3,4</sup>

Other recommended regimens

• CMV (cisplatin, methotrexate, and vinblastine) for 3 cycles<sup>5</sup>

- For patients who are not candidates for cisplatin, there are no data to support a recommendation for perioperative chemotherapy.
- Randomized trials and meta-analyses show a survival benefit for cisplatin-based neoadjuvant chemotherapy (3 or 4 cycles) in patients with muscle-invasive bladder cancer.<sup>1,6,7</sup>
- Meta-analysis suggests a survival benefit to adjuvant therapy for pathologic T3, T4 or N+ disease at cystectomy.<sup>7</sup>
- 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.<sup>2,8</sup> 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.<sup>4,9</sup>
- For gemcitabine/cisplatin, both 21- and 28-day regimens are acceptable. Better dose compliance may be achieved with fewer delays in dosing using the 21-day schedule.<sup>10</sup>
- Neoadjuvant chemotherapy may be considered for select patients with upper tract urothelial carcinoma, particularly for higher stage and/or grade tumors, as renal function will decline after nephroureterectomy and may preclude adjuvant therapy.
- Carboplatin should not be substituted for cisplatin in the perioperative setting.
- For patients with borderline renal function or minimal dysfunction, a split-dose administration of cisplatin may be considered (such as 35 mg/m<sup>2</sup> 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.

# Continued on BL-G 2 of 5

# References on BL-G 5 of 5

# Comprehensive NCCN Guidelines Version 2.2018 **Bladder Cancer**

	PRINCIPLES OF SYSTEMIC THERAPY	
First-line systemic therapy for locally advanced or metastatic disease (Stage IV)		
Cisplatin eligible	<ul> <li><u>Preferred regimens</u></li> <li>Gemcitabine and cisplatin<sup>4</sup> (category 1)</li> <li>DDMVAC with growth factor support (category 1)<sup>2,8</sup></li> </ul>	
Cisplatin ineligible	Preferred regimens • Gemcitabine and carboplatin <sup>11</sup> • Atezolizumab <sup>12</sup> • Pembrolizumab <sup>13</sup>	
	Other recommended regimens • Gemcitabine <sup>14</sup> • Gemcitabine and paclitaxel <sup>15</sup>	
	Useful under certain circumstances • Ifosfamide, doxorubicin, and gemcitabine <sup>16</sup> (for patients with good kidney function and good PS)	

 The presence of both non-nodal metastases and ECOG performance score ≥2 strongly predict poor outcome with chemotherapy. Patients without these adverse prognostic factors have the greatest benefit from chemotherapy. The impact of these factors in relation to immune checkpoint inhibition is not fully defined, but they remain poor prognostic indicators in general.

• For most patients, the risks of adding paclitaxel to gemcitabine and cisplatin outweigh the limited benefit seen in the randomized trial.<sup>17</sup>

• A substantial proportion of patients cannot receive cisplatin-based chemotherapy due to renal impairment or other comorbidities.

Participation in clinical trials of new or more tolerable therapy is recommended.

National

Cancer

Network<sup>®</sup>

NCCN

Continued on BL-G 3 of 5

References on BL-G 5 of 5


# NCCN Guidelines Version 2.2018 Bladder Cancer

NCCN Guidelines Index Table of Contents Discussion

### PRINCIPLES OF SYSTEMIC THERAPY

<u>Subsequent systemic therapy for locally advanced or metastatic disease (Stage IV) (post-platinum)</u> <sup>a</sup> Participation in clinical trials of new agents is recommended.		
Preferred regimen • Pembrolizumab (category 1) <sup>18</sup>	Other recommended regimens • Nab-paclitaxel <sup>26</sup> • Paclitaxel or docetaxel <sup>24</sup> • Gemcitabine <sup>14</sup> • Pemetrexed <sup>25</sup>	
Alternative preferred regimens • Atezolizumab <sup>19</sup> • Nivolumab <sup>20</sup> • Durvalumab <sup>21</sup> • Avelumab <sup>22,23</sup>	Useful in certain circumstances based on prior medical therapy • Ifosfamide <sup>27</sup> • Methotrexate • Ifosfamide, doxorubicin, and gemcitabine <sup>16</sup> • Gemcitabine and paclitaxel <sup>15</sup> • Gemcitabine and cisplatin <sup>4</sup> • DDMVAC with growth factor support <sup>2</sup>	

Subsequent systemic therapy for locally advanced or metastatic disease (Stage IV) (post-checkpoint inhibitor) Participation in clinical trials of new agents is recommended.		
Preferred regimen for cisplatin ineligible, chemotherapy naïve • Gemcitabine/carboplatin	Other recommended regimens • Nab-paclitaxel <sup>26</sup> • Paclitaxel or docetaxel <sup>24</sup> • Gemcitabine <sup>14</sup> • Pemetrexed <sup>25</sup>	
<ul> <li><u>Preferred regimens for cisplatin eligible,</u></li> <li><u>chemotherapy naïve</u></li> <li>Gemcitabine and cisplatin<sup>4</sup></li> <li>DDMVAC with growth factor support<sup>2</sup></li> </ul>	<u>Useful in certain circumstances based on prior medical therapy</u> • Ifosfamide <sup>27</sup> • Methotrexate • Ifosfamide, doxorubicin, and gemcitabine <sup>16</sup> • Gemcitabine and paclitaxel <sup>15</sup>	

#### Continued on BL-G 4 of 5

<sup>a</sup>If platinum (eg, cisplatin or carboplatin) more than 12 months ago, consider re-treatment with platinum if the patient is still platinum eligible.

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

# References on BL-G 5 of 5

BL-G 3 OF 5



# NCCN Guidelines Version 2.2018 Bladder Cancer

### PRINCIPLES OF SYSTEMIC THERAPY

Radiosensitizing chemotherapy regimens for organ-preserving chemoradiation
<ul> <li>Preferred regimens (doublet chemotherapy is preferred when feasible)</li> <li>Cisplatin<sup>b</sup> and 5-FU<sup>28</sup></li> <li>Cisplatin<sup>b</sup> and paclitaxel<sup>28,29</sup></li> <li>5-FU and mitomycin<sup>30</sup></li> <li>Cisplatin<sup>b</sup> alone<sup>31</sup></li> </ul>
Other recommended regimen • Low-dose gemcitabine <sup>32,33</sup> (category 2B)

Radiosensitizing chemotherapy given concurrently with conventionally fractionated radiation for palliation of metastases or recurrence Preferred regimen

Cisplatin<sup>b</sup>

Other recommended regimens

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

References on BL-G 5 of 5

<sup>b</sup>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.)

National Comprehensive NCCN Cancer Network<sup>®</sup>

# NCCN Guidelines Version 2.2018 **Bladder Cancer**

NCCN Guidelines Index **Table of Contents** Discussion

### PRINCIPLES OF SYSTEMIC THERAPY

- <sup>1</sup>Grossman HB, Natale RB, Tangen CM, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally educated block.<sup>16</sup>Siefker-B compared with cystectomy alone for locally advanced bladder cancer. N Engl J Med 2003;349:859-866.
- <sup>2</sup>Sternberg CN, de Mulder PH, Schornagel JH, et al. Randomized phase III trial of high-doseintensity 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.
- <sup>3</sup>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.
- <sup>4</sup>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.
- <sup>5</sup>Griffiths G, Hall R, Sylvester 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.
- <sup>6</sup>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.
- <sup>7</sup>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.
- <sup>8</sup>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.
- <sup>9</sup>von der Maase H, Sengelov L, Roberts JT, et al. Long-term survival results of a randomized trial comparing generitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. J Clin Oncol 2005;23:4602-4608.
- <sup>10</sup>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.
- <sup>11</sup>De Šantis 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 Clinl Oncol 2012;30:191-199.
- <sup>12</sup>Balar AV, Galsky MD, Rosenberg JE, et al. Atezolizumab as first-line treatment in cisplatinineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial. Lancet 2018;389:67-76.
- <sup>13</sup>Balar AV, Castellano DE, O'Donnell PH, et al. Pembrolizumab as first-line therapy in cisplatinineligible advanced urothelial cancer: Results from the total KEYNOTE-052 study population [abstract]. J Clin Oncol 2018;6S:Abstract 284.
- <sup>14</sup>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.
- <sup>15</sup>Calabro F, Lorusso V, Rosati G, et al: Gemcitabine and paclitaxel every 2 weeks in patients with previously untreated urothelial carcinoma. Cancer 2009;115:2652-2659.

<sup>16</sup>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. <sup>17</sup>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.

<sup>18</sup>Bellmunt, de Wit R, Vaughn D, et al. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. N Engl J Med 2018;376:1015-1026.

- <sup>19</sup>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 2018; 387:1909-1920.
- <sup>20</sup>Sharma P, Retz M, Šiefker-Radtke A, et al. Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): A multicentre, single-arm, phase 2 trial. Lancet Oncol 2018. <sup>21</sup>Powles T. et al. Updated efficacy and tolerability of durvalumab in locally advanced or metastatic urothelial carcinoma [abstract]. J Clin Oncol 2018;35: Abstract 286.
- <sup>22</sup>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 lb study. J Clin Oncol 2018; Apr 4.
- <sup>23</sup>Patel M, Ellerton J, Infante J, et al. Avelumab in patients with metastatic urothelial carcinoma: Pooled results from two cohorts of the phase 1b JAVELIN Solid Tumor trial [abstract]. J Clin Oncol 2018:6S:Abstract 330.
- <sup>24</sup>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.
- <sup>25</sup>Sweenev CJ, Roth BJ, Kabbinavar FF, et al: Phase II study of pemetrexed for second-line treatment of transitional cell cancer of the urothelium. J Clini Oncol 2008;24:3451-3457.
- <sup>26</sup>Ko YJ, Canil CM, Mukherjee SD, et al: Nanoparticle albumin-bound paclitaxel for second-line treatment of metastatic urothelial carcinoma: a single group, multicentre, phase 2 study. Lancet Oncol 2013:14:769-776.

<sup>27</sup>Witte RS, Elson P, Bono B, et al: Eastern Cooperative Oncology Group phase II trial of ifosfamide in the treatment of previously treated advanced urothelial carcinoma. J Clin Oncol 1997;15:589-593.

- <sup>28</sup>Mitin T, Hunt D, Shipley W, et al. Transurethral surgery and twice-daily radiation plus paclitaxelcisplatin 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.
- <sup>29</sup>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.
- <sup>30</sup>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.
- <sup>31</sup>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.
- <sup>32</sup>Kent E 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.
- <sup>33</sup>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.

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

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

	National
	Comprehensive
NCCN	Cancer
	Network®

# NCCN Guidelines Version 2.2018 Bladder Cancer

### PRINCIPLES OF RADIATION MANAGEMENT OF INVASIVE DISEASE

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

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

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

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

Continued on next page References on BL-H 3 of 3 I OF 3



# NCCN Guidelines Version 2.2018 Bladder Cancer

### PRINCIPLES OF RADIATION MANAGEMENT OF INVASIVE DISEASE

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

- Data support the use of radiation therapy for urothelial carcinoma and squamous cell carcinoma of the urethra (case series and experience treating these carcinomas arising from other disease sites); radiation can also be considered for adenocarcinomas of the urethra.
- Definitive Radiation Therapy (organ preservation)

► cT2 cN0

◊ 66 to 70 Gy EBRT delivered to gross disease with a margin to encompass areas of potential microscopic spread. Concurrent chemotherapy with regimens used for bladder cancer is encouraged for added tumor cytotoxicity.

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

### Postoperative adjuvant radiation therapy

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

References on BL-H 3 of 3



### PRINCIPLES OF RADIATION MANAGEMENT OF INVASIVE DISEASE

- 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.
- 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.
- Efstathiou JA, Zietman AL. Bladder Cancer. In Gunderson & Tepper, editors. Clinical Radiation Oncology. Churchill Livingstone Elsevier 2015.
- 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.
- Kamat AM, Hahn NM, Efstathiou JA, et al. Bladder cancer. Lancet 2018.
- 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.
- 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.
- 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.
- 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.
- 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, Ott OJ, 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 and radiation versus adjuvant chemotherapy alone for locally advanced bladder cancer [abstract]. Int J Radiat Oncol Biol Phys 2018;96:Abstract S94.



<sup>a</sup>See Principles of Imaging for Bladder/Urothelial Cancer (BL-A).

 <sup>b</sup>Montironi R, Lopez-Beltran A. The 2004 WHO classification of bladder tumors: A summary and commentary. Int J Surg Pathol 2005;13:143-153. <u>See Principles of Pathology Management (BL-C)</u>.
 <sup>c</sup><u>See Principles of Surgical Management (BL-B)</u>.
 <sup>d</sup><u>See Principles of Intravesical Treatment (BL-F)</u>.
 <sup>e</sup><u>See Principles of Systemic Therapy (BL-G 1 of 5)</u>.
 <sup>f</sup><u>See Principles of Systemic Therapy (BL-G 2 of 5)</u> and (<u>BL-G 3 of 5)</u>.





<sup>a</sup>See Principles of Imaging for Bladder/Urothelial Cancer (BL-A).

eSee Principles of Systemic Therapy (BL-G 1 of 5).

<sup>h</sup>The modifier "p" refers to pathologic staging based on cystectomy and lymph node dissection. <sup>i</sup>Follow recommendations for adjuvant chemotherapy after ensuring that patient is fully staged to rule out metastatic disease.

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

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



<sup>a</sup>See Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
 <sup>b</sup>See Principles of Surgical Management (BL-B).
 <sup>c</sup>See Principles of Systemic Therapy (BL-G 1 of 5).
 <sup>d</sup>Principles of Systemic Therapy (BL-G 2 of 5) and (BL-G 3 of 5).



