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**NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™)**

# **Bladder Cancer**

Version 2.2011

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# NCCN Guidelines™ Version 2.2011 Panel Members

## Bladder Cancer

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**James E. Montie, MD/Co-Chair** <sup>⊖</sup>  
University of Michigan Comprehensive  
Cancer Center

**Deborah A. Kuban, MD** <sup>§</sup>  
The University of Texas MD Anderson  
Cancer Center

**Jerome P. Richie, MD** <sup>⊖</sup>  
Dana-Farber/Brigham and Women's Cancer  
Center

\* **Peter E. Clark, MD** <sup>⊖</sup> Co-Chair  
Vanderbilt-Ingram Cancer Center

**Timothy M. Kuzel, MD** <sup>‡</sup>  
**Robert H. Lurie** Comprehensive Cancer  
Center of Northwestern University

**Wade J. Sexton, MD** <sup>⊖</sup>  
H. Lee Moffitt Cancer Center & Research  
Institute

**Neeraj Agarwal, MD** <sup>‡</sup>  
Huntsman Cancer Institute at the  
University of Utah

**Subodh M. Lele** <sup>≠</sup>  
UNMC Eppley Cancer Center at The  
Nebraska Medical Center

**William U. Shipley, MD** <sup>§</sup> <sup>⊖</sup>  
Massachusetts General Hospital Cancer  
Center

**Mario A. Eisenberger, MD** <sup>†</sup> <sup>⊖</sup>  
The Sidney Kimmel Comprehensive  
Cancer Center at Johns Hopkins

**Jeffrey Michalski, MD, MBA** <sup>§</sup>  
Siteman Cancer Center at Barnes-Jewish  
Hospital and Washington University School  
of Medicine

**Eric J. Small, MD** <sup>†</sup> <sup>⊖</sup>  
UCSF Helen Diller Comprehensive Cancer  
Center

**Rizk El-Galley, MD** <sup>⊖</sup>  
University of Alabama at Birmingham  
Comprehensive Cancer Center

**Anthony Patterson, MD** <sup>⊖</sup>  
St. Jude Children's Research  
Hospital/University of Tennessee Cancer  
Institute

**Donald L. Trump, MD** <sup>†</sup>  
Roswell Park Cancer Institute

**Richard E. Greenberg, MD** <sup>⊖</sup>  
Fox Chase Cancer Center

**Kamal S. Pohar, MD** <sup>⊖</sup>  
The Ohio State University Comprehensive  
Cancer Center -James Cancer Hospital and  
Solove Research Institute

**Phillip J. Walther, MD, PhD** <sup>⊖</sup>  
Duke Comprehensive Cancer Center

**Harry W. Herr, MD** <sup>⊖</sup>  
Memorial Sloan-Kettering Cancer Center

**Michael P. Porter, MD, MS** <sup>⊖</sup>  
Fred Hutchinson Cancer Research  
Center/Seattle Cancer Care Alliance

**Timothy G. Wilson, MD** <sup>⊖</sup>  
City of Hope Comprehensive Cancer Center

**Gary R. Hudes, MD** <sup>†</sup> <sup>‡</sup>  
Fox Chase Cancer Center

**NCCN**  
**Mary Dwyer, MS**  
**Maria Ho, PhD**

**Continue**

<sup>⊖</sup> Urology  
<sup>†</sup> Medical oncology  
<sup>‡</sup> Hematology/Hematology oncology  
<sup>§</sup> Radiotherapy/Radiation oncology  
<sup>≠</sup> Pathology  
\* Writing committee member

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

To find clinical trials online at NCCN member institutions, [click here: nccn.org/clinical\\_trials/physician.html](#)

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

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

#### [Staging \(ST-1\)](#)

The NCCN Guidelines™ are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representations or warranties of any kind regarding their content, use or application and disclaims any responsibility for their application or use in any way. The NCCN Guidelines are copyrighted by National Comprehensive Cancer Network®. All rights reserved. The NCCN Guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2011.



The 2.2011 version of the Bladder Cancer Guidelines represents the addition of the [discussion](#).

Summary of the changes in the 1.2011 version of the Bladder Cancer guidelines from the 1.2010 version include:

### [BL-1](#)

- Muscle invasive, workup: “chest x-ray” was changed to “chest imaging”.

### [BL-2:](#)

- cTa, high grade and above, the follow up was modified by removing “annually” and adding “increasing intervals as appropriate” to “cystoscopy and urine cytology every 3-6 mo for 2 y.”

### [BL-3](#)

- Footnote ‘j’ was modified by:
  - ▶ removing, “BCG + interferon has been reported to be effective, but data from phase III randomized trials is not yet available”
  - ▶ adding, “Valrubicin is approved for BCG-refractory carcinoma in situ.”

### [BL-4:](#)

- For primary treatment, radical cystectomy, “consider” was added to “neoadjuvant cisplatin-based combination” and was changed from a category 2A to a category 1 designation.

### [BL-6](#)

- For abnormal nodes or node only, “consider” was added to “biopsy of nodes”.

### [BL-C](#)

- “Approximate” was added to the title “probability of recurrence and progression” for clarification.

### [BL-D](#)

- Any small-cell component, “or neuroendocrine features” was added.

### [BL-E](#)

- Follow-up after partial cystectomy, subbullet was modified, “cystoscopy and urine cytology every 3-6 mo for 2 y, then increasing intervals as appropriate.”

### [UTT-1](#)

- Workup, “IVP/CT urogram” was changed to “imaging of upper tract collecting system” and a corresponding footnote, “Imaging may include one or more of the following: IVP, CT urography, retrograde pyelogram, ureteroscopy, or MRI urogram” was added.

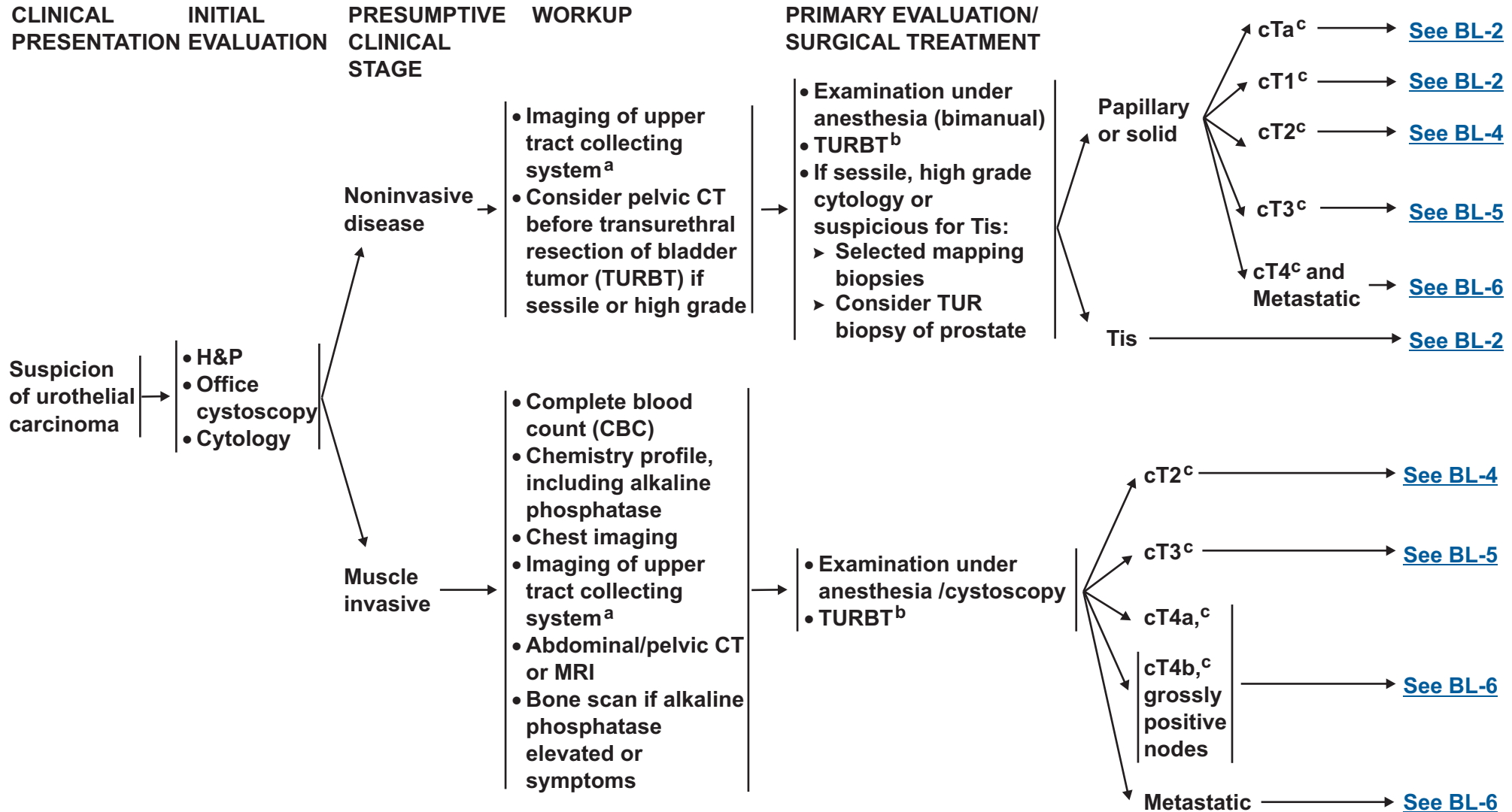
### [UTT-2](#)

- Primary treatment of distal with distal ureterectomy and regional lymphadenectomy, “consider neoadjuvant chemotherapy in selected patients” was added as a treatment option.



# NCCN Guidelines™ Version 2.011

## Bladder Cancer



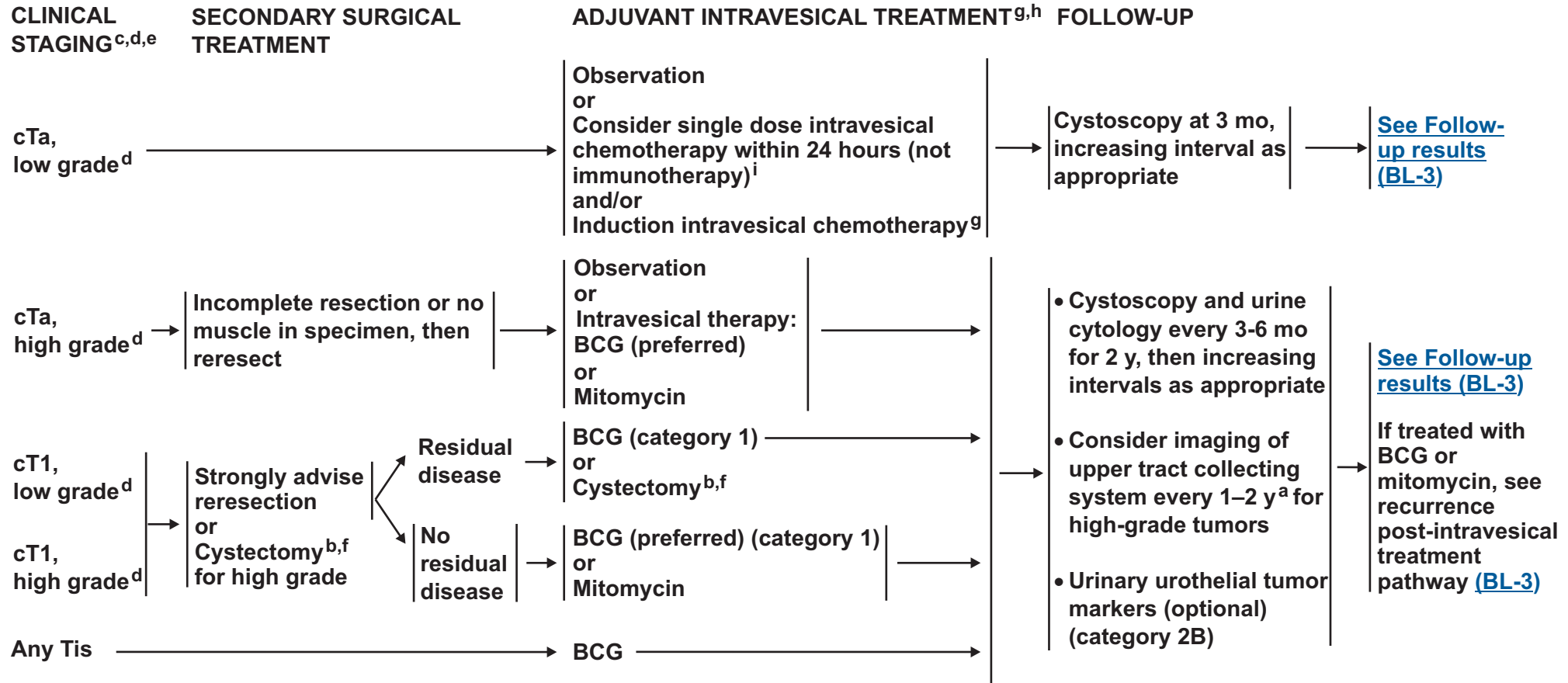
<sup>a</sup>Imaging may include one or more of the following: IVP, CT urography, renal ultrasound with retrograde pyelogram, ureteroscopy, or MRI urogram.