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





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

# Comprehensive NCCN Guidelines Version 2.2018 Staging **Bladder Cancer**

NCCN Guidelines Index **Table of Contents** Discussion

### Table 1

NCCN

National

Cancer

Network<sup>®</sup>

#### American Joint Committee on Cancer (AJCC) TNM Staging System for Bladder Cancer 8th ed., 2017) Primary Tumor (T) ANATOMIC STAGE/PROGNOSTIC GROUPS Primary tumor cannot be assessed TX Stage 0a Та N0 No evidence of primary tumor **T0** Noninvasive papillary carcinoma Та Stage 0is Tis N0 Tis Urothelial carcinoma in situ: "flat tumor" **T1** Tumor invades lamina propria (subepithelial connective tissue) T1 N0 Stage I **T2** Tumor invades muscularis propria pT2a Tumor invades superficial muscularis propria (inner half) N0 Stage II T2a pT2b Tumor invades deep muscularis propria (outer half) T2b N0 Т3 Tumor invades perivesical tissue pT3a Microscopically Stage IIIA T3a N0 pT3b Macroscopically (extravesical mass) T3b N0 **T4** Extravesical tumor directly invades any of the following: prostatic T4a N0 stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall T1-T4a N1 Extravesical tumor invades prostatic stroma, seminal vesicles, T4a uterus, vagina Stage IIIB T1-T4a N2,3 Extravesical tumor invades pelvic wall, abdominal wall T4b Stage IVA T4b Anv N M0 Regional Lymph Nodes (N) Any T Any N M1a NX Lymph nodes cannot be assessed Stage IVB N0 No lymph node metastasis Any T Any N M1b Single regional lymph node metastasis in the true pelvis (perivesical, N1

- obturator, internal and external iliac, or sacral lymph node) Histologic Grade (G)
- Multiple regional lymph node metastasis in the true pelvis (perivesical, obturator, internal and external iliac, or sacral lymph node metastasis)
- Lymph node metastasis to the common iliac lymph nodes N3

#### Distant Metastasis (M)

N2

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

#### 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:

M0

- Low-grade LG
- HG High-grade

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

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

### **Continued on next page**

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



### Table 1 (Continued)

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

#### Primary Tumor (T)

- **TX** Primary tumor cannot be assessed
- T0 No evidence of primary tumor
- **Ta** Papillary noninvasive carcinoma
- Tis Carcinoma in situ
- T1 Tumor invades subepithelial connective tissue
- **T2** Tumor invades the muscularis
- 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.

#### Regional Lymph Nodes (N)\*

- 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

\* Note: Laterality does not affect the N classification.

#### Distant Metastasis (M)

- M0 No distant metastasis
- M1 Distant metastasis

#### ANATOMIC STAGE/PROGNOSTIC GROUPS

Stage 0a	Та	N0	MO
Stage 0is	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	Т3	N0	M0
Stage IV	T4 Any T Any T Any T	NX N1 N2 Any N	M0 M0 M0 M1

#### 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

#### **Continued on next page**

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.

Version 2.2018, 02/07/18 © National Comprehensive Cancer Network, Inc. 2018, All rights reserved. The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.



### Table 2

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

#### Primary Tumor (T) (Male Penile Urethra and Female Urethra)

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

#### Primary Tumor (T) Prostatic Urethra

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

#### Regional Lymph Nodes (N)

- **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

#### Distant Metastasis (M)

- M0 No distant metastasis
- M1 Distant metastasis

#### ANATOMIC STAGE/PROGNOSTIC GROUPS

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

#### **Continued on next page**

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.

Version 2.2018, 02/07/18 © National Comprehensive Cancer Network, Inc. 2018, All rights reserved. The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.



NCCN Guidelines Index Table of Contents Discussion

### Table 2 (Continued)

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

#### 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

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 2.2018 Bladder Cancer

NCCN Guidelines Index Table of Contents Discussion

Discussion	This discussion is being updated to correspond with the newly updated algorithm. Last updated 05/25/17	
NCCN Categories	s of Evidence and Consensus	
<b>Category 1:</b> Base NCCN consensus	d upon high-level evidence, there is uniform that the intervention is appropriate.	
<b>Category 2A:</b> Bas	ed upon lower-level evidence, there is uniform that the intervention is appropriate.	
Category 2B: Bas	ed upon lower-level evidence, there is NCCN e intervention is appropriate.	
Category 3: Base	d upon any level of evidence, there is major ent that the intervention is appropriate.	ission
All recommendat	ions are category 2A unless otherwise noted.	to in
	upua	
NCCN Categories	of Preference	
Preferred interver efficacy, safety, an	ntion: Interventions that are based on superior and evidence; and, when appropriate, affordability.	jress
Other recommend be somewhat less data; or significant	<b>ded intervention:</b> Other interventions that may efficacious, more toxic, or based on less mature ly less affordable for similar outcomes.	
Useful in certain oused for selected precommendation).	circumstances: Other interventions that may be batient populations (defined with	
All recommendat	ions are considered appropriate.	



# NCCN Guidelines Version 2.2018 Bladder Cancer

# **Table of Contents**

Overview	MS-3
Literature Search Criteria and Guidelines Update Metho	odology.MS-3
Clinical Presentation and Workup	MS-3
Pathology and Staging	MS-4
Adjuncts to Traditional White Light Cystoscopy	MS-5
Histology	MS-7
Non-Muscle-Invasive Urothelial Bladder Cancer	MS-8
Intravesical Therapy	MS-8
Treatment of cTa, Low-Grade Tumors	MS-10
Treatment of cTa, High-Grade Tumors	MS-10
Treatment of cT1 Tumors	MS-10
Treatment of Tis	MS-11
Surveillance	MS-11
Posttreatment of Recurrent or Persistent Disease	MS-11
Muscle-Invasive Urothelial Bladder Cancer	MS-12
Additional Workup	MS-12
Radical Cystectomy	MS-13
Partial Cystectomy	MS-13
Neoadjuvant Chemotherapy	MS-14
Adjuvant Chemotherapy	MS-15
Adjuvant Radiation	MS-16
Bladder Preservation	MS-16
Treatment of T2, T3, and T4a Tumors	MS-18
Treatment of T4b Disease or Positive Nodes	MS-19
Follow-up	MS-20

Recurrence or Persistent Disease	MS-20
Metastatic Urothelial Bladder Cancer	MS-20
Evaluation of Metastatic Disease	MS-21
Chemotherapy for Metastatic Disease	MS-21
Chemoradiotherapy for Metastatic Disease	MS-23
Targeted Therapies	MS-23
Non-Urothelial Carcinomas of the Bladder	MS-25
Upper Genitourinary Tract Tumors	MS-26
Renal Pelvis Tumors	MS-26
Urothelial Carcinoma of the Ureter	MS-27
Urothelial Carcinomas of the Prostate	MS-27
Primary Carcinoma of the Urethra	MS-28
Summary	MS-29
References	MS-31

NCCN Network®

# NCCN Guidelines Version 2.2018 Bladder Cancer

NCCN Guidelines Index Table of Contents Discussion

### Overview

An estimated 79,030 new cases of urinary bladder cancer (60,490 men and 18,540 women) will be diagnosed in the United States in 2017 with approximately 16,870 deaths (12,240 men and 4630 women) occurring during this same period.<sup>1</sup> Bladder cancer, the sixth most common cancer in the United States,<sup>1</sup> is rarely diagnosed in individuals younger than 40 years of age. Given that the median age at diagnosis is 73 years,<sup>2</sup> medical comorbidities are a frequent consideration in patient management.

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

# Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines for Bladder Cancer, an electronic search of the PubMed database was performed to obtain key literature published between August 20, 2014 and September 8, 2016, using the following search terms: bladder cancer OR urothelial carcinoma OR urothelial carcinoma of the ureter OR upper genitourinary tract tumor OR renal pelvic tumor OR urothelial carcinoma of the prostate OR primary carcinoma of the urethra. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.<sup>3</sup>

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

The PubMed search resulted in 378 citations and their potential relevance was examined. The data from key PubMed articles as well as articles from additional sources deemed as relevant to these Guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available on the NCCN webpage.

# **Clinical Presentation and Workup**

The most common presenting symptom in patients with bladder cancer is microscopic or gross hematuria, although urinary frequency from irritation or a reduced bladder capacity can also develop. Less commonly, the presenting symptom is a urinary tract infection. Upper tract obstruction or pain may occur in patients with a more advanced lesion. Patients presenting with these symptoms should be evaluated

NCCN National Comprehensive Cancer Network®

# NCCN Guidelines Version 2.2018 Bladder Cancer

with office cystoscopy to determine if a lesion is present. If one is documented, the patient should be scheduled for a transurethral resection of the bladder tumor (TURBT) to confirm the diagnosis and determine the extent of disease within the bladder. Urine cytology may also be obtained around the time of cystoscopy.

If the cystoscopic appearance of the tumor is solid (sessile), high-grade, or suggests invasion into muscle, a CT scan or MRI of the abdomen and pelvis is recommended before the TURBT. In tumors with a purely papillary appearance or in cases where only the mucosa appears to be abnormal, suggesting carcinoma in situ (CIS), a CT scan or other upper tract imaging can be deferred until after surgery because the results of a CT scan rarely alter management. Additional workup for all patients should include urine cytology, if not already tested, and evaluation of the upper tracts with a CT or MR urography; a renal ultrasound or CT without contrast with retrograde pyelogram; a ureteroscopy; or a combination of techniques. CT urography is generally the preferred approach to upper tract imaging in patients who can safely receive intravenous contrast agents.

TURBT with a bimanual examination under anesthesia (EUA) is performed to resect visible tumor and to sample muscle within the area of the tumor to assess invasion. The goal of TURBT is to correctly identify the clinical stage and grade of disease while completely resecting all visible tumor. Therefore, an adequate sample that includes bladder muscle (ie, muscularis propria) must be in the resection specimen. A small fragment of tumor with few muscle fibers is inadequate for assessing the depth of invasion and guiding treatment recommendations. When a large papillary lesion is noted, more than one session may be needed to completely resect the tumor. With CIS, biopsy of sites adjacent to the tumor and multiple random biopsies may be performed to assess for a field change. Single-dose intravesical chemotherapy within 24 hours of TURBT should be considered if non-invasive disease is suspected (see *Intravesical Chemotherapy*). Although there is no standard for immediate perioperative intravesical chemotherapy, mitomycin is most commonly used.

The involvement of the prostatic urethra and ducts in male patients with non-muscle-invasive bladder tumors has been reported. The risk is higher in the case of tumors in the bladder neck. Therefore, if the lesion is sessile or if Tis or high-grade disease is suspected, selected mapping biopsies and transurethral biopsy of prostate may be considered.

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

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

# **Pathology and Staging**

The most commonly used staging system is the tumor, node, metastasis (TNM) staging system by the American Joint Committee on Cancer (AJCC)<sup>4</sup> (see *Staging* in the algorithm). The NCCN Guidelines for Bladder Cancer divide treatment recommendations for urothelial carcinoma of the bladder according to non-muscle-invasive disease (Ta, T1, and Tis) and muscle-invasive disease ( $\geq$ T2 disease). Management of bladder cancer is based on the findings of the biopsy specimen, with

NCCN Network®

# NCCN Guidelines Version 2.2018 Bladder Cancer

NCCN Guidelines Index Table of Contents Discussion

attention to histology, grade, and depth of invasion. These factors are used to estimate the probability of recurrence and progression to a more advanced stage.

Approximately 70% of newly detected cases are non-muscle-invasive disease—exophytic papillary tumors confined largely to the mucosa (Ta) (70%–75%) or, less often, to the lamina propria (T1) (20%–25%) or flat high-grade lesions (CIS, 5%–10%).<sup>5,6</sup> These tumors tend to be friable and have a high propensity for bleeding. Their natural history is characterized by a tendency to recur in the same portion or another part of the bladder, and these recurrences can be either at the same stage as the initial tumor or at a more advanced stage.

Papillary tumors confined to the mucosa or submucosa are generally managed endoscopically with complete resection. Progression to a more advanced stage may result in local symptoms or, less commonly, symptoms related to metastatic disease. An estimated 31% to 78% of patients with a tumor confined to the mucosa or submucosa will experience a recurrence or new occurrence of urothelial carcinoma within 5 years.<sup>7</sup> These probabilities of recurrence vary as a function of the initial stage and grade, size, and multiplicity. Refining these estimates for individual patients is an area of active research.

Muscle-invasive disease is defined by malignant extension past the basement membrane. Muscularis propria invasion is the criteria for T2 disease and perivesical tissue involvement defines T3 disease. Extravesical invasion into the surrounding organs (ie, the prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall) delineates T4 disease. The depth of invasion is the most important determinant of prognosis and treatment.

### Adjuncts to Traditional White Light Cystoscopy

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

### Blue-light Cystoscopy

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

Several prospective clinical studies have evaluated BLC in conjunction with WLC and found higher detection rates of non-muscle-invasive lesions with BLC.<sup>8-13</sup> Particularly CIS, which is often missed by WLC, was detected at a higher rate. A meta-analysis of fluorescence cystoscopy TURBT in non-muscle-invasive bladder cancer included 12 randomized controlled trials with a total of 2258 patients.<sup>14</sup> A lower recurrence rate was observed (OR, 0.5; *P* < .00001) with a delayed time to first recurrence by 7.39 weeks (*P* < .0001). Recurrence-free survival



# NCCN Guidelines Version 2.2018 Bladder Cancer

was improved at 1 year (HR, 0.69; P < .00001) and at 2 years (HR, 0.65; P = .0004). However, no significant reduction in the rate of progression to muscle-invasive bladder cancer was seen (OR, 0.85; P = .39).

In a meta-analysis from Burger et al,<sup>15</sup> 1345 patients with Ta, T1 or CIS disease showed improved detection of bladder tumors and a reduction in recurrence.<sup>15</sup> Compared to WLC, BLC detected more Ta tumors (14.7%; *P* < .001; OR, 4.898; 95% CI, 1.937–12.390) and CIS lesions (40.8%; *P* < .001; OR, 12.372; 95% CI, 6.343–0.924). Importantly, 24.9% of patients had at least one additional Ta/T1 tumor detected (*P* < .001) and improved detection was seen in both primary (20.7%; *P* < .001) and recurrent disease (27.7%; *P* < .001). Another review of the literature included 26 studies with 5-ALA, 15 studies with HAL, and 2 studies that used both methodologies. The results from this review also support greater detection and reduced recurrence but no reduction in disease progression.<sup>16</sup>

Although most studies have not found a significant reduction in disease progression, a recent analysis reported a trend towards a lower rate with the use of BLC compared to WLC (12.2% vs. 17.6%, respectively; P = .085) with a longer time to progression (P = .05).<sup>17</sup> Although BLC has demonstrated improved detection and reduced recurrence, the value of this technique in reducing disease progression remains less established. Therefore, BLC may have the greatest advantage in detecting difficult-to-visualize tumors (eg, CIS tumors) that may be missed by WLC but has more limited applicability in disease monitoring. Other impediments to BLC include the need for appropriate expertise and equipment to employ this new technology. High false positives are also attributed to this method and may be increased in patients who have had a recent TURBT or bacillus Calmette-Guérin (BCG)

instillation, or who have inflammation.<sup>16</sup> The limitations of BLC require judicious application of this additional diagnostic tool.

### Narrow Band Imaging

NBI uses two narrow bands of light at 415nm and 540nm that are absorbed by hemoglobin. The shorter wavelength provides analysis of the mucosa and the longer wavelength allows for evaluation of the deeper submucosal blood vessels. Studies suggest that there is an increase in bladder tumor detection compared with WLC, although the rate of false positives is higher.<sup>18-22</sup>

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

A randomized prospective trial followed patients for 1 year after NBI- or WLC-guided TUR to evaluate recurrence. NBI had a reduced 1-year recurrence rate (32.9%; 25 of 76 patients) compared to WLC (32.9% vs. 51.4%, respectively; OR = .62).<sup>23</sup> However, the small number of patients

NCCN National Comprehensive Cancer Network®

# NCCN Guidelines Version 2.2018 Bladder Cancer

NCCN Guidelines Index Table of Contents Discussion

in this study is limiting. An international multicenter randomized controlled trial to address the role of NBI was initiated in 2010,<sup>24</sup> though data are not yet available.

A benefit of NBI is that it does not require a contrast agent and can therefore be used as part of office cystoscopy. Higher detection rates of flat lesions and a reduction in tumor recurrence have been reported. However, the current implementation of NBI into routine practice is hindered by the increase in false positives and the lack of data for long-term clinical benefit. Furthermore, technical expertise may limit its application. Additional studies are needed to provide insight into the role of NBI.

# Histology

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

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

Urothelial (transitional cell) carcinomas are the most common histologic subtype in the United States and Europe and may develop anywhere

transitional epithelium is present, from the renal pelvis to the ureter, bladder, and proximal two thirds of the urethra. Variant histology is common with higher grades. The fourth edition of the WHO Classification of Tumors has reclassified these histologic subtypes into the following: infiltrating urothelial carcinoma with divergent differentiation; nested, including large nested; microcystic; micropapillary; lymphoepithelioma-like; plasmacytoid/signet ring cell/diffuse; sarcomatoid; giant cell; poorly differentiated; lipid-rich; and clear cell.<sup>25</sup> Two review articles highlight the changes between the third and fourth additions of this classification.<sup>26,27</sup> The presence of histologic variants in urothelial carcinoma should be documented as data suggest that the subtype may reflect the risk of disease progression, different genetic etiology, and subsequently determine whether a more aggressive treatment approach should be considered (see Bladder Cancer: Non-Urothelial and Urothelial With Variant Histology in the algorithm). In some cases with a mixed histology, systemic treatment may only target cells of urothelial origin and the non-urothelial component can remain.

Squamous cell neoplasms of the urothelial tract are a second histologic subtype, which constitute 3% of the urinary tumors diagnosed in the United States. In regions where Schistosoma is endemic, this subtype is more prevalent and may account for up to 75% of bladder cancer cases. The distal third of the urethra is dominated by squamous epithelium. The diagnosis of squamous cell tumors requires the presence of keratinization in the pathologic specimen.<sup>28</sup> 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.



# NCCN Guidelines Version 2.2018 Bladder Cancer

NCCN Guidelines Index Table of Contents Discussion

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 involve the mid-line/dome of the bladder secondarily.<sup>29</sup> Tumors arising within the genitourinary tract but not of urothelial origin (eg, tumors of müllerian type, melanocytic tumors, mesenchymal tumors) are beyond the scope of these guidelines.

# Non-Muscle-Invasive Urothelial Bladder Cancer

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

### **Intravesical Therapy**

Intravesical chemotherapy is implemented to reduce recurrence or delay progression of bladder cancer to a higher grade or stage. An immediate intravesical instillation of chemotherapy may be given within 24 hours of TURBT to prevent tumor cell implantation and early recurrence. Immediate intravesical chemotherapy, not immunotherapy, has been shown to decrease recurrence in select subgroups of patients. A meta-analysis of 7 randomized trials demonstrated a decreased risk of recurrence by 11% (from 48% down to 37%) following immediate postoperative intravesical chemotherapy in patients having either single or multiple tumors.<sup>30</sup> Later studies had mixed results, with two reporting a decrease in recurrence and one finding no advantage.<sup>31-33</sup>

The most commonly used agent is mitomycin. For tumors with a low risk of progression, immediate instillation of chemotherapy may be the only treatment given and data show a decrease in recurrence in these patients. For tumors with an intermediate or high risk of progression, subsequent treatment with intravesical induction (adjuvant) therapy may be given. There are no studies that have evaluated whether the immediate instillation of chemotherapy in these patients provides an additional reduction in progression or recurrence. Treatment should not be given to any patient if there is extensive TURBT or if there is suspected bladder perforation.

### Induction (Adjuvant) Intravesical Chemotherapy or BCG

Although only intravesical chemotherapy is recommended in the immediate postoperative setting, both intravesical chemotherapy and BCG have been given as induction therapy in patients with non-muscle-invasive bladder cancer.<sup>34</sup> The most commonly used chemotherapy agents are mitomycin C and gemcitabine.

Induction BCG has been shown to prevent bladder cancer recurrences following TURBT. BCG therapy is commonly given once a week for 6 weeks, followed by a rest period of 4 to 6 weeks, with a full re-evaluation at week 12 (ie, 3 months) after the start of therapy.<sup>35</sup> There are 4 meta-analyses demonstrating that BCG after TURBT is superior to TURBT alone, or TURBT and chemotherapy in preventing recurrences of high-grade Ta and T1 tumors.<sup>36-39</sup> A meta-analysis including 9 trials of 2820 patients with non-muscle-invasive bladder cancer reported that mitomycin C was superior to BCG without maintenance.<sup>40</sup> Using the SEER database, a reduction in mortality of 23% was reported in patients receiving BCG therapy. Another study reported long-term data that BCG was better at reducing recurrence in

NCCN Network®

# NCCN Guidelines Version 2.2018 Bladder Cancer

NCCN Guidelines Index Table of Contents Discussion

intermediate- and high-risk non-muscle-invasive bladder cancer when compared to mitomycin  $\mbox{C.}^{\mbox{\tiny 41}}$ 

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.<sup>42</sup> There were more frequent local and systemic side effects in the BCG arm; however, they were mild to moderate and the treatment was well-tolerated in both groups. The benefit of BCG with or without isoniazid compared to epirubicin alone in a long-term study of 957 patients with intermediate- or high-risk Ta or T1 disease was measured by a reduced recurrence, greater time to distant metastases, and greater overall and disease-specific survivals; progression was similar.<sup>43</sup> Long-term data comparing BCG to epirubicin in combination with interferon<sup>43,44</sup> in patients with T1 disease showed a better reduction in recurrence with BCG; however, no differences in progression or adverse events (AEs) were seen.<sup>44</sup> Patients in both studies received 2 to 3 years of maintenance therapy.

#### Maintenance Therapy

Maintenance intravesical therapy may be considered following induction with chemotherapy or BCG. The role of maintenance chemotherapy is controversial. When given, maintenance chemotherapy is generally monthly. The role of maintenance BCG in those patients with intermediate to high-risk non-muscle-invasive bladder cancer is more established, though the exact regimens have varied across studies. Some of the previous controversy over the effectiveness of BCG maintenance reflects the wide array of schedules and conflicting reports of efficacy. Quarterly and monthly installations as well as 3-week and 6-week schedules have been evaluated. To date, the strongest data support the 3-week BCG regimen used in the SWOG trial that demonstrated reduced disease progression and metastasis.<sup>45</sup> The

3-week timing of BCG has shown improved outcomes compared with epirubicin<sup>44</sup> or isoniazid.<sup>43</sup> 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.<sup>46</sup> A study of 1355 patients with a median follow-up of 7.1 years found no benefit in 3 years of maintenance BCG compared to 1 year for intermediate-risk patients.<sup>47</sup> Conversely, 3-year maintenance BCG reduced recurrence compared to 1-year maintenance but did not impact progression or survival in high-risk patients. These data suggest that 1 year may be suitable for patients at intermediate risk while 3 years of maintenance is preferred for high-risk disease. It should also be noted that duration of treatment may be limited by toxicity and patient refusal to continue.

For patients showing no residual disease at the follow-up cystoscopy, whether 1 or 2 courses of induction therapy were administered, maintenance therapy with BCG is preferred. This recommendation is based on findings that an induction course of intravesical therapy followed by a maintenance regimen produced better outcomes than intravesical chemotherapy.<sup>34,36,37,45,48,49</sup>

### **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.<sup>50</sup> Installation of BCG into the bladder also mimics a urinary tract infection and may produce intense local discomfort. The side effects of treatment have translated to patient refusal of BCG therapy. Local dysuria has been reported in 60% of patients in clinical trials.<sup>50</sup> However, the side effects are treatable in almost all cases<sup>51</sup> and no increase in toxicity has been reported with

NCCN Network®

# NCCN Guidelines Version 2.2018 Bladder Cancer

cumulative doses. Symptom management with single-dose, short-term quinolones and/or anticholinergics have been reported to reduce AEs.<sup>52,53</sup>

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.<sup>54</sup> Among all 4 groups, the percentage of patients with greater than or equal to 1 side effect was similar (P = .41). Though the one-third dose BCG was effective, side effects were not reduced. Conversely, other publications suggest that the one-third dose may reduce side effects.<sup>55-57</sup> Full-dose BCG is recommended by the panel until more data are available to evaluate the low-dose BCG regimen. However, dose reduction may be used if there are substantial local symptoms during maintenance.

### Treatment of cTa, Low-Grade Tumors

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

The need for adjuvant therapy depends on the patient prognosis. If the patient has a low risk for recurrence, a single immediate intravesical treatment may be sufficient. Factors to consider include the size, number, T category, and grade of the tumor(s), as well as concomitant

CIS and prior recurrence.<sup>7</sup> Meta-analyses have confirmed the efficacy of adjuvant intravesical chemotherapy in reducing the risk of recurrence.<sup>58,59</sup> Close follow-up of all patients is needed, although the risk for progression to a more advanced stage is low (see *Surveillance* in the discussion and algorithm).

# Treatment of cTa, High-Grade Tumors

Tumors staged as cTa, high-grade lesions are papillary tumors with a relatively high risk for recurrence and progression towards more invasiveness. Restaging TURBT detected residual disease in 27% of Ta patients when muscle was present in the original TURBT.<sup>60</sup> In the absence of muscularis propria in the initial TURBT specimen, 49% of patients with superficial disease will be understaged versus 14% if muscle is present.<sup>61</sup> Repeat resection is recommended if there is incomplete resection, or should be strongly considered if there is no muscle in the specimen.

After TURBT, patients with Ta, high-grade tumors may be treated with intravesical BCG (preferred), intravesical chemotherapy, or observation. In the literature, there are 4 meta-analyses confirming that BCG after TURBT is superior to TURBT alone, or TURBT and chemotherapy in preventing recurrences of high-grade Ta and T1 tumors.<sup>36-39</sup> The NCCN Bladder Cancer Panel Members recommend BCG as the preferred option over intravesical chemotherapy for adjuvant treatment of high-grade lesions.

# **Treatment of cT1 Tumors**

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



# NCCN Guidelines Version 2.2018 Bladder Cancer

These tumors are treated with a complete endoscopic resection. In patients with high-risk disease, especially if the complete resection is uncertain due to tumor size and location, lack of muscle in the specimen, presence of lymphovascular invasion, or inadequate staging, repeat TURBT is strongly advised.<sup>62</sup> 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.<sup>63</sup> All patients received adjuvant intravesical therapy. Although overall survival (OS) was similar, the 3-year recurrence-free survival was significantly higher in the repeat TURBT arm versus the control arm (69% vs. 37%, respectively), especially among patients with high-grade tumors.

If residual cT1 disease is found, treatment should consist of BCG (category 1) or cystectomy. Within T1 disease, a particularly high-risk stratum can be identified: multifocal lesions, tumors associated with CIS or lymphovascular invasion, micropapillary tumors, or lesions that recur after BCG treatment. There are data suggesting that early cystectomy may be preferred in these patients because of the high risk for progression to a more advanced stage.<sup>64</sup>

If no residual disease is found after the second resection, intravesical therapy with BCG (preferred; category 1) or intravesical chemotherapy is recommended. Observation may be reasonable in highly select cases where small-volume tumors had limited lamina propria invasion and no CIS.<sup>65,66</sup>

# **Treatment of Tis**

Primary Tis is a high-grade lesion that is believed to be a precursor of invasive bladder cancer. Standard therapy for this lesion is resection followed by intravesical therapy with BCG. If the patient is unable to

tolerate BCG, intravesical chemotherapy may be considered, but data supporting this approach are limited.