<sup>b</sup>[See Principles of Surgical Management \(BL-A\)](#).

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

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<sup>d</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. [See Principles of Pathology Management \(BL-B\)](#).

<sup>e</sup>[See Probability of Recurrence and Progression \(BL-C\)](#) and [Non-Urothelial Cell Carcinoma of the Bladder \(BL-D\)](#).

<sup>f</sup>[See Follow-Up After Cystectomy \(BL-E\)](#).

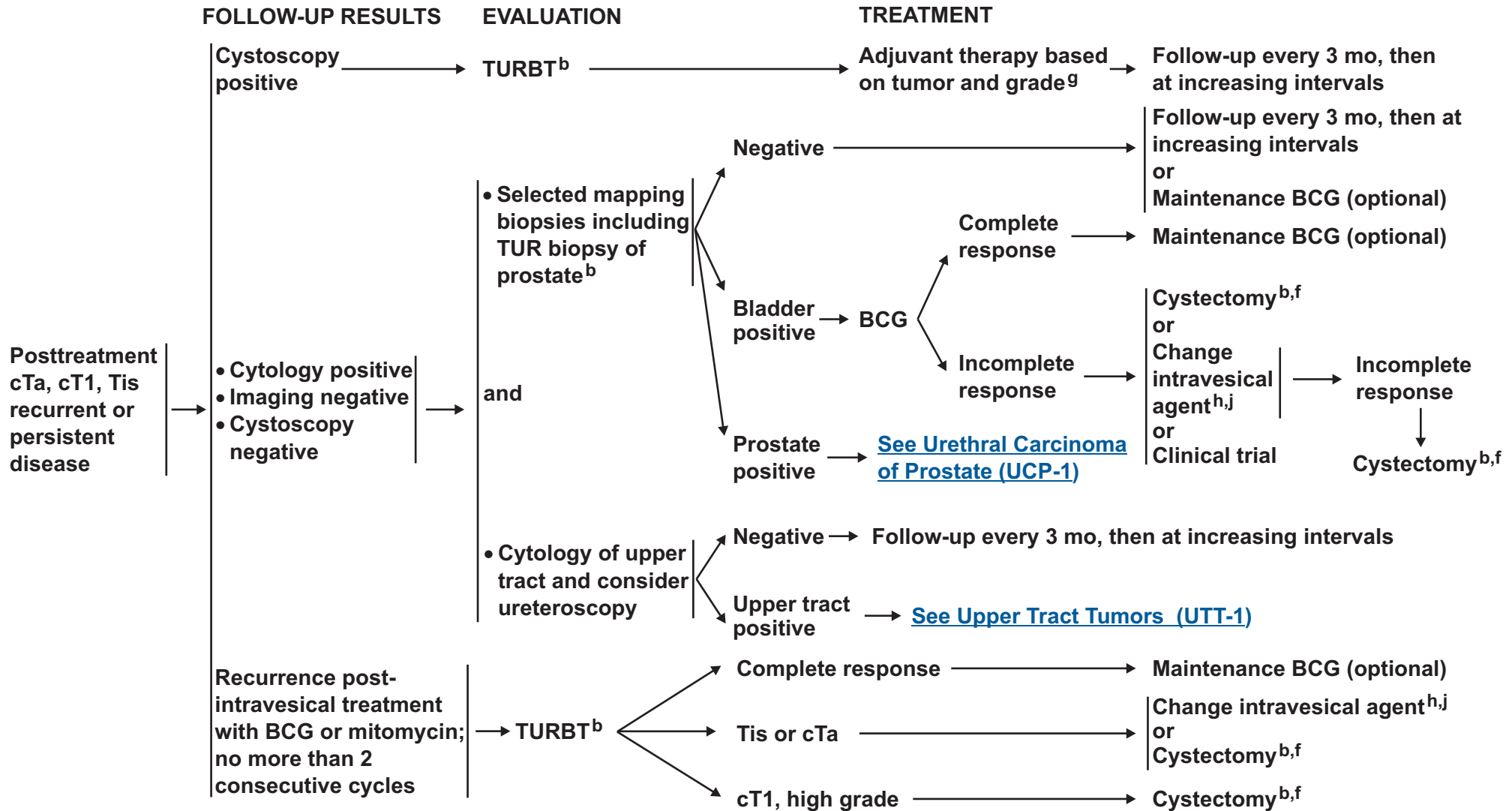
<sup>g</sup>Indications for adjuvant therapy: Based on probability of recurrence and progression to muscle invasive disease, such as size, number, and grade.

<sup>h</sup>[See Principles of Intravesical Treatment \(BL-F\)](#).

<sup>i</sup>Immediate intravesical chemotherapy, not immunotherapy, may decrease recurrence.

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

<sup>f</sup>See Follow-Up After Cystectomy (BL-E).

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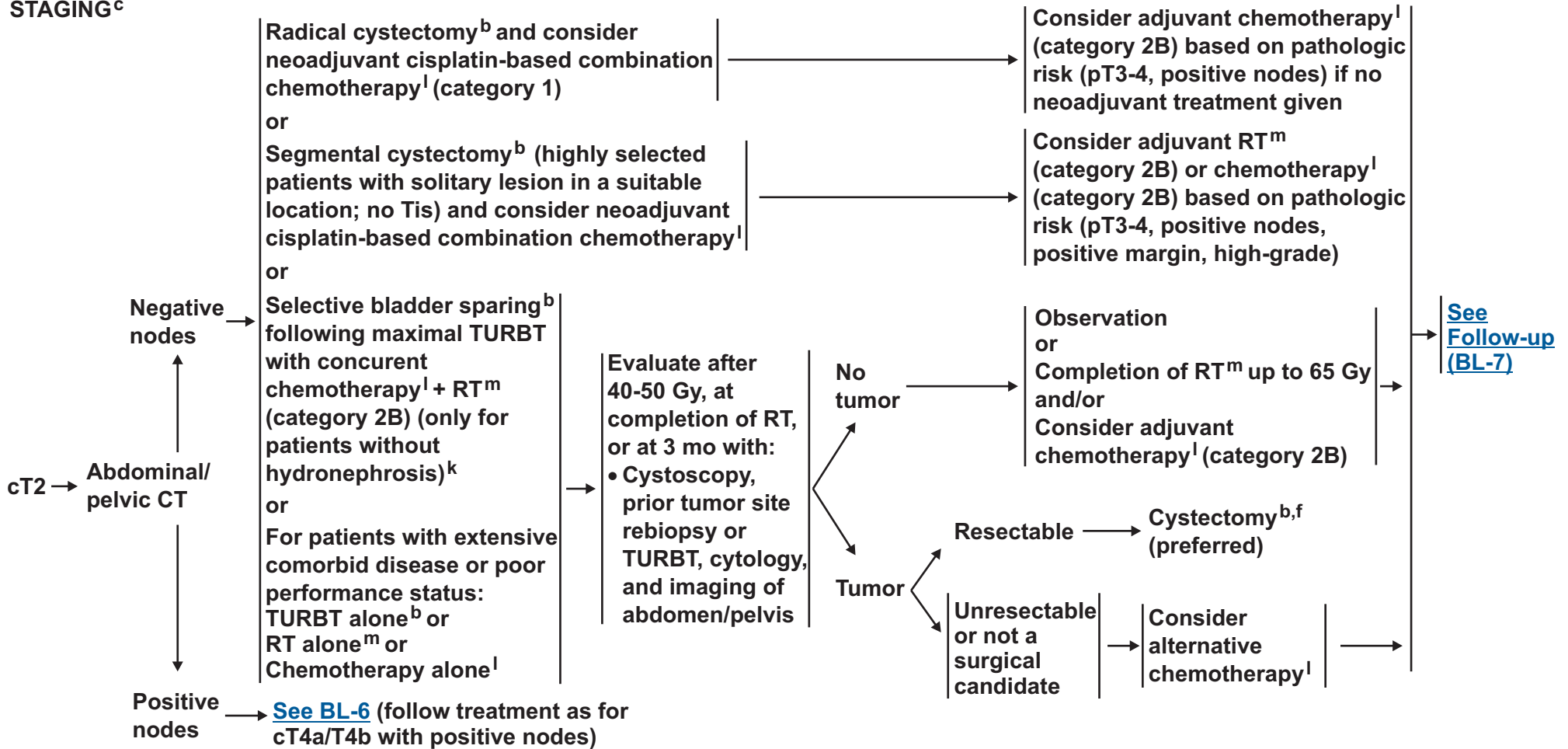
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**CLINICAL STAGING<sup>c</sup>**

**PRIMARY TREATMENT**

**ADJUVANT TREATMENT**



<sup>b</sup>See [Principles of Surgical Management \(BL-A\)](#).

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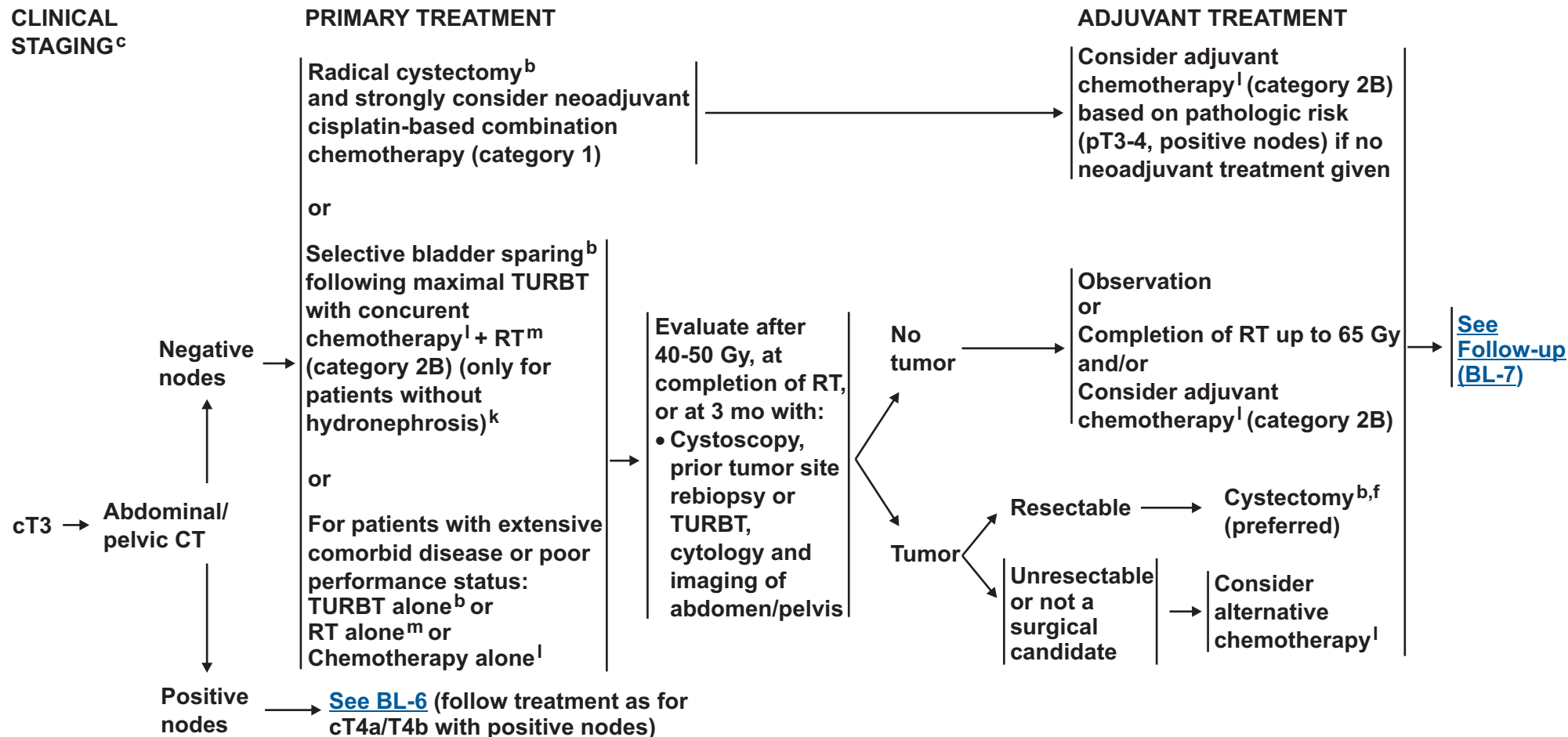
<sup>k</sup>There are data to support equivalent survival rates, but not uniform consensus about the role of these approaches. Not all institutions have experience with these multidisciplinary treatment approaches which require a dedicated team.