# Surveillance

Consideration may be given to FDA-approved urinary biomarker testing by fluorescence in situ hybridization (FISH) or nuclear matrix protein 22 in monitoring for recurrence.<sup>67,68</sup>

For cTa high grade, cT1, and Tis, follow-up is recommended with a urinary cytology and cystoscopy at 3- to 6-month intervals for the first 2 years, and at increasing intervals as appropriate thereafter. Imaging of the upper tract should be considered every 1 to 2 years for high-grade tumors (see *Follow-up* in the algorithm). Urine molecular tests for urothelial tumor markers are now available.<sup>69</sup> Most of these tests have a better sensitivity for detecting bladder cancer than urinary cytology, but specificity is lower. However, it remains unclear whether these tests offer additional information that is useful for detection and management of non-muscle-invasive bladder tumors. Therefore, the panel considers this to be a category 2B recommendation.

# Posttreatment of Recurrent or Persistent Disease

# Treatment of Patients With Positive Cystoscopy

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

# **Recurrence Following Intravesical Treatment**

In a phase II multicenter study of non-muscle-invasive bladder cancer that recurred following 2 courses of BCG, intravesical gemcitabine



# NCCN Guidelines Version 2.2018 Bladder Cancer

NCCN Guidelines Index Table of Contents Discussion

demonstrated activity that was relegated to high-risk non-muscle-invasive bladder cancer.<sup>70</sup> In the 47 patients with evaluable response, 47% had disease-free survival (DFS) at 3 months. The 1-year relapse-free survival (RFS) was 28% with all cases except for two attributed to the high-risk group. The 2-year RFS was 21%. Intravesical gemcitabine had some activity in the high-risk group, and may be an option if a candidate is not eligible for a cystectomy; however, the study results indicate that cystectomy is preferred when possible. Similarly, for patients with recurrence of high-grade cT1 disease after TURBT and induction BCG, cystectomy is the main option.<sup>71</sup>

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

If residual disease is seen following TURBT, patients with persistent high-grade cT1 tumors are recommended to proceed to cystectomy. Non-surgical candidates can consider concurrent chemoradiation, change of the intravesical agent (if Tis or cTa), or a clinical trial. Patients with persistent Tis, cTa, or cT1 low-grade disease after TURBT may be treated with a different intravesical agent or cystectomy. Valrubicin is approved for CIS that is refractory to BCG, although panelists disagree on its value.<sup>72</sup> For patients with disease that does not respond or shows an incomplete response to treatment, subsequent management is cystectomy. Concurrent chemoradiotherapy (category 2B) can be considered for non-cystectomy candidates.

### Treatment of Patients With Positive Cytology

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

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

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

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

# Muscle-Invasive Urothelial Bladder Cancer Additional Workup

Several workup procedures are recommended to accurately determine clinical staging of muscle-invasive disease. Laboratory studies, such as a complete blood cell count and chemistry profile, including alkaline



# NCCN Guidelines Version 2.2018 Bladder Cancer

NCCN Guidelines Index Table of Contents Discussion

phosphatase, must be performed, and the patient should be assessed for the presence of regional or distant metastases. This evaluation should include chest imaging and a bone scan in patients with symptoms or clinical suspicion of bone metastasis (eg, elevated alkaline phosphatase, focal bone pain). Imaging studies help assess the extent of tumor spread to lymph nodes or distant organs.<sup>73</sup> An abdominal/pelvic CT or MRI is used to assess the local and regional extent of disease. 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.<sup>74,75</sup> Different treatment modalities are discussed below. These include radical cystectomy, partial cystectomy, neoadjuvant or adjuvant therapy, bladder-preserving approaches, and chemotherapy for advanced disease.

### **Radical Cystectomy**

Radical surgical treatment of bladder cancer involves a cystoprostatectomy in men and a cystectomy and commonly a hysterectomy in women, followed by the formation of a urinary diversion. This surgery can be performed in an open or robotic manner. Prostatectomy includes removal of the prostate, seminal vesicles, proximal vas deferens, and proximal urethra. Hysterectomy should include removal of the uterus, ovaries, fallopian tubes, urethra, and part of the vagina. Forms of urinary diversion include an ileal conduit or directing urine to an internal urinary reservoir (such as a continent pouch), with drainage to the abdominal wall or the urethra (orthotopic neobladder). Relative contraindications to urethral drainage include Tis in the prostatic ducts or positive urethral margin. Orthotopic diversion or

a neobladder provides the closest bladder function to that of a native bladder albeit with an increased risk for nighttime incontinence as well as urinary retention requiring intermittent self-catheterization.

Unfortunately, the accuracy of the staging cystoscopy, examination under anesthesia (EUA), and TURBT is modest, even when combined with cross-sectional imaging and under-staging is frequently encountered. A retrospective study of 778 patients with bladder cancer found that 42% of patients were upstaged following cystectomy.<sup>76</sup> 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.<sup>77-81</sup> Patient factors that may preclude a PLND include severe scarring secondary to previous treatments or surgery, advanced age, or severe comorbidities.

### **Partial Cystectomy**

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

NCCN Network®

# NCCN Guidelines Version 2.2018 Bladder Cancer

NCCN Guidelines Index Table of Contents Discussion

candidates are patients with cancer in a diverticulum or with significant medical comorbidities.

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

### **Neoadjuvant Chemotherapy**

One of the most noteworthy issues in the treatment of bladder cancer is the optimal use of perioperative chemotherapy for muscle-invasive disease. Data support the role of neoadjuvant chemotherapy before cystectomy for T2, T3, and T4a lesions without nodal involvement.<sup>82-87</sup> In a SWOG randomized trial of 307 patients with muscle-invasive disease, radical cystectomy alone versus 3 (28 day) cycles of neoadjuvant methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) followed by radical cystectomy were compared. Neoadjuvant chemotherapy increased median survival (77 months vs. 46 months, P = .06) and lowered the rate of residual disease (15% vs. 38%, P < .001) with no apparent increase in treatment-related morbidity or mortality.<sup>82</sup> In a meta-analysis of 11 trials involving 3005 patients, cisplatin-based multi-agent neoadjuvant chemotherapy was associated with improved 5-year OS and DFS (5% and 9% absolute improvement, respectively).<sup>88</sup>

Since the neoadjuvant trial with MVAC, the use of dose-dense MVAC (ddMVAC) with growth factor support in the metastatic setting has been shown to have good comparable tolerance with an increased CR rate compared to standard (28 day) dosing of MVAC (11% vs. 25%; 2-sided

P = .006).<sup>89</sup> 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.<sup>90</sup> ddMVAC was anticipated to have a safer profile, a shorter time to surgery, and a similar pathologic complete response rate compared to historical control data for neoadjuvant MVAC chemotherapy given in previous studies. Patients receiving ddMVAC had no grade 3 or 4 renal toxicities and no toxicity-related deaths. Grade 1 or 2 treatment-related toxicities were seen in 82% of patients. The median time to cystectomy was 9.7 weeks from start of chemotherapy.<sup>90</sup> A separate single-arm phase II study also reported pathologic downstaging in 49% of patients receiving neoadjuvant ddMVAC with a similar safety profile.<sup>91</sup> An additional neoadjuvant clinical trial of ddMVAC with bevacizumab reported 5-year survival outcomes of 63% and 64% (OS and disease-specific survival, respectively; median follow-up, 49 months), with pT0N0 and less than or equal to pT1N0 downstaging rates of 38% and 53%, respectively.<sup>92</sup> Bevacizumab had no definitive impact on overall outcomes. In an international, multicenter, randomized trial (BA06 30894) that investigated the effectiveness of neoadjuvant cisplatin, methotrexate, and vinblastine (CMV) in 976 patients, neoadjuvant CMV resulted in a 16% reduction in mortality risk (HR, 0.84; 95% CI, 0.72–0.99; P = .037) at a median follow-up of 8 years.87

The NCCN Panel strengthened the recommendations for neoadjuvant chemotherapy for patients with cT2, cT3, and cT4a bladder cancer without nodal disease and for adjuvant chemotherapy for patients with pT3 or pT4 disease or positive nodes (see *cT2 Primary and Adjuvant Treatment* and *cT3*, *cT4a Primary and Adjuvant Treatment* in the



# NCCN Guidelines Version 2.2018 Bladder Cancer

algorithm). Neoadjuvant chemotherapy followed by radical cystectomy is a category 1 recommendation. Patients with hearing loss or neuropathy, poor performance status, or renal insufficiency may not be eligible for cisplatin-based chemotherapy. If neoadjuvant cisplatin-based chemotherapy cannot be given, neoadjuvant chemotherapy is not recommended. For patients with borderline renal function or minimal dysfunction, a split-dose administration of cisplatin may be considered (category 2B). Although split-dose is a safer alternative, the relative efficacy remains undefined.

# Adjuvant Chemotherapy

Data are less clear regarding the role of adjuvant systemic chemotherapy in invasive bladder cancer. Studies have shown that adjuvant chemotherapy may delay recurrences and improve OS,<sup>93-95</sup> but no randomized comparisons of adequate sample size have definitively shown a survival benefit in large part due to poor accrual.<sup>96</sup> 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.<sup>97-99</sup> However, methodologic issues call into question the applicability of these studies to all patients with urothelial tumors. In the MVEC trial, patients who experienced relapse in the control arm did not receive chemotherapy, which is not typical of more contemporary treatment approaches. Many of these trials were not randomized, raising the question of selection bias in the analysis of outcomes.

A meta-analysis of 6 trials found a 25% mortality reduction with adjuvant chemotherapy, but the authors pointed out several limitations of the data and concluded that evidence is insufficient for treatment decisions.<sup>100</sup> Interestingly, the follow-up analysis included 3 more studies for a total of 9 trials (N = 945 patients).<sup>95</sup> 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.<sup>95</sup> An observational study evaluated 5653 patients of which 23% received adjuvant chemotherapy post-cystectomy.<sup>94</sup> Patients who received adjuvant chemotherapy had an improved OS (HR, 0.70; 95% CI, 0.06–0.76).<sup>94</sup> Although evidence for adjuvant therapy is not as strong as for neoadjuvant therapy, the growing body of data support the administration of adjuvant chemotherapy for patients with a high risk for relapse who did not receive neoadjuvant therapy.

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

A minimum of three cycles of a cisplatin-based combination, such as ddMVAC; gemcitabine plus cisplatin (GC); or cisplatin, methotrexate, and vinblastine (CMV), may be used in patients undergoing perioperative chemotherapy. Regimen and dosing recommendations are mainly based on studies in advanced disease.<sup>82,87,101-103</sup> Carboplatin has not demonstrated a survival benefit and should not be substituted for cisplatin in the perioperative setting. It should be noted that patients with tumors that are pT2 or less and have no nodal involvement or lymphovascular invasion after cystectomy are considered to have lower risk and are not recommended to receive adjuvant chemotherapy.



# NCCN Guidelines Version 2.2018 Bladder Cancer

### **Adjuvant Radiation**

Patients with locally advanced disease (pT3-4) have high rates of pelvic failure and poor overall survival after radical cystectomy, pelvic lymph node dissection, and perioperative chemotherapy (pelvic failure 20-45% and survival 10-50% at 5 years, depending on risk factors factors).<sup>104-106</sup> 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.<sup>107</sup> A more recent randomized phase II trial comparing adjuvant sequential chemotherapy and radiation vs. adjuvant chemotherapy alone in 120 patients with locally advanced disease (pT3-4 or node-positive) demonstrated a significant improvement in local control for chemoradiation (3 year local control of 96% vs. 69%), however the improvement in DFS and OS was not significant. Late grade  $\geq 3$ gastrointestinal toxicity on the chemoradiation arm was low.<sup>108</sup>

While there is no conclusive data demonstrating improvements in overall survival, it is reasonable to consider adjuvant radiation in patients with pT3/pT4 pN0-2 urothelial bladder cancer following radical cystectomy. Patients meeting these characteristics with positive surgical margins and/or lymph nodes identified in the pelvic dissection have especially high pelvic failure rates (40-45% by 5 years) and adjuvant radiation is reasonably well tolerated and improves pelvic failure rates. Radiation with a dose range of 45 to 50.4 Gy without concurrent chemotherapy may be used. In patients who have not had prior neoadjuvant chemotherapy, it may be reasonable to sandwich adjuvant radiation between cycles of adjuvant chemotherapy and radiation in the adjuvant setting needs to be further studied.

### **Bladder Preservation**

All bladder-sparing approaches are based on the principle that not all cases require an immediate cystectomy, and the decision to remove the bladder can be deferred until the response to organ-sparing therapy is assessed. Bladder-preserving approaches are reasonable alternatives to cystectomy for patients who are medically unfit for surgery and those seeking an alternative to radical cystectomy. Combined modality chemoradiation therapy as an alternative to immediate cystectomy for muscle-invasive bladder cancer is endorsed by multiple international organizations that have developed evidence-based consensus guidelines and recommendations including the International Consultation on Urologic Diseases-European Association of Urology (ICUD-EAU), UK National Institute for Health and Care Excellence (NICE), and the AUA/ASCO/ASTRO/SUO.<sup>109-111</sup> There is an apparent underutilization of aggressive bladder-preserving therapies for non-cystectomy candidates, especially the elderly and racial minorities.<sup>112,113</sup> Between 23% and 50% of patients with muscle-invasive bladder cancer who are 65 years of age and older receive no treatment or non-aggressive therapy.

With any of the alternatives to cystectomy, there is a concern that bladders that appear to be endoscopically free of tumor based on a clinical assessment (cT0) that includes a repeat TURBT may not be pathologically free of tumor (pT0). Reports have suggested that up to 45% of bladders may be clinically understaged after TURBT.<sup>113-115</sup> Conversely, one series reported that all patients who achieved a complete response after radiotherapy with concurrent cisplatin and 5-FU were pT0 on immediate cystectomy.<sup>116</sup> Although studies report differing frequencies of residual disease after cytotoxic agents (either radiation or chemotherapy), there is consensus that the rate is lower for

NCCN Network®

# NCCN Guidelines Version 2.2018 Bladder Cancer

patients who present with T2 disease than with T3 disease, which should be considered when proposing a bladder-sparing approach.

The decision to use a bladder-preserving approach is partially based on the location of the lesion, depth of invasion, size of the tumor, status of the "uninvolved" urothelium, and status of the patient (eg, bladder capacity, bladder function, comorbidities). Bladder preservation as an alternative to cystectomy is generally reserved for patients with smaller solitary tumors, negative nodes, no CIS, no tumor-related hydronephrosis, and good pre-treatment bladder function. Patients who are medically fit for radical cystectomy but who have hydronephrosis are poor candidates for bladder-sparing procedures.<sup>117,118</sup> Maximal TURBT with concurrent chemoradiotherapy should be given as primary treatment for these patients, with radiotherapy alone, or TURBT alone reserved for select patients.

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

### Radiotherapy with Concurrent Chemotherapy Following TURBT 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.<sup>119-121</sup>

Radiation Therapy Oncology Group protocol 89-03 compared concurrent cisplatin and radiotherapy with or without 2 cycles of induction MCV (methotrexate, cisplatin, and vinblastine)

chemotherapy.<sup>118</sup> 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.<sup>120,122</sup>

Conversely, results from several prospective trials have demonstrated the effectiveness of this approach. In the RTOG 89-03 trial in which 123 patients with clinical stage T2-T4a were treated with radiotherapy plus concurrent cisplatin, with or without induction MCV chemotherapy, 5-year OS was approximately 49% in both arms.<sup>118</sup> The subsequent RTOG 95-06 trial treated 34 patients with twice-daily irradiation and concurrent cisplatin and 5-FU and reported a three-year OS of 83%.<sup>123</sup> The RTOG 97-06 trial treated 47 patients with twice-daily irradiation and concurrent cisplatin; patients also received adjuvant chemotherapy with CMV.<sup>124</sup> 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%.<sup>125</sup> In RTOG 0233, 97 patients received twice-daily radiation with concurrent paclitaxel plus cisplatin or 5-FU plus cisplatin. Five-year OS was 73%.<sup>126</sup> Taken together, the complete response rates ranged from 59% to 81%.

Up to about 80% of long-term survivors maintain an intact bladder, while other patients ultimately require radical cystectomy.<sup>117-125</sup> A combined analysis of survivors from these 4 trials, with a median follow-up of 5.4 years, showed that combined-modality therapy was associated with low rates of late grade 3 toxicity (5.7% genitourinary and 1.9% gastrointestinal).<sup>127</sup> No late grade 4 toxicities or treatment-related deaths were recorded.

NCCN National Comprehensive Cancer Network®

# NCCN Guidelines Version 2.2018 Bladder Cancer

#### Chemotherapy Following TURBT as Primary Treatment for Muscle-Invasive Bladder Cancer

Chemotherapy alone is considered to be inadequate without additional treatment to the bladder and remains investigational. Studies showed that the proportions of complete pathologic response in the bladder using neoadjuvant chemotherapy alone were only up to 38%.<sup>82</sup> 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.<sup>128,129</sup> In a randomized trial of 360 patients, radiotherapy with concurrent mitomycin C and 5-FU improved 2-year locoregional DFS from 54% (radiotherapy alone) to 67% (P = .01), and 5-year OS from 35% to 48% (P = .16), without increasing grade 3-4 acute or late toxicity.<sup>129</sup> 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 cT2, cT3, or cT4a 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.<sup>130</sup>

If considered for TURBT alone, patients should undergo an aggressive re-resection of the site within 4 weeks of the primary procedure to

ensure that no residual disease is present. If the repeat TURBT is negative for residual tumor, the patient can be managed conservatively with repeat endoscopic evaluations and cytologies every 3 months until a relapse is documented. The stage of the lesion documented at relapse would determine further management decisions.

# Treatment of T2, T3, and T4a Tumors

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

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

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



# NCCN Guidelines Version 2.2018 Bladder Cancer

Bladder preservation with maximal TURBT followed by concurrent chemoradiotherapy may be considered. Candidates for this bladder-sparing approach include patients with tumors that present without hydronephrosis or with tumors that allow a visibly complete or a maximally debulking TURBT. Radiotherapy with concurrent cisplatin-based chemotherapy or 5-FU plus mitomycin as a radiosensitizer is the most common and well-studied chemoradiation method used to treat muscle-invasive bladder cancer.<sup>116-120,128,129,131</sup> The following radiosensitizing regimens are recommended: cisplatin plus 5-FU; cisplatin plus paclitaxel; and 5-FU plus mitomycin C. Doublet chemotherapy is generally preferred. Cisplatin alone or low-dose gemcitabine (category 2B) may be considered as alternative regimens.

After a complete TURBT, 60 to 66 Gy of external beam radiotherapy is administered. Two doses of concurrent radiosensitizing chemotherapy may be given on weeks 1 and 4 (though weekly schedules are possible as well). Alternatively, an induction dose of 40 to 45 Gy radiotherapy may be given following complete TURBT. The overall tumor status should be reassessed 3 weeks after radiation if 40 to 45 Gy was initially administered or 2 to 3 months after if the full dose of 60 to 66 Gy was delivered. If no residual tumor is detected, appropriate options include observation or completion of radiation up to 66 Gy. If residual disease is present, cystectomy is preferred.

In patients with extensive comorbid disease or poor performance status who are non-cystectomy candidates, treatment options include concurrent chemoradiation, radiotherapy alone, or TURBT alone. Based on high-level evidence showing superiority to radiotherapy alone, the NCCN Panel recommends chemoradiotherapy with cisplatin alone or 5-FU and mitomycin C.<sup>128,129</sup> The overall tumor status should be reassessed 2 to 3 months after treatment. If no tumor is evident, the patient should be observed. If tumor is observed, chemotherapy,

concurrent chemoradiotherapy (if no prior radiotherapy), palliative TURBT, or best supportive care may be given.

### **Treatment of T4b Disease or Positive Nodes**

For patients with cT4b disease and negative nodes on abdominal/pelvic CT or MRI scans or biopsy, the primary treatment recommendation includes 2 to 3 courses of chemotherapy with or without radiotherapy followed by evaluation with cystoscopy, EUA, TURBT, and imaging of the abdomen and pelvis. If no evidence of tumor is present after primary treatment, consolidation chemotherapy or completion of definitive RT may be considered. If a partial radiation dose of 40-45 Gy was given as primary treatment, completion of definitive RT is recommended. Alternatively, adjuvant treatment with chemoradiotherapy may be initiated if the patient did not receive prior radiotherapy. In general, cT4b disease is considered unresectable. However, in patients with disease that responds to treatment, cystectomy may be an option if the tumor becomes technically resectable.

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

For patients with abnormal nodes documented by imaging, a biopsy should be considered, if technically possible, to confirm nodal spread. Patients with positive nodes should receive chemotherapy with or without radiation and should be evaluated with cystoscopy, EUA, TURBT, and abdominal/pelvic imaging. If no residual tumor is detected, patients may receive a radiation boost or a cystectomy. If
NCCN National Comprehensive Cancer Network®

# NCCN Guidelines Version 2.2018 Bladder Cancer

tumor is still present following primary therapy, these patients should follow treatment of recurrent or persistent disease.

#### Follow-up

Results from a meta-analysis of 13,185 patients who have undergone cystectomy reported a 0.75% to 6.4% prevalence of upper tract recurrence.<sup>132</sup> Surveillance by urine cytology or upper tract imaging detected recurrences in 7% and 30% of cases, respectively.

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

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

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

### **Recurrence or Persistent Disease**

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

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

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

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

### Metastatic Urothelial Bladder Cancer

Approximately 4% of patients have metastatic disease at the time of diagnosis.<sup>133</sup> Additionally, about half of all patients relapse after cystectomy depending on the pathologic stage of the tumor and nodal

NCCN Network®

# NCCN Guidelines Version 2.2018 Bladder Cancer

status. Local recurrences account for about 10% to 30% of relapses, whereas distant metastases are more common.

#### **Evaluation of Metastatic Disease**

If metastasis is suspected, additional workup to evaluate the extent of the disease is necessary. This includes a chest CT and a bone scan if enzyme levels are abnormal or the patient shows signs or symptoms of skeletal involvement. Central nervous system (CNS) imaging should be considered. An estimate GFR should be obtained to assess patient eligibility for cisplatin. If the evidence of spread is limited to nodes, nodal biopsy should be considered and patients should be managed as previously outlined for positive nodal disease ((see *Treatment of cT4b or Positive Nodes* in the discussion and *cT4b Primary and Adjuvant Treatment* in the algorithm). Patients who present with disseminated metastatic disease are generally treated with systemic chemotherapy. Management of persistent disseminated disease may involve chemotherapy, radiation, or a combination of the two.

#### **Chemotherapy for Metastatic Disease**

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

GC<sup>134,135</sup> and ddMVAC<sup>89,101</sup> are commonly used in combinations that have shown clinical benefit. A large, international, phase III study randomized 405 patients with locally advanced or metastatic disease to GC or standard (28 day) MVAC.<sup>103</sup> At a median follow-up of 19 months, OS and time to progression were similar in the two arms. Fewer toxic deaths were recorded among patients receiving GC compared to MVAC (1% vs. 3%), although this did not reach statistical significance. A 5-year update analysis confirmed that GC was not superior to MVAC in terms of survival (OS, 13.0% vs. 15.3%; progression-free survival [PFS], 9.8% vs. 11.3%, respectively).<sup>135</sup> Another large, randomized, phase III trial compared ddMVAC to standard (28 day) MVAC.<sup>89,101</sup> At a median follow-up of 7.3 years, 24.6% of patients were alive in the ddMVAC cohort compared with 13.2% in the standard MVAC cohort. There was one toxic death in each arm, but less overall toxicity was seen in the dose-dense group. From these data, ddMVAC had improved toxicity and efficacy as compared to standard MVAC; therefore, standard (28 day) MVAC is no longer used. Both GC and ddMVAC with growth factor support are category 1 recommendations for metastatic disease. Alternative first-line regimens also include carboplatin or taxane-based regimens (category 2B) or single-agent chemotherapy (category 2B).

The performance status of the patient is a major determinant in the selection of a regimen. Regimens with lower toxicity profiles are recommended in patients with compromised liver or renal status or serious comorbid conditions. In patients who are not cisplatin-eligible, atezolizumab or pembrolizumab are now appropriate first-line options (see *Targeted Therapies* in the discussion). Alternatively, carboplatin may be substituted for cisplatin in the metastatic setting for cisplatin-ineligible patients such as those with a glomerular filtration rate (GFR) less than 60 mL/min. A phase II/III study assessed 2 carboplatin-containing regimens in medically unfit patients (performance)

NCCN National Comprehensive Cancer Network®

# NCCN Guidelines Version 2.2018 Bladder Cancer

NCCN Guidelines Index Table of Contents Discussion

status 2).<sup>136</sup> The overall response rate was 42% for gemcitabine plus carboplatin and 30% for methotrexate, carboplatin, and vinblastine. However, the response rates dropped to 26% and 20%, respectively, with increased toxicity among patients who were both unfit and had renal impairment (GFR <60 mL/min).

Taxanes have been shown to be active as both front-line and palliative therapies. Based on these results, several groups are exploring 2- and 3-drug combinations using these agents, with and without cisplatin, as initial therapy. A randomized phase III trial was conducted to compare GC and GC plus paclitaxel in 626 patients with locally advanced or metastatic urothelial cancer.<sup>137</sup> The addition of paclitaxel to GC resulted in higher response rates and a borderline OS advantage, which was not statistically significant in the intent-to-treat analysis. Analysis of eligible patients only (92%) resulted in a small (3.2 months) but statistically significant survival advantage in favor of the 3-drug regimen (P = .03). There was no difference in PFS. The incidence of neutropenic fever was substantially higher with the 3-drug combination (13.2% vs. 4.3%; P < .001). Panelists feel that the risk of adding paclitaxel outweighs the limited benefit reported from the trial. The alternative regimens, including cisplatin/paclitaxel,<sup>138</sup> gemcitabine/paclitaxel,<sup>139</sup> cisplatin/gemcitabine/paclitaxel,<sup>140</sup> carboplatin/gemcitabine/paclitaxel,<sup>141</sup> and cisplatin/gemcitabine/docetaxel,<sup>142</sup> have shown modest activity in patients with bladder cancer in phase I-II trials. Category 1 level evidence now supports the use of checkpoint inhibitors in patients with advanced disease previously treated with a platinum-containing regimen (see Targeted Therapies in the discussion).

Although current data are insufficient to recommend the above alternative regimens as routine first-line options,

non-cisplatin-containing regimens may be considered in patients who cannot tolerate cisplatin because of renal impairment or other

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

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

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

Clinical trial enrollment is recommended by the NCCN panel for all patients when appropriate, but is strongly recommended for subsequent-line therapy since data for locally advanced or metastatic disease treated with subsequent-line therapy are highly variable. The NCCN National Comprehensive Cancer Network®

# NCCN Guidelines Version 2.2018 Bladder Cancer

NCCN Guidelines Index Table of Contents Discussion

available options depend on what was given as first line. Regimens used in this setting include checkpoint inhibitors, and the following chemotherapies: docetaxel, paclitaxel, gemcitabine, or pemetrexed monotherapy.<sup>143-146</sup> Other options include Nab-paclitaxel; ifosfamide; methotrexate; ifosfamide, doxorubicin, and gemcitabine; gemcitabine and paclitaxel; GC; and ddMVAC.

#### **Chemoradiotherapy for Metastatic Disease**

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

#### **Targeted Therapies**

Platinum-based chemotherapy has been the standard of care in patients with metastatic disease with an OS of 9 to 15 months.<sup>135,147</sup> However, in patients with disease that relapses after this type of chemotherapy, the median survival is reduced to 5 to 7 months.<sup>148</sup> Several new agents, notably checkpoint inhibitors for the treatment of metastatic urothelial carcinoma, have data supporting improved outcomes compared to standard therapies. Cancers with higher rates of somatic mutations have been shown to respond better to checkpoint inhibitors.<sup>149-154</sup> Data from the Cancer Genome Atlas rank bladder cancer as the third highest mutated cancer,<sup>155,156</sup> suggesting that checkpoint inhibitors may have a substantial impact as a treatment option for this cancer.