<sup>l</sup>See [Principles of Chemotherapy Management \(BL-G\)](#).

<sup>m</sup>See [Principles of Radiation Management of Invasive Disease \(BL-H\)](#).

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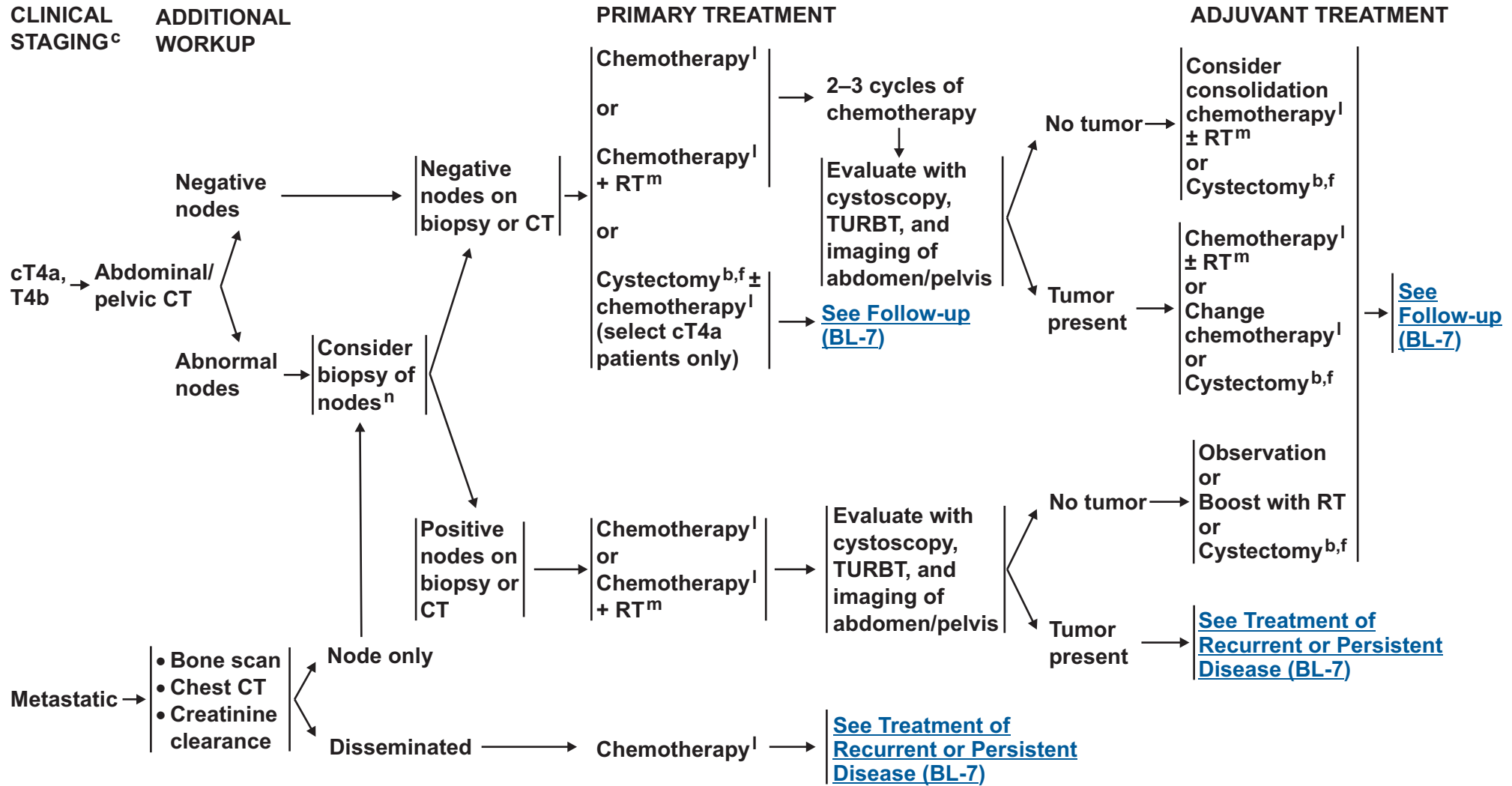
<sup>f</sup>See [Follow-Up After Cystectomy \(BL-E\)](#).

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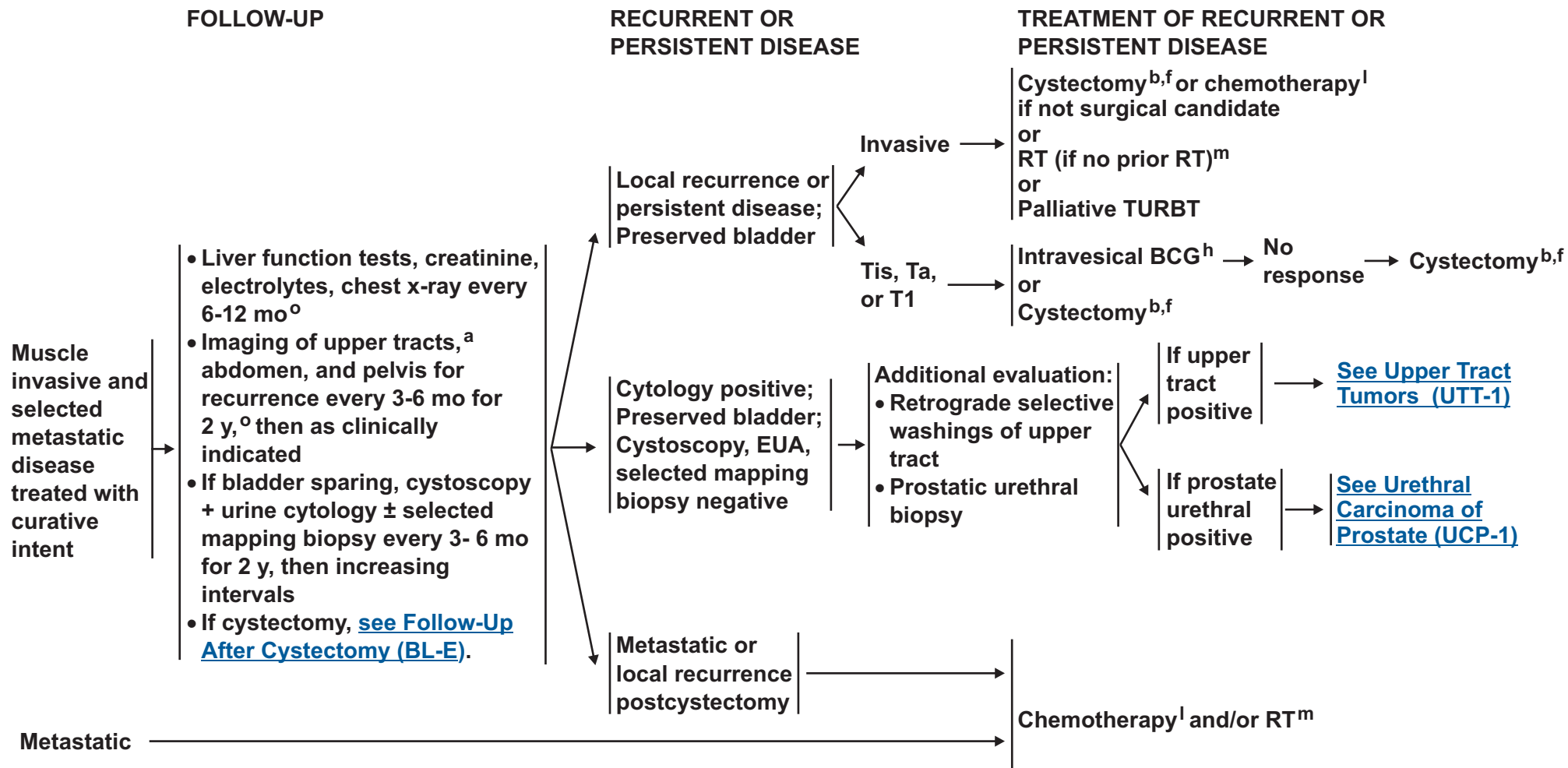
<sup>l</sup>See Principles of Chemotherapy Management (BL-G).

<sup>m</sup>See Principles of Radiation Management of Invasive Disease (BL-H).

<sup>n</sup>If technically possible.

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<sup>h</sup>[See Principles of Intravesical Treatment \(BL-F\)](#).

<sup>l</sup>[See Principles of Chemotherapy Management \(BL-G\)](#).

<sup>m</sup>[See Principles of Radiation Management of Invasive Disease \(BL-H\)](#).

<sup>o</sup>Depending on risk of recurrence.

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## PRINCIPLES OF SURGICAL MANAGEMENT

### TURBT: Papillary

- Adequate resection with muscle if papillary high-grade lesion
- Reresection if incomplete initial resection, no muscle in specimen or large lesion

### TURBT: Tis

- Multiple random biopsies
- Biopsy adjacent to tumor
- Prostate urethral biopsy

### TURBT: Invasive

- Repeat resection:
  - Any T1, any grade
  - If no muscle in biopsy
  - Small fragment of T2 insufficient to attribute risk
- Repeat TURBT should be considered if first TURBT does not allow adequate staging or attribution of risk factor for treatment selection or when using bladder-preserving treatment by chemotherapy and/or RT

### SEGMENTAL CYSTECTOMY

- Solitary lesion in location amenable to segmental resection with adequate margin, no Tis
- Pelvic lymphadenectomy should be performed in conjunction with the segmental cystectomy

### RADICAL CYSTECTOMY

- Radical cystectomy should include bilateral node dissection at a minimum including common, internal and external iliac nodes, and obturator nodes

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**PRINCIPLES OF PATHOLOGY MANAGEMENT**

- Tumors in many cases that would have been classified as grade 2 by the WHO 1973 grading system are now classified as high-grade using the WHO 2004 and the ISUP/WHO 1998 systems.
- The pathology report on biopsy/TURBT specimens should specify:
  - ▶ If muscularis propria (detrusor muscle) is present and if present whether this structure is invaded by tumor
  - ▶ Presence or absence of lymphovascular space invasion
  - ▶ Presence or absence of subjacent carcinoma-in-situ

**Malignancy Grading of Bladder Carcinoma: Old and New Systems\***

<u>Modified Bergkvist 1987</u>	<u>WHO 1973</u>	<u>WHO/ISUP 1998 Consensus WHO, 2004</u>
Papilloma grade 0	Papilloma	Papilloma
Papilloma with atypia grade 1	TCC grade 1	Papillary urothelial neoplasm of low malignant potential
Urothelial carcinoma grade 2A	TCC grade 1	Urothelial carcinoma, low-grade
Urothelial carcinoma grade 2B	TCC grade 2	Urothelial carcinoma, low-grade or high-grade
Urothelial carcinoma grade 3	TCC grade 3	Urothelial carcinoma, high-grade

\*From Droller MJ: Bladder Cancer, Current Diagnosis and Treatment. Totowa, NJ, 2001. With kind permission of Springer Science + Business Media.

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**APPROXIMATE PROBABILITY OF RECURRENCE AND PROGRESSION**

<u>Pathology</u>	<u>Approximate Probability of Recurrence in 5 years</u>	<u>Approximate Probability of Progression to Muscle Invasion</u>
Ta, low grade	50%	Minimal
Ta, high grade	60%	Moderate
T1, low grade (rare)	50%	Moderate
T1, high grade	50- 70%	Moderate- High
Tis	50%- 90%	High

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## NON-UROTHELIAL CELL CARCINOMA OF THE BLADDER

Same as urothelial cell carcinoma management with the following issues:

### Mixed Histology:

- Urothelial carcinoma plus pure squamous, adenocarcinoma, micropapillary, nested, plasmacytoid, sarcomatoid should be identified because of the potential to have a more aggressive natural history.
- Follow [Urothelial Carcinoma of the Bladder \(BL-1\)](#) with complete response less likely if bladder sparing considered.

### Pure Squamous:

- Cystectomy, RT, or other agents commonly used with squamous cell carcinoma of other sites such as 5-FU, taxanes, methotrexate, etc.

### Adenocarcinoma:

- Radical cystectomy or segmental (partial) cystectomy.
- Conventional chemotherapy (eg, MVAC) for urothelial carcinoma is not effective, however, the use of chemotherapy or RT should be individualized and maybe of potential benefit in select patients.
- Consider alternative therapy or clinical trial

### Any Small-cell component (or neuroendocrine features):

- Neoadjuvant or adjuvant chemotherapy using small-cell regimens and local treatment (cystectomy or radiotherapy).
- Primary chemotherapy regimens similar to small cell lung cancer. [See NCCN Small Cell Lung Cancer Guidelines](#)

### Urachal Carcinoma:

- Requires complete urachal resection.
- Conventional chemotherapy for urothelial carcinoma is not effective, however, the use of chemotherapy or RT should be individualized and maybe of potential benefit in select patients.

### Primary Bladder Sarcoma:

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

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## FOLLOW-UP AFTER CYSTECTOMY

### After a radical cystectomy

- Urine cytology, creatinine, electrolytes, every 3 to 6 months for 2 years and then as clinically indicated
- Imaging of the chest, abdomen, and pelvis every 3 to 12 months for 2 years based on risk of recurrence and then as clinically indicated
- Urethral wash cytology, every 6 to 12 month; particularly if Tis was found within the bladder or prostatic urethra
- If a continent diversion was created, monitor for vitamin B12 deficiency annually

### After a segmental (partial) cystectomy

- Same follow-up as above, in addition to the following:
  - ▶ Cystoscopy and urine cytology every 3-6 mo for 2 y, then increasing intervals as appropriate

For Recurrent or Persistent Disease ([See BL-7](#))

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## PRINCIPLES OF INTRAVESICAL TREATMENT

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

### Immediate Intravesical Chemotherapy

- **Initiated within 24 hrs after resection**
- **Use after TUR lowers recurrence rate in Ta low grade tumors**
- **Treatment should not be given if extensive TURBT or if suspected bladder perforation**

### Induction Intravesical Chemotherapy

- **Initiated 3-4 wks after resection**
- **Maximum of 2 inductions without complete response**
- **Role of maintenance therapy uncertain**

### Induction Intravesical Immunotherapy

- **Initiated 3-4 wks after resection**
- **Withhold if traumatic catheterization, bacteriuria, persistent gross hematuria, persistent severe local, or systemic symptoms**
- **Maximum of 2 inductions without complete response**
- **Some data suggest benefit of maintenance therapy**
- **Dose reduction is encouraged if substantial local symptoms during maintenance therapy**

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## PRINCIPLES OF CHEMOTHERAPY MANAGEMENT

### First-line chemotherapy (neoadjuvant, adjuvant, and metastatic)

- **Gemcitabine and cisplatin (preferred, category 1).** A large randomized trial comparing this regimen to MVAC demonstrated that gemcitabine/cisplatin had efficacy similar to MVAC in terms of objective response rate, progression-free and overall survival, and demonstrated a more favorable toxicity profile. This combination is considered the standard first-line choice for most patients.
- **MVAC (methotrexate, vinblastine, doxorubicin and cisplatin) (category 1).** Concern regarding toxicity limit this regimen's use, however it is the historical standard of care based on improved survival and response rates when compared to older regimens.
- **Three drug regimens such as gemcitabine, cisplatin, and paclitaxel have not been proven superior to gemcitabine and cisplatin.**
- **Carboplatin should not be substituted for cisplatin in patients with normal renal function. 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.
- **Presence of both visceral 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.**
- **A modest survival benefit of neoadjuvant chemotherapy in patients with muscle-invasive bladder cancer was noted in randomized trials and meta-analyses performed in patients receiving 3 cycles prior to cystectomy but not radiotherapy.**

### First-line chemotherapy (alternative regimens)

- **A substantial proportion of patients cannot receive cisplatin-based chemotherapy due to renal impairment or other co-morbidities. Carboplatin and taxane-based regimens, or single agent therapy can be considered for these patients.**

### Second-line chemotherapy (metastatic)

- **No standard therapy exists in this setting. Participation in clinical trials of new agents is recommended. Depending on first line therapies, palliative options include single agent therapy such as bleomycin, cisplatin, carboplatin, docetaxel, doxorubicin, 5-fluorouracil, gemcitabine, ifosfamide, paclitaxel, pemetrexed, methotrexate, and vinblastine.**

### Radiosensitizing chemotherapy regimens (For concurrent treatment with radiation therapy for selective bladder preservation)

- **First-line chemotherapy**
  - **Cisplatin alone, or in combination with 5-fluorouracil**
  - **Mitomycin C in combination with 5-fluorouracil (category 2B)**
- **Alternative Regimens**
  - **Clinical trial**

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## PRINCIPLES OF RADIATION THERAPY MANAGEMENT OF INVASIVE DISEASE

- **External beam radiation is rarely appropriate for patients with recurrent Ta-T1 tumors or diffuse Tis.**
- **External beam radiation is most successful on patients without hydronephrosis.**
- **External beam radiation can also be used for medically inoperable patients or for palliation.**
- **Precede radiation by maximal TUR of the tumor when safely possible.**
- **Combining concurrent chemotherapy with radiation is encouraged for added tumor cytotoxicity. Such therapy is optimally given by dedicated multidisciplinary teams.**
- **Simulate and treat patients with the bladder empty.**
- **Use multiple fields from high-energy linear accelerator beams.**
- **Treat the whole bladder with or without pelvic lymph nodes with 40- 45 Gy and then boost the bladder tumor to a total dose of 64-66 Gy excluding, if possible, normal areas of the bladder from the high-dose volume.**
- **Consider low-dose pre-operative radiation therapy prior to segmental resection for invasive tumors (category 2B).**

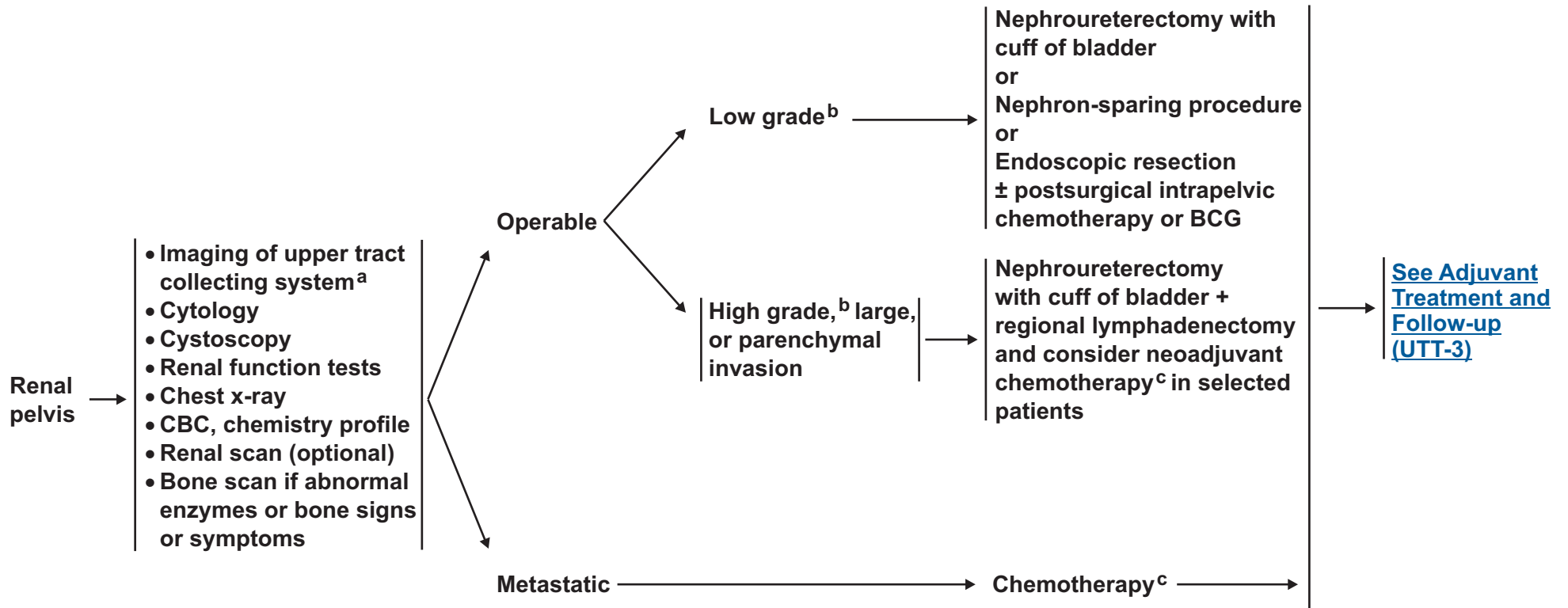
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**WORKUP**

**PRIMARY TREATMENT**

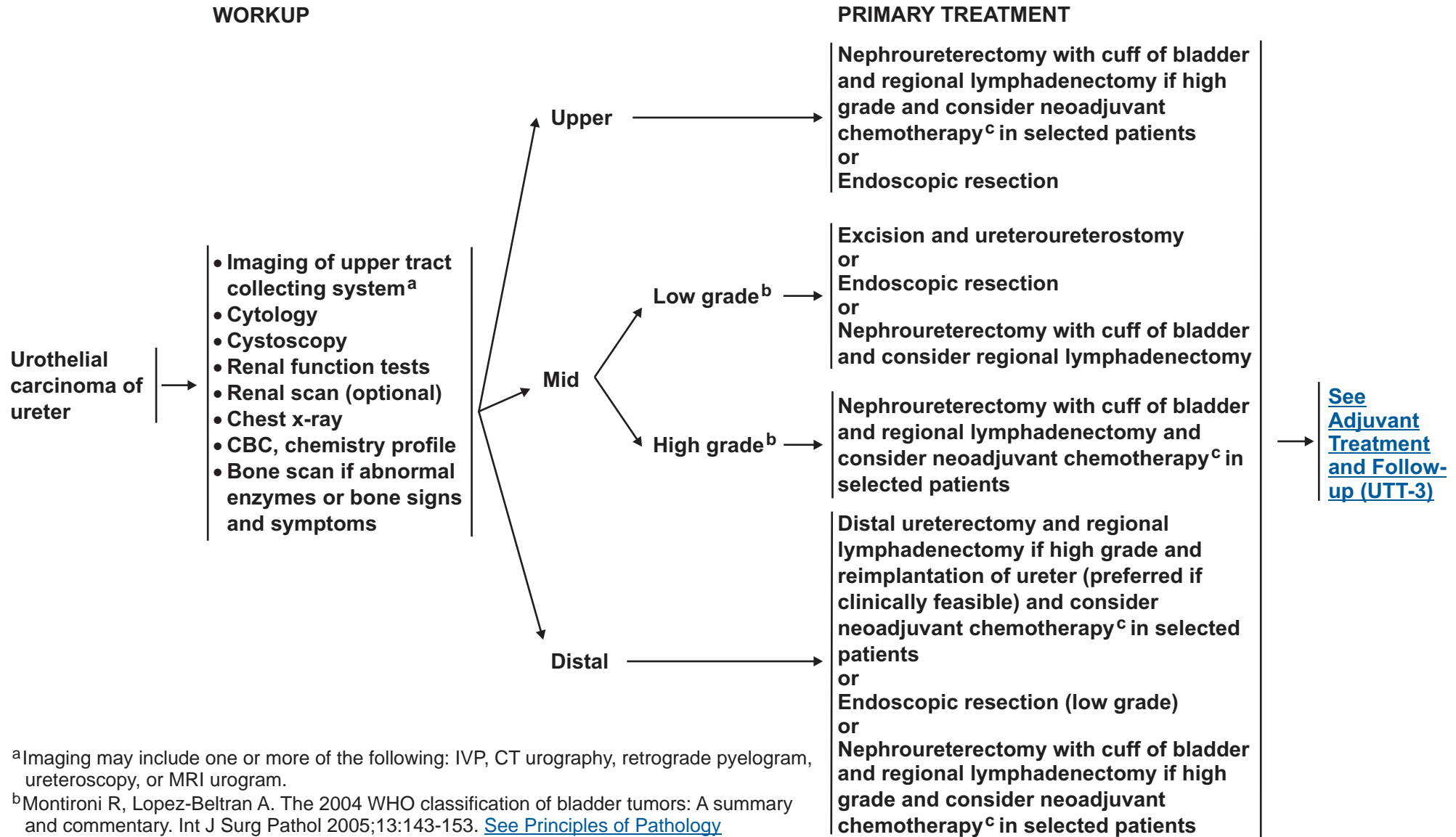


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[See Principles of Pathology Management \(BL-B\).](#)

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**PATHOLOGIC STAGING<sup>d</sup>**

**ADJUVANT TREATMENT**

**FOLLOW-UP**

**Primary Treatment  
Renal Pelvis  
and TCC Ureter**

pT0, pT1

None

- Cystoscopy every 3 mo for 1 y, then at increasing intervals
- Imaging of upper tract collecting system<sup>a</sup> at 3-12 mo intervals, if endoscopic resection
  - ± CT scan or MRI
  - ± Chest x-ray

pT2, pT3,  
pT4, pN+

Consider adjuvant  
chemotherapy<sup>c,e</sup>  
± RT

- Cystoscopy every 3 mo for 1 y, then at increasing intervals
- Imaging of upper tract collecting system<sup>a</sup> at 3-12 mo intervals
  - ± CT scan or MRI
  - ± Chest x-ray

<sup>a</sup>Imaging may include one or more of the following: IVP, CT urography, retrograde pyelogram, ureteroscopy, or MRI urogram.