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

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.<sup>157</sup> An open-label, randomized, phase III trial compared pembrolizumab to chemotherapy (paclitaxel, docetaxel, or vinflunine) in 542 patients with advanced urothelial carcinoma that recurred or progressed after platinum-based chemotherapy. Data from this trial showed a longer median OS for patients treated with pembrolizumab compared to chemotherapy (10.3 months vs. 7.4 months; *P*=0.002). 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%).<sup>158</sup> Results from this phase 3 trial have lead the NCCN Panel to assign pembrolizumab a category 1 recommendation as a second-line therapy. A phase II trial evaluated pembrolizumab as a first-line therapy in 370 patients with advanced

NCCN Network®

## NCCN Guidelines Version 2.2018 Bladder Cancer

NCCN Guidelines Index Table of Contents Discussion

urothelial carcinoma who were ineligible for cisplatin-based therapy. Data from this study showed an overall response rate of 29%, with 7% of patients achieving a complete response. Grade 3 or 4 treatmentrelated AEs occurred in 18% of patients treated with pembrolizumab.<sup>159</sup>

Data from a two-cohort, multicenter, phase II trial evaluated atezolizumab in patients with metastatic disease. Cohort 2 of the trial enrolled 310 patients with metastatic urothelial carcinoma post-platinum treatment and showed a significantly improved overall response rate compared to historical controls (15% vs. 10%; P = .0058).<sup>160</sup> Follow up to date suggests these responses may be durable with ongoing responses recorded in 38 (84%) of 45 responders with a median follow-up of 11.7 months. Although a similar response rate was seen regardless of PD-L1 status of tumor cells, a greater response was associated with increased PD-L1 expression status on infiltrating immune cells in the tumor microenvironment. Grade 3 or 4 treatment-related or immune-mediated AEs occurred in 16% and 5% of patients, respectively. Furthermore, there were no treatment-related deaths in this trial suggesting good tolerability. In cohort 1 of the same phase II trial, atezolizumab was evaluated as a first-line therapy in 119 patients with locally advanced or metastatic urothelial carcinoma who were ineligible for cisplatin. Data from this study showed an objective response rate (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.<sup>161</sup> A May 2017 press release reported that the phase III IMvigor211 study evaluating atezolizumab compared to chemotherapy in patients with metastatic urothelial carcinoma postplatinum treatment did not meet its primary endpoint of OS. Further examination of the data is ongoing to better understand the results and define the role of atezolizumab as a post-platinum treatment option for metastatic urothelial carcinoma.<sup>162</sup>

Data from a phase II trial in patients with locally advanced or metastatic urothelial carcinoma who progressed after at least one platinum-containing regimen, reported an overall objective response in 52 of 265 patients (19.6%; 95% CI, 15.0–24.9) following treatment with nivolumab that was unaffected by PD-1 tumor status.<sup>163</sup> 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.<sup>163</sup> The median OS was 8.74 months (95% CI, 6.05–not yet reached). Based on PD-L1 expression of less than 1% and 1% or greater, OS was 5.95 months to 11.3 months, respectively. These data are comparable to the early phase I/II data that reported an ORR of 24% (95% CI, 15.3%–35.4%) that was unaffected by PD-1 tumor status.<sup>164</sup> Out of the 78 patients enrolled in this study, 2 experienced grade 5 treatment-related AEs, and grade 3 or 4 treatment-related AEs were reported in 22% of patients.<sup>164</sup>

Early results from a phase I/II multicenter study of durvalumab for 61 patients with PD-L1–positive inoperable or metastatic urothelial bladder cancer who have tumor that has progressed during or after one standard platinum-based regimen showed that 46.4% of patients who were PD-L1 positive had disease that responded to treatment; no response was seen in patients who were PD-L1 negative.<sup>165</sup> A 2017 update on this study (N=103) showed a 29.5% ORR for PD-L1 high disease and a 7.7% ORR for PD-L1 low or negative disease. OS at 6 months was 68.4% for the PD-L1 high group and 44.7% for the PD-L1 low/negative group. Median duration of response was not yet reached at time of data cutoff. Grade 3 or 4 treatment-related AEs occurred in 5.2% of treated patients and 3 patients had a grade 3 or 4 immune-mediated AE.<sup>166</sup>

Avelumab is another PD-L1 inhibitor currently in clinical trials to evaluate its activity in the treatment of bladder cancer. Results from the



## NCCN Guidelines Version 2.2018 Bladder Cancer

phase 1b trial for 44 patients with platinum-refractory disease demonstrated an ORR of 18.2% that consisted of 5 complete responses and 3 partial responses following treatment with avelumab. The median PFS was 11.6 weeks and the median OS was 13.7 months with a 54.3% OS rate at 12 months. Grade 3 or 4 treatment-related AEs occurred in 6.8% of patients treated with avelumab.<sup>167</sup> A recent abstract reported results of the same trial for 241 patients with platinumrefractory metastatic urothelial carcinoma or who are ineligible for cisplatin based chemotherapy. This study reported an ORR of 17.6% with 9 complete responses and 18 partial responses. Median PFS was 6.4 weeks and median OS was 7.0 months. Grade 3 or 4 treatmentrelated AEs occurred in 7.5% of patients treated with avelumab and 2.5% of patients had a grade 3 or 4 immune-related AE.<sup>168</sup>

The value of checkpoint inhibitors is reflected in the unanimous decision by the NCCN Panel to include pembrolizumab, atezolizumab, nivolumab, durvalumab, and avelumab as second-line systemic therapy options after platinum-based therapy (and in the case of atezolizumab and pembrolizumab, as first-line therapy options for patients who are not eligible for cisplatin-containing chemotherapy) for locally advanced or metastatic disease (see *Systemic Therapy* in the algorithm). With the exception of pembrolizumab as a subsequent treatment option (category 1), the use of checkpoint inhibitors are all category 2A recommendations.

### Non-Urothelial Carcinomas of the Bladder

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

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

Data are limited to support perioperative chemotherapy for non-urothelial carcinomas; however, neoadjuvant chemotherapy may have benefit in patients with small cell carcinoma of the bladder and is recommended by the panel for any patient with small-cell component histology with localized disease regardless of stage.<sup>169-173</sup> In patients with non-urothelial carcinomas of any stage, no data support the use of adjuvant chemotherapy, although the risk for relapse may be high. Some of the general principles of management applicable to urothelial carcinomas are appropriate with minor variations.

Patients with small cell carcinoma of the bladder are best treated with initial chemotherapy (see <u>NCCN Guidelines for Small Cell Lung Cancer</u>) followed by either radiation therapy or cystectomy as consolidation, if there is no metastatic disease. Primary bladder sarcomas are treated as per the <u>NCCN Guidelines for Soft Tissue Sarcoma</u>.

NCCN Network®

## NCCN Guidelines Version 2.2018 Bladder Cancer

NCCN Guidelines Index Table of Contents Discussion

### **Upper Genitourinary Tract Tumors**

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

### **Renal Pelvis Tumors**

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

### Workup

The evaluation of a patient with a suspected renal pelvic tumor should include cystoscopy and imaging of the upper tract collecting system with CT or MR urography; renal ultrasound or CT without contrast with retrograde pyelogram; or ureteroscopy. A chest radiograph can help evaluate for possible metastasis and assess any comorbid diseases that may be present. Urine cytology obtained from a urine sample or during a cystoscopy may help identify carcinoma cells. Hematologic, renal, and hepatic function should also be evaluated. Additional imaging studies, such as a renal scan or bone scan, may be needed if indicated by the test results or by the presence of specific symptoms.

### Primary Treatment

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

Well-differentiated tumors of low grade may be managed with a nephroureterectomy with a bladder cuff, a nephron-sparing procedure through a transureteroscopic approach, or a percutaneous approach with or without postsurgical intrapelvic chemotherapy or BCG. High-grade tumors or those that are large and/or invade the renal parenchyma are managed through nephroureterectomy with a bladder cuff and regional lymphadenectomy. Decline in renal function following surgery may preclude adjuvant therapy. Hence, in selected patients, neoadjuvant chemotherapy may be considered based on extrapolation of data from bladder cancer series.<sup>82-84</sup> If metastatic disease is documented or associated comorbid conditions are present, treatment should include systemic chemotherapy with regimens similar to those used for metastatic urothelial bladder tumors.

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

### Follow-up

Subsequent management is dictated by the extent of disease at surgery. Tumors that are pT0 or pT1 should be followed up with serial cystoscopies at 3-month intervals for the first year and, if negative, at increasing intervals. Such tumors should also be followed up with ureteroscopy and upper tract imaging at 3- to 12-month intervals if endoscopic resection is considered.

Patients with pT2, pT3, pT4, or nodal disease should be considered for adjuvant chemotherapy. Follow-up should be the same as pT0/pT1 disease with the addition of chest imaging.

NCCN Network®

# NCCN Guidelines Version 2.2018 Bladder Cancer

NCCN Guidelines Index Table of Contents Discussion

### **Urothelial Carcinoma of the Ureter**

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

#### Workup

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

#### **Primary Treatment**

For resectable ureteral tumors, the primary management is surgery. The specific procedure required varies depending on the location of the tumor (upper, mid, or distal location) and disease extent. Neoadjuvant chemotherapy may be considered in selected patients, such as when the degree of invasiveness is established before definitive surgery.<sup>174</sup>

Tumors that originate in the upper ureter occasionally can be managed endoscopically but more commonly are treated with nephroureterectomy with a bladder cuff plus regional lymphadenectomy for high-grade tumors. Neoadjuvant chemotherapy should be considered in select patients including patients with retroperitoneal lymphadenopathy; bulky (>3 cm) high-grade tumor; sessile histology; or suspected parenchymal invasion. A portion of the bladder is removed to ensure complete removal of the entire intramural ureter. Tumors that originate in the mid portion can be divided by grade and size. Small, low-grade tumors can be managed with excision followed by ureteroureterostomy, segmental or complete ureterectomy, or ileal ureter interposition in highly selected patients. Alternatively, endoscopic resection or nephroureterectomy with a bladder cuff can be performed. Larger, high-grade lesions are managed with nephroureterectomy with a bladder cuff and regional lymphadenectomy. Neoadjuvant chemotherapy can be considered in select patients. Distal ureteral tumors may be managed with a distal ureterectomy and regional lymphadenectomy if high grade followed by reimplantation of the ureter (preferred if clinically feasible). Other primary treatment options include endoscopic resection, or, in some cases, a nephroureterectomy with a bladder cuff, and regional lymphadenectomy if high grade. Neoadjuvant chemotherapy can be considered for select patients with distal ureteral tumors following distal ureterectomy or the nephroureterectomy with cuff of bladder.

### Follow-up

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

Patients with more extensive disease are advised to consider systemic adjuvant treatment with chemotherapy, depending on the patient's anticipated tolerance to the regimen based on comorbidities. The reasons for considering adjuvant therapy are similar to those for tumors that originate in the bladder.

### **Urothelial Carcinomas of the Prostate**

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



# NCCN Guidelines Version 2.2018 Bladder Cancer

NCCN Guidelines Index Table of Contents Discussion

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

#### Workup

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

#### Primary Treatment

Pending histologic confirmation, tumors that are limited to the prostatic urethra with no acinar or stromal invasion can be managed with TURP and intraprostatic BCG, with follow-up similar to that for superficial disease of the bladder. If local recurrence is seen, cystoprostatectomy with or without urethrectomy is recommended. Patients with tumors that invade the ducts, acini, or stroma should undergo an additional workup with chest radiograph, or CT if necessary, to exclude metastatic disease, and then a cystoprostatectomy with or without urethrectomy should be performed. Based on data extrapolated from bladder cancer therapy, neoadjuvant chemotherapy may be considered in patients with stromal invasion.<sup>82-84</sup> Adjuvant chemotherapy may be advised for stromal invasion after primary treatment if neoadjuvant therapy was not given. Alternatively, TURP and intraprostatic BCG may be offered to patients with only ductal and acini invasion. Local recurrences in patients undergoing TURP and BCG therapy are treated with cystoprostatectomy with or without urethrectomy.

### Primary Carcinoma of the Urethra

Primary carcinoma that arises in the urethra is rare. Unlike for bladder cancer, squamous cell carcinoma is the most common histologic subtype for urethral cancer.<sup>175</sup> The 5-year OS is 42%.<sup>176,177</sup> Stage and disease location are the most important prognostic factors for male patients, while tumor size and histology are prognostically significant for female patients.<sup>175,177</sup> Unfortunately, there is a lack of robust, prospective data to support treatment decisions due to disease rarity. Treatment recommendations typically encompass all of the respective histologies (ie, squamous, transitional, adenocarcinomas) with the treatment approach based on location (ie, proximal versus distal urethral tumors).

#### Workup

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

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

#### Treatment

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

Treatment for T2 disease is based on patient gender and tumor location. For male patients with pendulous urethra, a distal urethrectomy or partial penectomy are viable options. Patients may



# NCCN Guidelines Version 2.2018 Bladder Cancer

consider neoadjuvant chemotherapy (category 2B) or chemoradiation (category 2A) before a urethrectomy. Patients who have positive margins may undergo additional surgery or radiation preferably with chemotherapy. At recurrence, options include systemic therapy, total penectomy, radiation, or a combination.

Male patients with T2 tumors in the bulbar urethra should undergo urethrectomy with or without cystoprostatectomy. Adjuvant chemotherapy or chemoradiation may be considered if pT3, pT4, or nodal disease is found. Recurrent cases may be treated with systemic therapy and/or radiation.

Initial treatment options for female patients with T2 tumors include chemoradiation or urethrectomy with cystectomy. Partial urethrectomy was associated with a high urethral recurrence rate.<sup>178</sup> At recurrence, the patient may receive systemic therapy or chemoradiotherapy (both category 2A) or pelvic exenteration (category 2B).