<sup>c</sup>[See Principles of Chemotherapy Management \(BL-G\)](#).

<sup>d</sup>The modifier “p” refers to pathologic staging based on cystectomy and lymph node dissection.

<sup>e</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 cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.



# NCCN Guidelines™ Version 2.2011

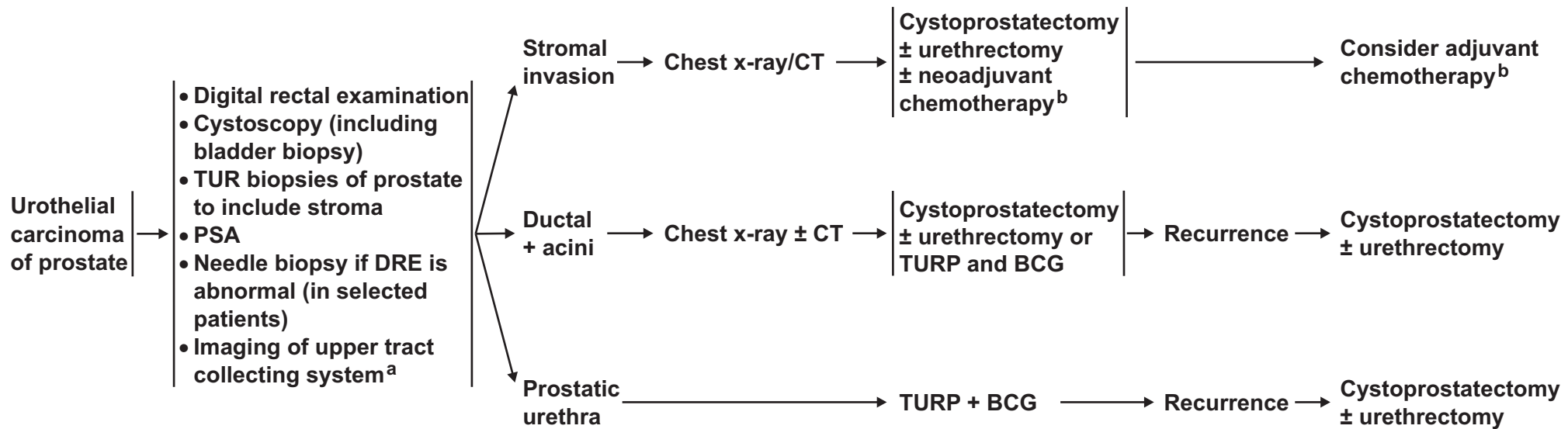
## Urothelial Carcinoma of the Prostate

### WORKUP

### PATHOLOGY

### ADDITIONAL WORKUP

### PRIMARY TREATMENT



<sup>a</sup>Imaging may include one or more of the following: IVP, CT urography, retrograde pyelogram, ureteroscopy, or MRI urogram.

<sup>b</sup>[See Principles of Chemotherapy Management \(BL-G\)](#).

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

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



**Table 1**

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

**Primary Tumor (T)**

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

**ANATOMIC STAGE/PROGNOSTIC GROUPS**

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

**Regional Lymph Nodes (N)**

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

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

**Distant Metastasis (M)**

- M0** No distant metastasis
- M1** Distant metastasis

[Continued on next page](#)

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

**Table 1 (Continued)****American Joint Committee on Cancer (AJCC)  
TNM Staging System for Bladder Cancer (7th ed., 2010)****Clinical Staging**

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

**Pathologic Staging**

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

**Histologic Grade (G)**

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

**LG** Low grade  
**HG** High grade

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

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

**Histopathologic Type**

The histologic types are as follows:

**Urothelial (transitional cell) carcinoma**

In situ

Papillary  
Flat  
With squamous differentiation  
With glandular differentiation  
With squamous and glandular differentiation

**Squamous cell carcinoma****Adenocarcinoma****Undifferentiated carcinoma**

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

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**Table 2****American Joint Committee on Cancer (AJCC)  
TNM Staging System for Renal Pelvis and Ureter Cancer (7th ed., 2010)****Primary Tumor (T)**

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

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

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

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

**Distant Metastasis (M)**

<b>M0</b>	No distant metastasis
<b>M1</b>	Distant metastasis

**ANATOMIC STAGE/PROGNOSTIC GROUPS**

<b>Stage 0a</b>	Ta	N0	M0
<b>Stage 0is</b>	Tis	N0	M0
<b>Stage I</b>	T1	N0	M0
<b>Stage II</b>	T2	N0	M0
<b>Stage III</b>	T3	N0	M0
<b>Stage IV</b>	T4	N0	M0
	Any T	N1	M0
	Any T	N2	M0
	Any T	N3	M0
	Any T	Any N	M1

[Continued on next page](#)

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**Table 2 (Continued)**

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

**Histologic Grade (G)**

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

- LG** Low grade
- HG** High grade

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

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

**Histopathologic Type**

The histologic types are as follows:

**Urothelial (transitional cell) carcinoma**

- In situ
  - Papillary
  - Flat
    - With squamous differentiation
    - With glandular differentiation
    - With squamous and glandular differentiation

**Squamous cell carcinoma**

**Adenocarcinoma**

**Undifferentiated carcinoma**

The predominant cancer is urothelial (transitional cell) carcinoma.

Histologic variants include micropapillary and nested subtypes.

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## Discussion

### NCCN Categories of Evidence and Consensus

**Category 1:** The recommendation is based on high-level evidence (e.g. randomized controlled trials) and there is uniform NCCN consensus.

**Category 2A:** The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

**Category 2B:** The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).

**Category 3:** The recommendation is based on any level of evidence but reflects major disagreement.

**All recommendations are category 2A unless otherwise noted.**

### Overview

An estimated 70,530 new cases of urinary bladder cancer will be diagnosed in the United States (52,810 men and 18,170 women) in 2010.<sup>1,2</sup> Bladder cancer, the fourth most common cancer, is three times more common in men than in women in the United States. During the same period, approximately 14,680 deaths (10,410 men and 4,270 women) from bladder cancer are anticipated. Bladder cancers are rarely diagnosed in individuals younger than 40 years. Because the median age of diagnosis is 65 years, medical comorbidities are a frequent consideration in patient management.<sup>2</sup>

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-invasive tumors, for which treatment is directed at reducing recurrences and preventing progression to a more advanced stage. The second group encompasses the invasive lesions, and the goal of therapy is to determine if the bladder should be removed or 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 of therapy for the third group, consisting of metastatic lesions, is how to prolong life. Numerous agents with different mechanisms of action have antitumor effects in this disease. The issue has become how to use these agents to achieve the best possible outcome.

### 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 (transitional cell) carcinomas, the most common histologic subtype in the United States, may develop anywhere transitional epithelium is present, from the renal pelvis to the ureter, bladder, and proximal two thirds of the urethra. The distal third of the urethra is dominated by squamous epithelium. The diagnosis of squamous cell tumors, which constitute 3% of the urinary tumors diagnosed in the United States, requires the presence of keratinization in the pathologic specimen.

Of the other histologic subtypes, 2% are adenocarcinomas and 1%, small-cell tumors (with or without an associated paraneoplastic syndrome). Adenocarcinomas often occur in the dome of the bladder in the embryonal remnant of the urachus, in the periurethral tissues, or with a signet ring–cell histology. Urothelial tumors often have a mixture of divergent histologic subtypes, such as urothelial (transitional cell)



and squamous, adenocarcinoma, and more recently appreciated nested micropapillary, and sarcomatoid subtypes.<sup>3</sup> These should be treated as urothelial carcinomas.

The systemic chemotherapy regimens used to treat urothelial carcinomas (transitional cell tumors) are generally ineffective for tumors with pure non-urothelial (non-transitional cell) histology, such as adenocarcinoma or squamous carcinoma. In some cases with a mixed histology, only the non-urothelial (non-transitional cell) component remains after systemic treatment.

### Clinical Presentation and Workup

The most common presenting symptom in patients with bladder cancer is microscopic hematuria, although urinary frequency from irritation or a reduced bladder capacity can also develop. Less commonly, a urinary tract infection is the presenting symptom, or upper tract obstruction or pain may occur for a more advanced lesion. Patients presenting with these symptoms should be evaluated with office cystoscopy to determine if a lesion is present. If one is documented, the patient should be scheduled for a transurethral resection of the bladder tumor (TURBT) to confirm the diagnosis and determine the extent of disease within the bladder. Urine cytology may also be obtained during the cystoscopy.

If the cystoscopic appearance of the tumor is solid (sessile), high-grade, or suggests invasion into muscle, a computed tomographic (CT) scan or magnetic resonance imaging (MRI) of the abdomen and pelvis is recommended before the TURBT. Because the results of a CT scan rarely alter the management of tumors with a purely papillary appearance or cases in which only the mucosa appears abnormal, suggesting carcinoma in situ (CIS), a CT scan is not recommended in these situations. Additional workup for all patients should include urine

cytology if not already tested and evaluation of the upper tracts with an intravenous pyelogram (IVP), renal ultrasound with retrograde pyelogram, CT urography, ureteroscopy, or MRI urogram. CT urography is used as an alternative to conventional intravenous urography. Especially in invasive tumors of the upper tract, CT urography gives more information than IVP. However, CT urography has the disadvantage of a much higher radiation exposure than IVP.

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 whether invasion has occurred. 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. A transurethral resection (TUR) biopsy of the prostate may also be considered. Finally, if an invasive tumor is noted, an adequate sample of muscle must be obtained. A small fragment of tumor with few muscle fibers is inadequate for assessing the depth of invasion and guiding treatment recommendations.

Additional diagnostic tests, such as a bone scan, should be performed if elevated levels of alkaline phosphatase are seen in the blood. Treatment decisions are then based on disease extent within the 3 general categories: non-invasive, invasive, or metastatic. Chest imaging is indicated if invasive disease is suspected.

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 must be considered.



Management of bladder cancer is based on the pathologic findings of the biopsy specimen, with attention to histology, grade, and depth of invasion. These factors are used to estimate the probability of recurrence and progression to a more advanced stage. Because the clinical benefit of ploidy, vascularity, p53 status, other urinary markers (e.g., NMP-22, BTA, M344), and chromosomal alterations by FISH is uncertain, they are not used to guide treatment decisions outside of the experimental protocol setting.

### Pathology and Natural History

Approximately 70% of newly detected cases are exophytic papillary tumors confined largely to the mucosa (Ta) (70%) or, less often, to the submucosa (T1) (30%).<sup>4</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 10% to 70% of patients with a tumor confined to the mucosa will experience a recurrence or new occurrence of urothelial (transitional cell) carcinoma within 5 years. These probabilities of progression 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.<sup>5</sup>

### Staging and Grading

The most commonly used staging system is the tumor, node, metastasis (TNM) system,<sup>6</sup> by the American Joint Committee on Cancer (AJCC) as shown in the algorithm.

Tumor grade has been recognized as an important prognostic indicator with regard to the potential for disease recurrence and progression. The most widely used classification for grading of non-muscle invasive urothelial neoplasms has been the 1973 World Health Organization (WHO) classification. This system has designations for papilloma and Grades 1, 2, and 3 carcinomas. In 2004, members of the WHO and International Society of Urological Pathology (ISUP) published and recommended a revised consensus classification for papillary neoplasms.<sup>7</sup> A new category of papillary urothelial neoplasm of low malignant potential was created to describe lesions with an increased number of urothelial layers when compared with papilloma but without cytologic features of malignancy. Under the WHO 2004 system, some Grade 2 lesions are classified as low grade and others as high grade tumors. This new system potentially allows for enhanced prognostic significance but is dependent on the pathologist for making these distinctions. The 2004 WHO classification is yet to be validated by clinical trials, therefore, tumors are graded using both the 1973 and the 2004 WHO classifications. The different classification systems are compared on Table 1: "Principles of Pathology Management". The 7<sup>th</sup> edition of the AJCC staging system has replaced the previous 4 grade system to match current WHO/ISUP recommended grading system.

After stage and grade have been determined, treatment decisions are based on the depth of invasion and extent of disease.



## Treatment

The disciplines of urologic surgical, radiation, and medical oncology are required for treating bladder cancer. For many of the complex strategies, the involvement of multidisciplinary teams optimizes results. The general principles for surgery, follow up after cystectomy, intravesical treatment, chemotherapy, and radiation therapy are explained in the algorithm.

### Treatment of Non–Muscle-Invasive Disease

A physical examination usually does not reveal non-muscle invasive disease. Non–muscle-invasive tumors are divided into non-invasive papillomas or carcinomas (Ta), those invading the lamina propria (T1), and carcinoma in situ (CIS) or Tis.<sup>8</sup> These tumors have previously been referred to as *superficial*, which is an imprecise term that should be avoided. In some cases, a papillary or T1 lesion will be documented as having an associated in situ component (Tis).

Non-invasive disease may be diagnosed by initial cystoscopy and cytology. Once suspected, imaging of upper tract collecting systems must be performed. In addition, a pelvic CT scan must be performed before transurethral resection of bladder tumor (TURBT) if sessile or high grade is suspected.

Standard treatment for Ta, T1, and Tis is TURBT. It is used to diagnose, to stage and to treat visible tumors. 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 whether invasion has occurred. The involvement of the prostatic urethra and ducts in male patients with Ta, T1, and Tis bladder tumors has been reported. The risk is higher in the case of tumors in the bladder neck. Therefore, if sessile, high grade cytology is seen or Tis is

suspected, selected mapping biopsies and TUR biopsy of prostate must be considered.

Clinical investigation of the specimen obtained by TUR 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 examination under anesthesia and endoscopic surgery (biopsy or TUR) and imaging studies. A modifier “p” would refer to pathologic staging based on cystectomy and lymph node dissection.

A second TUR is performed when a high-grade, T1 tumor and possibly a Ta has been detected at the initial TUR. However, depending on the depth of invasion and grade, intravesical therapy may be recommended. This suggestion is based on the estimated probability of recurrence (i.e., new tumor formation within the bladder) and progression to a more advanced, usually muscle invasive stage, which are events that should be considered independently. Cystectomy is rarely considered for a Ta, low grade lesion.

Intravesical therapy is used in two general settings: as prophylactic or adjuvant therapy after a complete endoscopic resection or, rarely, as therapy with the goal of eradicating residual disease that could not be completely resected. This distinction is important, because most published data reflect prophylactic or adjuvant use with the goal of preventing recurrence or delaying progression to a higher grade or stage. In many cases, intravesical therapy may be over used if given to patients who have a low probability of recurrence or progression is slow. Bacillus Calmette-Guérin (BCG) has been shown to be effective as prophylaxis to prevent bladder cancer recurrences following TURBT. Management of the different histologic subtypes of non-invasive bladder tumors of different grades is outlined in subsequent sections.



### ***cTa, low grade tumors***

Transurethral resection is the standard treatment for cTa, low grade tumors. Although a complete TUR by itself can eradicate cTa low grade tumors, these tumors have a relatively high risk for recurrence. Therefore, after TUR the panel recommends that, in addition to observation, the clinicians should consider administering a single dose of immediate intravesicular chemotherapy (not immunotherapy) within 24 hours of resection. Immediate use of intravesicular therapy (within 24 hours of TUR) lowers recurrence risk in Ta low grade tumors. A meta analysis of seven randomized trials confirmed that immediate intravesicular therapy decreased risk of recurrence by 12% (from 48% down to 36.7%) in patients having either single or multiple tumors.<sup>9</sup> The immediate intravesicular chemotherapy may be followed by a 6 week induction of intravesicular chemotherapy. Mitomycin C is the agent most commonly used, immunotherapy is not recommended in these patients.

The need for adjuvant therapy depends on the patient prognosis, if the patient has low risk of recurrence, single immediate intravesicular treatment may be sufficient. Factors to consider include the size, number, and grade of the tumor(s), as well as concomitant CIS, lymphovascular invasion, and prostatic urethral involvement.<sup>10</sup> Meta-analyses have confirmed the efficacy of adjuvant intravesicular chemotherapy in reducing the risk of recurrence.<sup>11, 12</sup> Immediate intravesicular treatment should be avoided in the case if TURBT was extensive or if bladder perforation is suspected.

Close follow-up of all patients is needed, although the risk for progression to a more advanced stage is low. As a result, these patients are advised to undergo a cystoscopy at 3 months initially, and then at increasing intervals.

### ***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. In the absence of muscularis propria in the TUR specimen, data suggests that 20% to 40% of patients will have either residual tumor and/or unrecognized muscle invasive disease.<sup>13, 14</sup> Repeat resection is recommended if there is incomplete resection, or there is no muscle in specimen.

Post TUR, in addition to observation, patients with Ta, high grade tumors may be treated with intravesicular BCG or mitomycin C. In the literature, there are four meta-analyses data confirming that BCG after TUR is superior to TUR alone or TUR and chemotherapy in preventing recurrences of high grade Ta and T1 tumors.<sup>15-18</sup> The NCCN Bladder Cancer panel members recommend BCG as the preferred option for adjuvant treatment of high grade lesions.

Follow-up is recommended, with a urinary cytology and cystoscopy at 3-6 month intervals for the first 2 years, and at increasing intervals as appropriate thereafter. Imaging of the upper tract should be considered every 1-2 years for high-grade tumors. Urine molecular tests for urothelial tumor markers are now available.<sup>19</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 which is useful for detection and management of non-muscle-invasive bladder tumors. Therefore, the NCCN Bladder Cancer panel members consider this a category 2B recommendation.

### ***cT1 tumors***

T1 tumors are those that invade subepithelial connective tissue (also referred to as lamina propria). Based on the histological 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 in situ component.

These are also treated with a complete endoscopic resection. In patients with high-risk disease especially if the complete resection is uncertain because of the tumor size and location, no muscle is shown in the specimen, lymphovascular invasion has occurred, or inadequate staging is speculated, repeat resection of tumor is strongly advised. If residual disease is found after a second resection, immunotherapy with BCG (category 1 recommendation) or cystectomy is recommended.

Within the category of T1 disease, a particularly high risk strata can be identified: multifocal lesions, tumors associated with vascular invasion, or lesions that recur after BCG treatment. There is data suggesting that early cystectomy may be preferred if residual disease is found, because of the high risk for progression to a more advanced stage.<sup>4</sup> If high-risk disease is managed conservatively and does not respond to BCG or mitomycin C, a cystectomy should be performed. If no residual disease is found after the second resection, intravesical therapy with BCG (preferred; category 1 recommendation) or mitomycin C is recommended. Follow-up is similar to that for high grade Ta disease.

### Tis

Primary carcinoma in situ (CIS) or Tis is a high-grade lesion that is believed to be a precursor of invasive bladder cancer. Standard therapy for this lesion is a complete endoscopic resection followed by intravesical therapy with BCG. This therapy is generally 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 (i.e., 3 months) after the start of therapy. If

the patient is unable to tolerate BCG, intravesical mitomycin C may be administered.

Follow-up is recommended, with a urinary cytology and cystoscopy at 3-6 month intervals for the first 2 years, then at increasing intervals as appropriate. Imaging of the upper tract should be considered every 1-2 years. Urine molecular marker testing is optional (Category 2B recommendation).

### ***Management of Posttreatment recurrent or persistent cTa, cT1 and TIS disease***

#### *Based on cystoscopy results*

Patients who were under observation after initial TURBT, who show a documented recurrence by positive cystoscopy results are treated again with TURBT followed by adjuvant intravesical therapy (see section below on “Adjuvant Chemotherapy”) based on the stage and grade of the recurrent lesion, and then followed-up at 3-month intervals.

Patients with recurrent/persistent tumors that responded to induction intravesical therapy, after initial intravesical treatment, and 12-week (3-month) evaluation can be given a second induction course of BCG or mitomycin C induction therapy (no more than 2 consecutive induction courses). If a second course of BCG is given and residual disease is seen at the second 12-week (3-month) follow-up, TURBT is performed. Depending on prior treatment, extent of the disease, and frequency of recurrences, intravesical therapy with a different intravesical agent is an alternative to cystectomy. Valrubicin has been approved for CIS that is refractory to BCG, although panelists disagree on its value. The combination of intravesical BCG and interferon alpha-2B has been shown to be potentially effective in this setting,<sup>20</sup> but data from the phase III randomized study are not currently available. In some centers,



however, these patients might still be candidates for investigational therapies.

For patients showing complete response at the follow-up cystoscopy, whether 1 or 2 courses of induction therapy were administered, maintenance therapy with BCG is optional. This recommendation is based on findings that induction course of intravesical therapy followed by a maintenance regimen, have better outcomes than intravesical chemotherapy.<sup>15, 16, 18, 21-23</sup>

If progression to an invasive lesion is documented at any point during follow-up, a radical cystectomy is recommended. Although controversial, patients who present with recurrent superficial tumors before a muscle-invading lesion is documented are generally not considered candidates for bladder-sparing approaches.

### *Based on Cytology Results*

In patients without a documented recurrence but cytology positive, cystoscopy and imaging negative, TUR must be performed with directed or selected mapping biopsies including TUR biopsies of the prostate. In addition, cytology of the upper tract must be evaluated and ureteroscopy must 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 treatment followed by maintenance BCG (optional) if a complete response is seen. For tumors that fail BCG or show an incomplete response, the subsequent management options include cystectomy; or changing the intravesical agent to mitomycin C; or participation in a clinical trial. Further investigation and validation of results is warranted for establishing the efficacy of alternative agents in the second-line treatments.<sup>24, 25</sup>

If TUR biopsy of the prostate is positive, the treatment is described below under the section on Urethral Carcinoma of the Prostate. If cytology of the upper tract and/or ureteroscopy results is positive, then the treatment is described below under the section on Upper Tract Tumors.

If the TUR biopsies of the bladder and prostate are negative, then follow-up at 3 month intervals is recommended and maintenance therapy with BCG is optional. If the cytology of the upper tract and ureteroscopy is negative, follow up at 3 month intervals is recommended.

### **Treatment of Muscle-Invasive Disease**

Before any treatment is advised, several workup procedures are recommended to accurately determine the clinical staging. Laboratory studies, such as complete blood cell count and chemistry profile, including alkaline phosphate, must be performed, and the patient should be assessed for the presence of regional or distant metastases. This evaluation should include a cystoscopy, chest radiograph or CT scan, bone scan in patients with symptoms or elevated alkaline phosphate, and evaluation of the upper tracts with a CT or magnetic resonance scan of the abdomen and pelvis. Imaging studies help assess the extent of local tumor invasion, spread to lymph nodes and to other distant organs. CT and MRI may be used to assess local invasion. Unfortunately, CT scans, ultrasound, and MRI cannot accurately predict the true depth of invasion.<sup>26</sup>

TURBT is the initial treatment. The goal of the TUR is to correctly identify the stage therefore bladder muscle must be included in the resection biopsies. All muscle invasive tumors are high grade urothelial carcinomas.<sup>27</sup>



### **T2 and T3 tumors**

The critical issues in the management and prognosis of these patients are whether a palpable mass is appreciated at examination under anesthesia 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 to the perivesical fat (T3) and beyond.

Primary surgical treatment for T2 and T3 lesion (with no nodal disease seen on CT scan) is a radical cystectomy, with the consideration of neoadjuvant chemotherapy based on two randomized trials (category 1).<sup>28, 29</sup> There is stronger evidence to support neoadjuvant chemotherapy for T3 disease. If no neoadjuvant chemotherapy was given, postoperative adjuvant chemotherapy is considered based on pathologic risk, such as positive nodes and pathologic T3-T4 lesions. Details of the neoadjuvant and adjuvant chemotherapy regimen are discussed in sections below.

Segmental cystectomy can be considered only in T2 patients with a single tumor (solitary lesion in a suitable location) and no presence of Tis; or previous multifocal bladder cancers along with consideration of neoadjuvant chemotherapy. Segmental cystectomy is not an option for T3 patients. If segmental cystectomy was performed, adjuvant radiotherapy or chemotherapy based on pathologic risk, such as positive nodes, positive margin, high-grade, and pathologic T3-T4 lesions, should be considered (category 2B recommendation).

Bladder preservation strategy (discussed in detail below) with concurrent chemotherapy and radiation (Category 2B recommendation) is an option in highly selected patients. Candidates for bladder sparing approaches are those without hydronephrosis that allow a visibly complete TURBT.

In patients with extensive comorbid disease or poor performance status treatment options include TURBT alone, or chemotherapy alone, or radiotherapy alone.

Follow up after primary treatment for T2 and T3 tumors is recommended at 3 months or at completion of 40-50 Gy of radiation therapy with cystoscopy, primary tumor site re-biopsy or TURBT, cytology, and imaging of abdomen/pelvis.

If no tumor is found on evaluation, then the patients may be closely observed. If radiation therapy was offered initially, it may be continued up to 65 Gy. In addition, chemotherapy may be offered to these patients to sustain remission (category 2B recommendation).

If the tumor does not respond to primary therapy, the preferred management is to perform a cystectomy if the tumor is resectable. If the patient is not a candidate for surgery or the tumor is unresectable, consider administering alternative chemotherapy regimens.