A multimodal treatment approach (ie, surgery, chemotherapy, radiation) is common for advanced disease. A cohort study reported a 72% response rate with the following treatment scheme before surgery: cisplatin, gemcitabine, and ifosfamide for squamous cell carcinoma; 5-FU, gemcitabine, and cisplatin-based regimens for adenocarcinoma; and MVAC for urothelial tumors.<sup>179</sup> Combined chemoradiation with 5-FU and mitomycin C has shown efficacy in a series of male patients with squamous cell carcinoma of the urethra.<sup>180</sup> Patients receiving surgery after chemoradiation had a higher 5-year DFS rate (72%) than those receiving chemoradiation alone (54%). If chemotherapy is used, the choice of regimen should be based on histology.

Patients with T3 or T4 disease but no clinical nodes should receive neoadjuvant chemotherapy followed by consolidative surgery or

radiation, or radiation preferably with chemotherapy. If positive nodes are present, radiation preferably with chemotherapy is the preferred treatment for squamous cell carcinoma. Chemotherapy or chemoradiotherapy followed by consideration of consolidative surgery are also treatment options. At recurrence, the patient may undergo pelvic exenteration (category 2B) with or without ilioinguinal lymphadenectomy and/or chemoradiotherapy. Systemic therapy is a category 2B option.

Patients with distant metastases should receive systemic therapy or chemoradiotherapy based on histology.

Systemic therapies include chemotherapy and checkpoint inhibitors as subsequent-line options. However, it should be noted that checkpoint inhibitors have only been evaluated in patients with urothelial histology.

### Summary

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

For patients with more extensive disease, newer treatments typically involve combined modality approaches using recently developed surgical procedures or 3-dimensional treatment planning for more precise delivery of radiation therapy. Although these are not appropriate



### NCCN Guidelines Version 2.2018 Bladder Cancer

NCCN Guidelines Index Table of Contents Discussion

in all cases, they offer the promise of an improved quality of life and prolonged survival.

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



NCCN Network®

# NCCN Guidelines Version 2.2018 Bladder Cancer

NCCN Guidelines Index Table of Contents Discussion

### References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin 2017;67:7-30. Available at:

https://www.ncbi.nlm.nih.gov/pubmed/28055103.

2. Cancer Stat Facts: Bladder Cancer. NIH NCI: Surveillance, Epidemiology, and End Results Program; 2017. Available at: <u>https://seer.cancer.gov/statfacts/html/urinb.html</u>. Accessed July 25, 2017.

3. U.S. National Library of Medicine-Key MEDLINE® Indicators. Available at: <u>http://www.nlm.nih.gov/bsd/bsd\_key.html</u>. Accessed February 8, 2017.

4. Edge S, Byrd D, Compton C, eds. AJCC Cancer Staging Manual, 7th ed. New York: Springer; 2010.

5. American Urological Association. Guideline for the management of nonmuscle invasive bladder cancer: (stages Ta,T1, and Tis): Update (2007). 2007. Available at:

https://www.auanet.org/common/pdf/education/clinicalguidance/Bladder-Cancer.pdf. Accessed February 8, 2017.

6. 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: <u>http://www.ncbi.nlm.nih.gov/pubmed/18470273</u>.

7. 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:

http://www.ncbi.nlm.nih.gov/pubmed/16442208.

8. 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: <a href="http://www.ncbi.nlm.nih.gov/pubmed/14665861">http://www.ncbi.nlm.nih.gov/pubmed/14665861</a>.

9. 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: http://www.ncbi.nlm.nih.gov/pubmed/16093971.

10. 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: http://www.ncbi.nlm.nih.gov/pubmed/17499283.

11. 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: <u>http://www.ncbi.nlm.nih.gov/pubmed/17499291</u>.

12. 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: <a href="http://www.ncbi.nlm.nih.gov/pubmed/20850152">http://www.ncbi.nlm.nih.gov/pubmed/20850152</a>.

13. 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: http://www.ncbi.nlm.nih.gov/pubmed/21414125.

14. 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: http://www.ncbi.nlm.nih.gov/pubmed/24058522.



# NCCN Guidelines Version 2.2018 Bladder Cancer

15. 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: http://www.ncbi.nlm.nih.gov/pubmed/23602406.

16. 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: http://www.ncbi.nlm.nih.gov/pubmed/23906669.

17. 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: <u>https://www.ncbi.nlm.nih.gov/pubmed/27376146</u>.

18. 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: <u>https://www.ncbi.nlm.nih.gov/pubmed/20223505</u>.

19. 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: <u>https://www.ncbi.nlm.nih.gov/pubmed/22079940</u>.

20. 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: <u>https://www.ncbi.nlm.nih.gov/pubmed/23024703</u>.

21. 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: <u>https://www.ncbi.nlm.nih.gov/pubmed/21792663</u>.

22. Tatsugami K, Kuroiwa K, Kamoto T, et al. Evaluation of narrowband imaging as a complementary method for the detection of bladder cancer. J Endourol 2010;24:1807-1811. Available at: <u>https://www.ncbi.nlm.nih.gov/pubmed/20707727</u>.

23. 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.

24. Naito S, van Rees Vellinga S, de la Rosette J. Global randomized narrow band imaging versus white light study in nonmuscle invasive bladder cancer: accession to the first milestone-enrollment of 600 patients. J Endourol 2013;27:1-3. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23305128.

25. Moch H, Humphrey PA, Ulbright TM, Reuter VE. Chapter 2: Tumours of the urinary tract. WHO classification of tumours of the urinary system and male genital organs. Lyon: IARC; 2016.

26. Humphrey PA, Moch H, Cubilla AL, et al. The 2016 WHO classification of tumours of the urinary system and male genital organs-Part B: Prostate and bladder tumours. Eur Urol 2016;70:106-119. Available at: <u>https://www.ncbi.nlm.nih.gov/pubmed/26996659</u>.

27. Athanazio DA, Trpkov K. What is new in genitourinary pathology? Recent developments and highlights of the new 2016 World Health Organization classification of tumors of the urinary system and male genital organs. Applied Cancer Research 2016;36:1. Available at: http://dx.doi.org/10.1186/s41241-016-0003-7.

28. 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: http://www.ncbi.nlm.nih.gov/pubmed/20019984.

NCCN Network®

## NCCN Guidelines Version 2.2018 Bladder Cancer

NCCN Guidelines Index Table of Contents Discussion

29. Siefker-Radtke A. Urachal adenocarcinoma: a clinician's guide for treatment. Semin Oncol 2012;39:619-624. Available at: <u>https://www.ncbi.nlm.nih.gov/pubmed/23040259</u>.

30. Sylvester RJ, Oosterlinck W, van der Meijden AP. A single immediate postoperative instillation of chemotherapy decreases the risk of recurrence in patients with stage Ta T1 bladder cancer: a metaanalysis of published results of randomized clinical trials. J Urol 2004;171:2186-2190, quiz 2435. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15126782.

31. Berrum-Svennung I, Granfors T, Jahnson S, et al. A single instillation of epirubicin after transurethral resection of bladder tumors prevents only small recurrences. J Urol 2008;179:101-105; discussion 105-106. Available at: <u>http://www.ncbi.nlm.nih.gov/pubmed/17997459</u>.

32. Bohle A, Leyh H, Frei C, et al. Single postoperative instillation of gemcitabine in patients with non-muscle-invasive transitional cell carcinoma of the bladder: a randomised, double-blind, placebo-controlled phase III multicentre study. Eur Urol 2009;56:495-503. Available at: <u>http://www.ncbi.nlm.nih.gov/pubmed/19560257</u>.

33. Gudjonsson S, Adell L, Merdasa F, et al. Should all patients with non-muscle-invasive bladder cancer receive early intravesical chemotherapy after transurethral resection? The results of a prospective randomised multicentre study. Eur Urol 2009;55:773-780. Available at: <u>http://www.ncbi.nlm.nih.gov/pubmed/19153001</u>.

34. 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 91-92. Available at:

http://www.ncbi.nlm.nih.gov/pubmed/15947584.

35. 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: http://www.ncbi.nlm.nih.gov/pubmed/820877.

36. Bohle A, Jocham D, Bock PR. Intravesical bacillus Calmette-Guerin versus mitomycin C for superficial bladder cancer: a formal metaanalysis of comparative studies on recurrence and toxicity. J Urol 2003;169:90-95. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12478111.

37. 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: <a href="http://www.ncbi.nlm.nih.gov/pubmed/16765182">http://www.ncbi.nlm.nih.gov/pubmed/16765182</a>.

38. 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:

http://www.ncbi.nlm.nih.gov/pubmed/11488731.

39. 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.

40. 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: <u>http://www.ncbi.nlm.nih.gov/pubmed/19409692</u>.

41. 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: <a href="https://www.ncbi.nlm.nih.gov/pubmed/19395154">https://www.ncbi.nlm.nih.gov/pubmed/19395154</a>.



# NCCN Guidelines Version 2.2018 Bladder Cancer

42. 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: http://www.ncbi.nlm.nih.gov/pubmed/23545101.

43. 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: http://www.ncbi.nlm.nih.gov/pubmed/20034729.

44. 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: <u>http://www.ncbi.nlm.nih.gov/pubmed/19819617</u>.

45. 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: <u>http://www.ncbi.nlm.nih.gov/pubmed/10737480</u>.

46. 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: <a href="http://www.ncbi.nlm.nih.gov/pubmed/23711538">http://www.ncbi.nlm.nih.gov/pubmed/23711538</a>.

47. 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: http://www.ncbi.nlm.nih.gov/pubmed/23141049.

48. 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: http://www.ncbi.nlm.nih.gov/pubmed/15072879.

49. 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: http://www.ncbi.nlm.nih.gov/pubmed/12394686.

50. U.S. Food and Drug Administration. Prescribing Information. TICE® (BCG live), for intravesical use. 2009. Available at: http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM163039.pdf. Accessed February 8, 2017.

51. 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.

52. 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: <u>http://www.ncbi.nlm.nih.gov/pubmed/16890660</u>.

53. 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: http://www.ncbi.nlm.nih.gov/pubmed/19298412.

54. Brausi M, Oddens J, Sylvester R, et al. Side effects of Bacillus Calmette-Guerin (BCG) in the treatment of intermediate- and high-risk



# NCCN Guidelines Version 2.2018 **Bladder Cancer**

Ta, T1 papillary carcinoma of the bladder: results of the EORTC genitourinary 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: http://www.ncbi.nlm.nih.gov/pubmed/23910233.

55. Lebret 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: http://www.ncbi.nlm.nih.gov/pubmed/10604315.

56. Martinez-Pineiro JA, Martinez-Pineiro L, Solsona E, et al. Has a 3fold 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:

http://www.ncbi.nlm.nih.gov/pubmed/16145378.

57. Mugiya S, Ozono S, Nagata M, et al. Long-term outcome of a lowdose 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: http://www.ncbi.nlm.nih.gov/pubmed/15976065.

58. 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:

http://www.ncbi.nlm.nih.gov/pubmed/11299841.

59. 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: http://www.ncbi.nlm.nih.gov/pubmed/10941943.

60. 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: http://www.ncbi.nlm.nih.gov/pubmed/12853793.

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

62. 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: http://www.ncbi.nlm.nih.gov/pubmed/22367558.

63. 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: http://www.ncbi.nlm.nih.gov/pubmed/16600720.

64. 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: http://www.ncbi.nlm.nih.gov/pubmed/11547061.

65. 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: http://www.ncbi.nlm.nih.gov/pubmed/16413659.

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

67. Kamat AM, Dickstein RJ, Messetti F, et al. Use of fluorescence in situ hybridization to predict response to bacillus Calmette-Guerin therapy for bladder cancer: results of a prospective trial. J Urol 2012;187:862-867. Available at:

http://www.ncbi.nlm.nih.gov/pubmed/22245325.

NCCN Network®

## NCCN Guidelines Version 2.2018 Bladder Cancer

NCCN Guidelines Index Table of Contents Discussion

68. Grossman HB, Soloway M, Messing E, et al. Surveillance for recurrent bladder cancer using a point-of-care proteomic assay. JAMA 2006;295:299-305. Available at:

http://www.ncbi.nlm.nih.gov/pubmed/16418465.

69. Lokeshwar VB, Habuchi T, Grossman HB, et al. Bladder tumor markers beyond cytology: International Consensus Panel on bladder tumor markers. Urology 2005;66:35-63. Available at: <u>http://www.ncbi.nlm.nih.gov/pubmed/16399415</u>.

70. 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: <u>http://www.ncbi.nlm.nih.gov/pubmed/23597452</u>.

71. 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: <u>http://www.ncbi.nlm.nih.gov/pubmed/17382713</u>.

72. 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: http://www.ncbi.nlm.nih.gov/pubmed/10687972.

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

74. 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: <a href="https://www.ncbi.nlm.nih.gov/pubmed/20620402">https://www.ncbi.nlm.nih.gov/pubmed/20620402</a>.

75. 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.

76. 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: <u>https://www.ncbi.nlm.nih.gov/pubmed/16793197</u>.

77. 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:

http://www.ncbi.nlm.nih.gov/pubmed/10792159.

78. 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: <u>http://www.ncbi.nlm.nih.gov/pubmed/11832716</u>.

79. 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: <a href="http://www.ncbi.nlm.nih.gov/pubmed/15199091">http://www.ncbi.nlm.nih.gov/pubmed/15199091</a>.

80. 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: <u>http://www.ncbi.nlm.nih.gov/pubmed/12576819</u>.

81. 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: <u>http://www.ncbi.nlm.nih.gov/pubmed/18383515</u>.

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

NCCN National Comprehensive Cancer Network®

# NCCN Guidelines Version 2.2018 Bladder Cancer

NCCN Guidelines Index Table of Contents Discussion

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

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

84. Winquist 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: <a href="http://www.ncbi.nlm.nih.gov/pubmed/14713760">http://www.ncbi.nlm.nih.gov/pubmed/14713760</a>.

85. 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:

http://www.ncbi.nlm.nih.gov/pubmed/25515347.

86. 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: http://www.pabi.alm.pib.gov/pubmed/15020524

http://www.ncbi.nlm.nih.gov/pubmed/15939524.

87. Griffiths G, Hall R, Sylvester 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: <u>http://www.ncbi.nlm.nih.gov/pubmed/21502557</u>.