Tumors that are pathologic stage T2 and T3 *with* nodal involvement seen on CT and confirmed by a biopsy, have a high risk (> 50%) for systemic relapse and, therefore, should be managed in a similar manner as for T4 nodal disease (see below).

### **T4 Disease**

For patients who show no nodal disease on abdominal/pelvic CT scans or biopsy, the primary treatment recommendation includes 2 to 3 courses of chemotherapy with or without radiotherapy followed by evaluation with TURBT, cystoscopy, and CT scan of abdomen and pelvis. In highly selected T4a node-negative patients, cystectomy with or without chemotherapy is another primary treatment option. If tumor responds well to the primary chemotherapy, one may consider consolidation chemotherapy regimen with or without radiation.



Alternatively, cystectomy may also be considered as subsequent management option for these patients. However, upon evaluation after primary therapy, if no response is noted, a new chemotherapy regimen with or without radiation can be used. Cystectomy, if feasible, is again an option for both patients that respond and those that do not respond to primary therapy.

For patients with positive nodes, documented on imaging, a biopsy is considered if possible to confirm nodal spread. Patients with positive nodes should receive chemotherapy with or without radiation and evaluated with cystoscopy, TURBT, and abdomen/pelvis imaging. If no residual tumor is detected, patients may be observed. Other options include a radiation boost or a cystectomy. If cancer is still present following primary therapy, patients should follow the pathway for metastatic disease.

Chemotherapy options are discussed under “Metastatic Disease,” whereas combined modality approaches using chemotherapy and radiotherapy are discussed in sections below. For patients who cannot tolerate multidrug combinations with radiotherapy, an alternative is to use radiotherapy with a radiation sensitizer, such as cisplatin alone; or cisplatin or mitomycin C in combination with 5-FU. Patients are initially treated with 40-45 Gy of radiation to whole bladder with or without pelvic lymph nodes, with a boost to a total dose of 64-66 Gy to sites of disease within the bladder excluding the normal areas.

### ***Metastatic Disease***

About half of all patients relapse after cystectomy depending on the pathological stage of the tumor and nodal status. Local recurrences account for about 10-30% of relapses, whereas distant metastases are more common. If invasive local recurrence or persistent disease is evident following primary treatment in patients with preserved bladder,

several options are available: cystectomy, chemotherapy, radiation (if not previously irradiated), or palliative TURBT. Patients with small recurrent tumors (Tis, Ta, or T1) may either undergo cystectomy directly or choose to receive intravesical BCG first. Patients who present with unresectable metastatic disease or who subsequently develop disseminated metastatic disease are generally treated with systemic chemotherapy. Patients who cannot tolerate chemotherapy may receive radiation. In some cases, the tumor may recur as an upper tract tumor or urethral carcinoma of the prostate. These should follow the respective pathway following confirmation by retrograde selective washings or prostatic urethral biopsy.

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 (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.

Currently 3 drug types are active in the management of advanced bladder cancer: cisplatin, the taxanes, and gemcitabine. Combinations of 2 or 3 of these agents have shown clinical benefit (Table 2). A commonly used combination is gemcitabine and cisplatin (GC)<sup>30</sup> or a multidrug cisplatin-based regimen, such as MVAC.<sup>31</sup> Although both are Category 1 recommendations, cisplatin and gemcitabine is considered the standard first-line choice for most patients and preferred over MVAC. This recommendation is based on a direct comparison to



MVAC in a large randomized trial,<sup>32</sup> which showed that although GC was not inferior to MVAC in terms of survival. GC has demonstrated similar activity and somewhat less toxicity when compared to MVAC.<sup>33</sup>

The performance status of the patient is a major determinant of which regimen is used, and regimens with lower toxicity profiles are recommended in patients with compromised liver or renal status or serious comorbid conditions. In patients with glomerular filtration rate (GFR) < 60 mL/min, carboplatin may be substituted for cisplatin in the above mentioned regimen. However, data are limited regarding the therapeutic equivalence of such carboplatin regimen.

More recently, the 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. The alternative regimens, including cisplatin/paclitaxel, gemcitabine/paclitaxel,<sup>34</sup> cisplatin/gemcitabine/paclitaxel,<sup>35</sup> or carboplatin/gemcitabine/paclitaxel,<sup>36</sup> and cisplatin/gemcitabine/docetaxel, have also shown modest activity in bladder cancer in phase I-II trials. However the data are too preliminary to recommend these regimen as first-line options outside the setting of a clinical trial.

The regimens effective for urothelial carcinoma (transitional cell) histologies have limited efficacy for patients with nonurothelial (nontransitional cell) carcinomas. These individuals are often treated based on the identified histology (e.g., adenocarcinomas are managed surgically with radical or segmental cystectomy and individualizing the adjuvant chemotherapy and radiotherapy for maximum benefit; and for pure squamous cell tumors cystectomy, radiation therapy, or other agents commonly used with squamous cell carcinoma of other sites

such as 5-fluorouracil or taxanes are used. However, overall experience with chemotherapy in nonurothelial carcinomas (nontransitional cell tumors) is limited.

Independent of the specific regimen used, patients with metastatic disease are reevaluated after 2 to 3 cycles of chemotherapy, and treatment is continued for 2 more cycles in patients whose disease responds or remains stable. Surgery or radiotherapy may be considered in patients who show a major partial response in an unresectable primary tumor or 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. Patients for whom surgery or radiotherapy are not considered options are generally treated with chemotherapy for a maximum of 6 cycles, depending on their 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 administered. The same applies to patients who experience systemic relapse after adjuvant chemotherapy.

Second-line chemotherapy data are highly variable and unclear in this setting therefore no standard therapy exists. The NCCN Bladder Cancer panel members highly recommend enrollment in a clinical trial. The available options for palliative chemotherapy based on what was offered as first line include: bleomycin, 5-fluorouracil, cisplatin, carboplatin, docetaxel, doxorubicin, gemcitabine, ifosfamide, paclitaxel, pemetrexed, methotrexate, and vinblastine all of which have shown modest benefit in small phase II trials.<sup>36-44</sup>

***Surgical Approaches***

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

***Radical Cystectomy***

Unfortunately, the accuracy of the staging cystoscopy and TURBT is modest, with under-staging encountered frequently. 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, is associated with better survival, and lower pelvic recurrence rate. There are some patient factors which may preclude a PLND such as severe scarring secondary to previous treatments or surgery, advanced age, or severe comorbidities.

Follow-up after a cystectomy should include urine cytology, liver function tests, creatinine, electrolytes, every 3 to 6 months for 2 years and then as clinically indicated. Chest, abdomen, and pelvis imaging every 3-12 months for 2 years based on the risk of recurrence and then as clinically indicated. Patients should be monitored annually for vitamin B<sub>12</sub> deficiency if a continent diversion was created. Urethral wash cytology every 6 to 12 months is advised; particularly if Tis was found within the bladder or prostatic urethra.

***Partial (Segmental) Cystectomy***

In fewer than approximately 5% of cases, an initial invasive tumor develops in an area of the bladder where an adequate margin of soft tissue and a minimum of 2 cm of noninvolved urothelium can be removed along with the tumor without compromising continence or significantly reducing bladder capacity. Partial cystectomy is most frequently recommended for lesions that develop on the dome of the bladder and have no associated Tis in other areas of the urothelium. Relative contraindications to this procedure are lesions that occur in the trigone or bladder neck. The requirement for a ureteral reimplantation, however, is not an absolute contraindication.

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

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 at 3-month intervals. A local recurrence within the preserved bladder should be evaluated as a new cancer. Patients with Tis, Ta, or T1 recurrences may be considered for intravesical treatment. Those with an invasive recurrence should undergo cystectomy or, if they are not surgical candidates, radiotherapy (if no prior radiotherapy was given), chemotherapy, or both should be considered. Palliative TURBT is also an option.



### **Neoadjuvant Chemotherapy**

Increasing data support the role of neoadjuvant chemotherapy before cystectomy for T2 and T3 lesions.<sup>28, 29, 45</sup> Two randomized trials show a survival benefit with neoadjuvant chemotherapy, particularly in patients with clinical T3 disease (palpable mass during examination under anesthesia or unequivocal mass on CT).<sup>28, 29</sup> After 3 cycles of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC), the study by Grossman et al showed no apparent increase in postoperative morbidity or mortality.<sup>28</sup> In the most recent meta-analysis, a statistically significant decrease in the death rate was seen corresponding to an improvement in overall survival.<sup>46</sup>

The NCCN Bladder Cancer panel members recommend considering cisplatin-based neoadjuvant combination chemotherapy (Category 1 recommendation for T3 lesions and category 2A for T2 lesions). Neoadjuvant chemotherapy is not recommended in patients with ECOG performance status of 2 or greater. In patients with impaired renal function, either carboplatin or taxane based chemotherapy regimens or single agent therapy may be considered.

### **Adjuvant Chemotherapy**

Data conflict regarding the role of adjuvant systemic chemotherapy in invasive bladder cancer because no randomized comparisons of adequate sample size have definitively shown a survival benefit of such therapy.<sup>47</sup> Many trials showing a survival benefit were not randomized, raising the question of selection bias in the analysis of outcomes.

Two trials<sup>48</sup> showed a survival advantage from therapy with cyclophosphamide, doxorubicin, and cisplatin (CAP) study and with MVAC or methotrexate, vinblastine, epirubicin, and cisplatin (MVEC).<sup>49</sup> However, methodologic issues have raised questions as to the applicability of these studies to all patients with urothelial tumors. In the

MVEC trial, patients who experienced relapse in the control arm did not undergo chemotherapy, which is not typical of more contemporary series.

Nevertheless, the results of currently available trials suggest that adjuvant chemotherapy can delay recurrences, which may justify the administration of chemotherapy in those at a high risk for relapse. A minimum of 3 cycles of a cisplatin-based combination, such as MVAC,<sup>51</sup> or more commonly now gemcitabine, cisplatin (GC)<sup>33, 52</sup> may be used in patients undergoing adjuvant therapy. No data support the use of adjuvant chemotherapy for nonurothelial (nontransitional cell) carcinomas, regardless of stage.

Patients with tumors that are pathologic stage T2 or less and have no nodal involvement or lymphovascular invasion are considered to have lower risk and do not necessarily require adjuvant chemotherapy. Some groups suggest stratifying patients based on the p53 status of the tumor, because tumors with more than 20% of positive cells seem to have a higher risk for systemic relapse. Determining the p53 status of the tumor is still considered an experimental procedure and is not part of routine management.

### **Bladder-Sparing or Bladder-Preserving Options**

Within the categories of T2 and T3a urothelial (transitional cell) carcinomas, selected patients may be considered for bladder-sparing approaches. Options include aggressive endoscopic transurethral resection alone, transurethral resection followed by chemotherapy alone, radiotherapy alone, or a combination of chemotherapy and radiotherapy. No uniform consensus was reached about the applicability of these approaches to the management of T2 tumors.



Bladder-preserving approaches are reasonable alternatives to cystectomy for patients who are medically unfit for surgery and those seeking an alternative. The decision to use a bladder-sparing 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 (e.g., bladder capacity, bladder function, and comorbidities). The antecedent history of bladder cancer should also be considered. Those with hydronephrosis are poor candidates for bladder-sparing procedures. Patients for whom a bladder-sparing approach is considered should undergo as complete a transurethral resection of the tumor as possible, examination under anesthesia, and metastatic workup before therapy is initiated.

With any of the alternatives to cystectomy, a concern exists over the ability to determine with certainty which bladders that appear to be endoscopically free of tumor (T0) based on a clinical assessment that includes a repeat TURBT, are in fact pathologically free of tumor (pT0). Depending on the series, upward of 30% to 40% of bladders believed to be free of disease preoperatively after chemotherapy were found to have residual disease at cystectomy.<sup>53</sup> The frequency of residual disease is lower for patients who present with T2 disease but, nevertheless, must be considered when proposing a bladder-sparing approach. When possible, bladder-sparing options should be chosen in the context of clinical trials. The guidelines indicate that after maximal transurethral resection, observation, chemotherapy alone, radiotherapy alone, or chemotherapy combined with radiotherapy are appropriate treatment options. These approaches have been shown to be beneficial in selected cases. However, only chemotherapy combined with radiotherapy has been formally evaluated in prospective randomized comparisons; the others are still considered investigational.

All bladder-sparing approaches are based on the principle that not all cases require an immediate cystectomy and that the decision to remove the bladder can be deferred until the response to therapy is assessed. When chemotherapy combined with radiotherapy is used, commonly a cystoscopy with bladder biopsy is performed midway through treatment (induction phase). If disease is seen, cystectomy is recommended. For all of the other methods, repeat transurethral resection is performed 2 to 3 months after induction therapy. If persistent disease is observed, a prompt salvage cystectomy is recommended when possible.