88. 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: http://www.ncbi.nlm.nih.gov/pubmed/15939524.

89. 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: <u>http://www.ncbi.nlm.nih.gov/pubmed/16330205</u>.

90. 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: http://www.ncbi.nlm.nih.gov/pubmed/24821881.

91. 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: http://www.ncbi.nlm.nih.gov/pubmed/24821883.

92. McConkey DJ, Choi W, Shen Y, et al. A prognostic gene expression signature in the molecular classification of chemotherapy-naive 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:

http://www.ncbi.nlm.nih.gov/pubmed/26343003.

93. 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: <u>http://www.ncbi.nlm.nih.gov/pubmed/11600601</u>.

94. 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: <u>http://www.ncbi.nlm.nih.gov/pubmed/26786930</u>.

NCCN National Comprehensive Cancer Network®

## NCCN Guidelines Version 2.2018 Bladder Cancer

NCCN Guidelines Index Table of Contents Discussion

95. 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: <u>http://www.ncbi.nlm.nih.gov/pubmed/24018020</u>.

96. 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: <u>http://www.ncbi.nlm.nih.gov/pubmed/19858384</u>.

97. 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: http://www.ncbi.nlm.nih.gov/pubmed/16336326.

98. 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: <u>http://www.ncbi.nlm.nih.gov/pubmed/8973669</u>.

99. 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: <u>http://www.ncbi.nlm.nih.gov/pubmed/1997689</u>.

100. 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:

http://www.ncbi.nlm.nih.gov/pubmed/15939530.

101. 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: http://www.ncbi.nlm.nih.gov/pubmed/11352955.

102. 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: <u>http://www.ncbi.nlm.nih.gov/pubmed/18823036</u>.

103. 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: <u>http://www.ncbi.nlm.nih.gov/pubmed/11001674</u>.

104. 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.

105. 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.

106. 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.

107. 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:

http://www.ncbi.nlm.nih.gov/pubmed/1612951.

108. Zaghloul MS, Christodouleas JP, Smith A, et al. Adjuvant sandwich chemotherapy and radiation versus adjuvant chemotherapy alone for

NCCN National Comprehensive Cancer Network®

# NCCN Guidelines Version 2.2018 Bladder Cancer

NCCN Guidelines Index Table of Contents Discussion

locally advanced bladder cancer [abstract]. Int J Radiat Oncol Biol Phys 2016;96. Available at: <u>http://www.redjournal.org/article/S0360-3016(16)30561-2/fulltext</u>.

109. 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.

110. Bladder cancer: diagnosis and management. National Institute for Health and Care Excellence (NICE); 2015. Available at: <u>https://www.nice.org.uk/guidance/ng2</u>. Accessed August 7, 2017.

111. Chang SS, Bochner BH, Chou R, et al. Treatment of Non-Metastatic Muscle-Invasive Bladder Cancer: AUA/ASCO/ASTRO/SUO Guideline. J Urol 2017. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28456635.

112. 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: <u>http://www.ncbi.nlm.nih.gov/pubmed/21074192</u>.

113. 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: <u>https://www.ncbi.nlm.nih.gov/pubmed/23200811</u>.

114. 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: <u>http://www.ncbi.nlm.nih.gov/pubmed/9552029</u>.

115. 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. 116. 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: <a href="http://www.ncbi.nlm.nih.gov/pubmed/8229129">http://www.ncbi.nlm.nih.gov/pubmed/8229129</a>.

117. 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: http://www.ncbi.nlm.nih.gov/pubmed/12100923.

118. 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: http://www.ncbi.nlm.nih.gov/pubmed/9817278.

119. 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: <a href="http://www.ncbi.nlm.nih.gov/pubmed/12118019">http://www.ncbi.nlm.nih.gov/pubmed/12118019</a>.

120. 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: <u>http://www.ncbi.nlm.nih.gov/pubmed/22101114</u>.

121. 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: <u>https://www.ncbi.nlm.nih.gov/pubmed/28081860</u>.

122. 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

NCCN National Comprehensive Cancer Network®

# NCCN Guidelines Version 2.2018 Bladder Cancer

radio-chemotherapy. Urology 2012;80:1056-1062. Available at: <a href="https://www.ncbi.nlm.nih.gov/pubmed/22999456">https://www.ncbi.nlm.nih.gov/pubmed/22999456</a>.

123. Kaufman DS, Winter KA, Shipley WU, et al. The initial results in muscle-invading 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: <u>http://www.ncbi.nlm.nih.gov/pubmed/11110598</u>.

124. 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:

http://www.ncbi.nlm.nih.gov/pubmed/14529770.

125. 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: <a href="http://www.ncbi.nlm.nih.gov/pubmed/19100600">http://www.ncbi.nlm.nih.gov/pubmed/19100600</a>.

126. 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: http://www.ncbi.nlm.nih.gov/pubmed/23823157.

127. 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: <u>http://www.ncbi.nlm.nih.gov/pubmed/19636019</u>.

128. 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: <u>http://www.ncbi.nlm.nih.gov/pubmed/8918486</u>.

129. 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: <a href="http://www.ncbi.nlm.nih.gov/pubmed/22512481">http://www.ncbi.nlm.nih.gov/pubmed/22512481</a>.

130. Herr HW. Conservative management of muscle-infiltrating bladder cancer: prospective experience. J Urol 1987;138:1162-1163. Available at: <u>http://www.ncbi.nlm.nih.gov/pubmed/3669160</u>.

131. Mak RH, Zietman AL, Heney NM, et al. Bladder preservation: optimizing radiotherapy and integrated treatment strategies. BJU Int 2008;102:1345-1353. Available at:

http://www.ncbi.nlm.nih.gov/pubmed/19035903.

132. 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: <a href="http://www.ncbi.nlm.nih.gov/pubmed/23083867">http://www.ncbi.nlm.nih.gov/pubmed/23083867</a>.

133. National Cancer Institute. SEER stat fact sheets: Bladder cancer. 2016. Available at: <u>https://seer.cancer.gov/statfacts/html/urinb.html</u>. Accessed February 8, 2017.

134. 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: <u>http://www.ncbi.nlm.nih.gov/pubmed/10784633</u>.

135. 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: <u>http://www.ncbi.nlm.nih.gov/pubmed/16034041</u>.



## NCCN Guidelines Version 2.2018 Bladder Cancer

NCCN Guidelines Index Table of Contents Discussion

136. 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: <u>http://www.ncbi.nlm.nih.gov/pubmed/19786668</u>.

137. 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: http://www.ncbi.nlm.nih.gov/pubmed/22370319.

138. 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: http://www.ncbi.nlm.nih.gov/pubmed/11025699.

139. 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: <u>http://www.ncbi.nlm.nih.gov/pubmed/11408496</u>.

140. 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: <u>http://www.ncbi.nlm.nih.gov/pubmed/10986057</u>.

141. 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: <u>http://www.ncbi.nlm.nih.gov/pubmed/11331332</u>.

142. 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: http://www.ncbi.nlm.nih.gov/pubmed/11886001.

143. Lorusso V, Pollera CF, Antimi M, et al. A phase II study of gemcitabine in patients with transitional cell carcinoma of the urinary tract previously treated with platinum. Italian Co-operative Group on Bladder Cancer. Eur J Cancer 1998;34:1208-1212. Available at: <u>http://www.ncbi.nlm.nih.gov/pubmed/9849481</u>.

144. 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: <a href="http://www.ncbi.nlm.nih.gov/pubmed/9164195">http://www.ncbi.nlm.nih.gov/pubmed/9164195</a>.

145. Papamichael D, Gallagher CJ, Oliver RT, et al. Phase II study of paclitaxel in pretreated patients with locally advanced/metastatic cancer of the bladder and ureter. Br J Cancer 1997;75:606-607. Available at: <u>http://www.ncbi.nlm.nih.gov/pubmed/9052419</u>.

146. 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: http://www.ncbi.nlm.nih.gov/pubmed/11844814.

147. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22162575.

148. Bellmunt J, Theodore C, Demkov T, et al. Phase III trial of vinflunine plus best supportive care compared with best supportive care alone after a platinum-containing regimen in patients with advanced transitional cell carcinoma of the urothelial tract. J Clin Oncol 2009;27:4454-4461. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19687335.



### NCCN Guidelines Version 2.2018 Bladder Cancer

NCCN Guidelines Index Table of Contents Discussion

149. Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med 2015;372:2018-2028. Available at: <u>http://www.ncbi.nlm.nih.gov/pubmed/25891174</u>.

150. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med 2015;373:123-135. Available at: <a href="http://www.ncbi.nlm.nih.gov/pubmed/26028407">http://www.ncbi.nlm.nih.gov/pubmed/26028407</a>.

151. Postow MA, Chesney J, Pavlick AC, et al. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. N Engl J Med 2015;372:2006-2017. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25891304.

152. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med 2015;373:23-34. Available at:

http://www.ncbi.nlm.nih.gov/pubmed/26027431.

153. Wolchok JD, Kluger H, Callahan MK, et al. Nivolumab plus ipilimumab in advanced melanoma. N Engl J Med 2013;369:122-133. Available at: <u>http://www.ncbi.nlm.nih.gov/pubmed/23724867</u>.

154. Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med 2015;372:2509-2520. Available at: <u>http://www.ncbi.nlm.nih.gov/pubmed/26028255</u>.

155. Alexandrov LB, Nik-Zainal S, Wedge DC, et al. Signatures of mutational processes in human cancer. Nature 2013;500:415-421. Available at: <u>http://www.ncbi.nlm.nih.gov/pubmed/23945592</u>.

156. Cancer Genome Atlas Research N. Comprehensive molecular characterization of urothelial bladder carcinoma. Nature 2014;507:315-322. Available at: <u>http://www.ncbi.nlm.nih.gov/pubmed/24476821</u>.

157. 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: <a href="https://www.ncbi.nlm.nih.gov/pubmed/28081914">https://www.ncbi.nlm.nih.gov/pubmed/28081914</a>.

158. Bellmunt J, de Wit R, Vaughn DJ, et al. Pembrolizumab as secondline therapy for advanced urothelial carcinoma. N Engl J Med 2017;376:1015-1026. Available at: <u>https://www.ncbi.nlm.nih.gov/pubmed/28212060</u>.

159. O'Donnell PH, Grivas P, Balar AV, et al. Biomarker findings and mature clinical results from KEYNOTE-052: First-line pembrolizumab (pembro) in cisplatin-ineligible advanced urothelial cancer (UC) [abstract]. J Clin Oncol 2017;35 (suppl; abstr 4502). Available at: <u>http://abstracts.asco.org/199/AbstView\_199\_188592.html</u>.

160. 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:

http://www.ncbi.nlm.nih.gov/pubmed/26952546.

161. Balar AV, Galsky MD, Rosenberg JE, et al. Atezolizumab as firstline 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.

162. Roche provides update on phase III study of TECENTRIQ® (atezolizumab) in people with previously treated advanced bladder cancer. 2017. Available at:

http://www.roche.com/media/store/releases/med-cor-2017-05-10.htm. Accessed July 26, 2017.

163. 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. Available at: <u>https://www.ncbi.nlm.nih.gov/pubmed/28131785</u>.



# NCCN Guidelines Version 2.2018 Bladder Cancer

164. Sharma P, Bono P, Kim JW, et al. Efficacy and safety of nivolumab monotherapy in metastatic urothelial cancer: Results from the phase I/II CheckMate 032 study. Oral presentation at The American Society of Clinical Oncology (ASCO) 2016 Annual Meeting 2016;June 3-7. Available at: <u>http://meetinglibrary.asco.org/content/122886?media=vm</u>.

165. 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.

166. Powles T, O'Donnell PH, Massard C, et al. Updated efficacy and tolerability of durvalumab in locally advanced or metastatic urothelial carcinoma [abstract]. J Clin Oncol 2017;35 (suppl 6S; abstract 286). Available at: <u>http://meetinglibrary.asco.org/content/178823-197</u>.

167. 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:Jco2016716795. Available at: <u>https://www.ncbi.nlm.nih.gov/pubmed/28375787</u>.

168. Patel MR, Ellerton JA, Infante JR, et al. Avelumab in patients with metastatic urothelial carcinoma: Pooled results from two cohorts of the phase 1b JAVELIN Solid Tumor trial [abstract]. J Clin Oncol 2017;35 (suppl 6S; abstract 330). Available at:

http://meetinglibrary.asco.org/content/178781-197.

169. Ismaili N. A rare bladder cancer--small cell carcinoma: review and update. Orphanet J Rare Dis 2011;6:75. Available at: <u>http://www.ncbi.nlm.nih.gov/pubmed/22078012</u>.

170. 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: http://www.ncbi.nlm.nih.gov/pubmed/15247709.

171. 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: <u>http://www.ncbi.nlm.nih.gov/pubmed/19414678</u>.

172. 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: <u>http://www.ncbi.nlm.nih.gov/pubmed/25761779</u>.

173. 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.

174. 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: <a href="https://www.ncbi.nlm.nih.gov/pubmed/20884249">https://www.ncbi.nlm.nih.gov/pubmed/20884249</a>.

175. 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.

176. Dalbagni G, Zhang ZF, Lacombe L, Herr HW. Male urethral carcinoma: analysis of treatment outcome. Urology 1999;53:1126-1132. Available at: <u>http://www.ncbi.nlm.nih.gov/pubmed/10367840</u>.

177. Grigsby PW. Carcinoma of the urethra in women. Int J Radiat Oncol Biol Phys 1998;41:535-541. Available at: <u>http://www.ncbi.nlm.nih.gov/pubmed/9635699</u>.

178. 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: <u>http://www.ncbi.nlm.nih.gov/pubmed/15464921</u>.



### NCCN Guidelines Version 2.2018 Bladder Cancer

NCCN Guidelines Index Table of Contents Discussion

179. 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: http://www.ncbi.nlm.nih.gov/pubmed/22534087.

180. 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: http://www.ncbi.nlm.nih.gov/pubmed/18076921.