Routine follow-up to rule out recurrence after completion of therapy involves cystoscopy or prior tumor site re-biopsy or TURBT. Attention to the bladder as a site of recurrence is only one part of the overall management of patients undergoing bladder preservation, because these individuals remain at risk for recurrence elsewhere in the urothelial tract and distantly. Imaging studies should also be performed as outlined under post-cystectomy follow-up. Continued monitoring of the urothelium with urinary cytologies (with or without mapping biopsy) is a routine part of the management of all cases in which the bladder is preserved. Follow-up intervals are typically every 3-6 months for the first 2 years, then at increasing intervals at the clinician’s discretion.

#### *Transurethral Resection Alone*

Transurethral resection alone may be curative in selected cases in which the lesion is solitary, less than 2 cm in size, and has minimally invaded the muscle. These cases should also have no associated in situ component, palpable mass, or associated hydronephrosis.<sup>54</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. At that point, management would depend on the stage of the lesion documented at relapse.

### *Radiotherapy Alone*

Radiation alone is not considered standard treatment for patients with an invasive bladder tumor. Because the initial complete response and long-term bladder preservation rates are higher with chemotherapy combined with radiotherapy, this is the preferred treatment. Because the results of radiotherapy alone are considered inferior to those of radical surgery, radiotherapy alone is only indicated for those who cannot tolerate a cystectomy or chemotherapy because of medical comorbidities.<sup>55</sup>

### *Chemotherapy Alone*

The use of chemotherapy alone is not considered adequate without additional treatment to the bladder and remains investigational. This view is based on reported series showing that the proportions of complete pathologic response in the bladder using neoadjuvant chemotherapy alone were only 20% to 30%.<sup>28, 29</sup> A higher proportion of bladders can be rendered tumor-free and therefore preserved when chemotherapy is combined with concurrent radiotherapy.

When chemotherapy alone is used, 3 cycles of therapy are generally administered, and a reassessment that includes a cystoscopy and biopsy is advised. This evaluation is performed to exclude progression or a negative response, which would warrant an immediate cystectomy.

Patients who respond to 3 cycles of chemotherapy may be advised to complete an additional 1 to 3 cycles followed by a cystoscopy and biopsy. At that point, management of the bladder is determined. In

general, if residual disease is documented after 3 cycles of chemotherapy, a cystectomy should be performed. Even when no disease is documented (T0), the possibility of occult residual disease in the bladder must be factored into the therapeutic recommendations.

### *Combined Modality Strategies*

Recent organ-preservation strategies combine TURBT, chemotherapy and radiation to maximally achieve local tumour control.

### *Chemotherapy Followed by Partial Cystectomy:*

Less than 5% of invasive tumors present initially in a location and pattern that is amenable to curative resection with partial cystectomy.<sup>56</sup> In one series, 27% of tumors that were originally believed to require radical cystectomy for control could be removed with partial cystectomy after MVAC chemotherapy. This approach is currently not widely used. This procedure has the advantages of surgically removing the diseased portion of the bladder and allowing for definitive lymph node staging. Follow-up is the same as partial cystectomy.

### *Chemotherapy and Radiotherapy*

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. The 2 main approaches that have been examined are 1) concurrent chemotherapy with radiotherapy, and 2) neoadjuvant and concurrent chemotherapy with radiotherapy.

Radiation Therapy Oncology Group protocol 89-03 compared 2 cycles of neoadjuvant MCV (methotrexate, cisplatin, and vinblastine) induction chemotherapy, followed by concurrent cisplatin and radiotherapy, with concurrent cisplatin and radiotherapy alone.<sup>57</sup> No difference in complete clinical response and 5-year overall survival was observed between the



treatment arms. This study was not adequately powered to assess the survival benefit of neoadjuvant chemotherapy before administering concurrent chemotherapy with radiation therapy. Thus, there are no clear data to suggest a significant benefit for neoadjuvant chemotherapy before bladder preserving chemotherapy with radiation therapy.

Concurrent cisplatin plus radiotherapy is the most common and well-studied chemoradiation method used to treat muscle-invasive bladder cancer. After a complete TURBT, 40 Gy of external beam radiotherapy is administered, typically with a 4-field technique. Two doses of concurrent cisplatin are given on weeks 1 and 4. After this induction phase, an endoscopic reevaluation is performed. If residual disease is noted, a cystectomy is advised. If no disease is visible and the cytology and biopsy are negative (T0), an additional 25 Gy of external-beam radiotherapy is administered along with one additional dose of cisplatin. The patient is then followed up with serial urine cytologies and cystoscopies as outlined previously.

In prospective, single-, and multi-institution series, upward of 70% of patients who completed this regimen were rendered tumor-free in the bladder at the initial post-treatment cystoscopy examination. However, during follow-up, approximately one fourth of these individuals developed a new lesion requiring additional therapy. These patients must also be monitored for possible systemic relapses, as described previously.

An older experience using 5-fluorouracil (5-FU) with radiotherapy showed activity for this combination.<sup>33, 59, 60</sup> More recently, the concomitant use of cisplatin, 5-FU, and radiotherapy has been studied and the results have improved.<sup>61-63</sup> Also incorporated in some of these trials is the use of twice-daily irradiation. Initial complete response rates

have been more than 85%. Although the results are promising, whether these regimens are better than the simpler concurrent cisplatin plus radiotherapy approach described above is unclear. Including patients in clinical trials using these newer approaches is of paramount importance.

### ***Relapses in the Bladder after Bladder-Sparing Approaches:***

Relapses are treated based on the extent of disease at relapse, with consideration of prior treatment.

Tis, Ta, or T1 tumors are generally managed with intravesical BCG therapy. If no response is noted, a cystectomy is advised. A positive cytology with no evidence of disease in the bladder should prompt selective washings of the upper tracts and an evaluation of the prostatic urethra. If the selective cytologies are positive, patients are managed as described in the sections below.

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 (> 65 Gy) of external-beam radiotherapy and has bulky residual disease. For these patients, palliative chemotherapy is advised, generally with a regimen that is non-cross-resistant to the one previously received. If the patient has not undergone radiotherapy, a course of radiotherapy should be considered. Metastatic disease is managed with palliative chemotherapy using a regimen to which the patient has not been previously exposed.

## **Upper Genitourinary Tract Tumors**

Upper tract tumors, including those that originate in the renal pelvis or in the ureter, are relatively uncommon.



## 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 IVP, CT urography, retrograde pyelogram, ureteroscopy, or MRI urogram, or a combination of techniques. A chest radiograph can help evaluate for possible metastatic disease 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 renal scan or bone scan, may be needed if indicated by the results of these tests or the presence of specific symptoms.

### **Primary Treatment**

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

Well-differentiated tumors, low grade may be managed with a nephroureterectomy with a cuff of bladder, 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 invade the renal parenchyma are managed through nephroureterectomy with a cuff of

bladder and regional lymphadenectomy. In selected patients neoadjuvant chemotherapy may be considered based on extrapolation of data from bladder cancer series.<sup>28, 29, 45</sup> If metastatic disease is documented or associated comorbid conditions are present, treatment should include systemic chemotherapy with regimens similar to those used for urothelial (transitional cell) 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 pathologic stage pT0 or pT1 should be followed up with serial cystoscopies at 3-month intervals for the first year and, if negative, every 6 months thereafter. Such tumors should also be followed up with ureteroscopy and upper tract imaging (such as IVP, retrograde pyelogram, or CT, if available or MRI urogram) at 3- to 12-month intervals if endoscopic resection is considered.

Patients with pathological stage pT2, pT3, pT4, or nodal disease should be considered for adjuvant chemotherapy with or with radiation therapy, as discussed earlier. Serial evaluations of the urothelial tract, along with imaging studies to exclude metastatic disease, should also be performed.

## Ureteral Tumors

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.

**Treatment**

For ureteral tumors that are resectable, the primary management is surgery. The specific procedure required varies depending on the location of the tumor (upper, mid, or distal location) and on disease extent. Neoadjuvant chemotherapy may be considered in selected patients, such as when the degree of invasiveness is established before definitive surgery.<sup>64</sup>

Tumors that originate in the upper ureter occasionally can be managed endoscopically but more commonly are treated with nephroureterectomy with a cuff of bladder plus regional lymphadenectomy for high-grade tumors. 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 and ureteroureterostomy, endoscopic resection, or nephroureterectomy with a cuff of bladder and consideration of regional lymphadenectomy. Larger, high-grade lesions are managed with nephroureterectomy with a cuff of bladder and regional lymphadenectomy. Distal ureteral tumors may be managed with a distal ureterectomy and reimplantation of the ureter (preferred if clinically feasible), endoscopic resection, or in some cases, a nephroureterectomy with a cuff of bladder, with the addition of regional lymphadenectomy recommended for high-grade tumors.

**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”) 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 (Transitional Cell) 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 (transitional cell) carcinomas of bladder origin that invade into the prostate through the bladder wall. Urothelial (transitional cell) carcinomas of the prostate may occur de novo or, more typically, concurrently or after treatment of a bladder cancer. As in the case with tumors originating in other sites of the urothelium, management of prostate urothelial (transitional cell) carcinomas is based on extent of disease with particular reference to the urethra, ductal 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 a TUR biopsy of the prostate that includes the prostatic stroma. Multiple stromal biopsies are also advised and, if the DRE is abnormal, determination of the prostate-specific antigen level and



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 BCG and transurethral resection of the prostate (TURP), with follow-up similar to that for superficial disease of the bladder. 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. Neoadjuvant chemotherapy may be considered in patients with stromal invasion, based on extrapolation of data from bladder cancer therapy.<sup>28, 29, 45</sup> Alternatively, TURP and BCG may be offered to patients with only ductal and acini invasion. Adjuvant chemotherapy may be advised for stromal invasion after primary treatment. Recurrences in patients undergoing TURP and BCG therapy are treated with cystoprostatectomy with or without urethrectomy.

### **Nonurothelial (Nontransitional Cell) 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. Patients with non-urothelial invasive disease are generally treated with cystectomy, although those with certain urachal tumors require complete urachal resection or may be appropriately treated with partial cystectomy. 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 (transitional cell) carcinomas are appropriate with minor variations. These variations are documented in the algorithm.

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

### **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 a different, or at the same location and with a similar or more advanced stage. Continued monitoring for recurrence is an essential part of management because most recurrences are superficial and can be treated endoscopically. Within each category of disease, more refined methods to determine prognosis and guide management, based on molecular staging, are under development with the goal of optimizing each patient's likelihood of cure and chance for organ preservation.

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

Finally, within the category of metastatic disease, several new agents have been identified that seem superior to those currently considered



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standard therapies. Experts believe, therefore, that the treatment of urothelial tumors will evolve rapidly over the next few years, with improved outcomes for patients at all stages of disease.

**Table 1. Principles of Pathology Management: Malignancy Grading of Bladder Carcinoma: Old and New Systems<sup>a,b</sup>**

Modified Bergkvist 1987	WHO 1973	WHO/ISUP 1998 Consensus WHO, 2004
Papilloma grade 0	Papilloma	Papilloma
Papilloma with atypia grade 1	TCC grade 1	Papillary urothelial neoplasm of low malignant potential
Urothelial carcinoma grade 2A	TCC grade 1	Urothelial carcinoma, low-grade
Urothelial carcinoma grade 2B	TCC grade 2	Urothelial carcinoma, low-grade or high-grade
Urothelial carcinoma grade 3	TCC grade 3	Urothelial carcinoma, high-grade

<sup>a</sup>From Droller MJ. Bladder Cancer, Current Diagnosis and Treatment. Totowa (NJ): Humana Press, 2001.

<sup>b</sup>Several classifications have been proposed for grading of tumors of the bladder epithelium. Because they are in general usage, the current NCCN guidelines for bladder and upper tract cancers continue to use the World Health Organization (WHO) histologic classification of tumors of the urinary tract from 1973. However, a revised classification has been adopted by numerous organizations, including the WHO in their most recent publication in 2004. This classification has also been adopted by the College of American Pathologists, the American Society of Clinical Pathology, and the International Society of Urologic Pathologists.

Please note several major changes in this classification. First, the term *transitional cell* is changed to *urothelial*. Also, dysplastic changes of the urothelium without invasion are now classified either as carcinoma in situ or as dysplasia without specification of mild, moderate, or severe. Any dysplastic, flat, non-invasive lesion that does not meet the criteria of CIS is referred to as *dysplasia*.

The criteria used for the new classification system are more specific than those for the 1973 WHO classification system. The entire classification system, including the range of types of tumors, is presented on pages 90–91 of the new WHO classification of tumors.

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**Table 2. Combination Chemotherapy Regimens**

Regimen	Dosage	
<b>Gemcitabine/ Cisplatin</b> <sup>33, 52</sup>	Gemcitabine*	1000 mg/m <sup>2</sup> on days 1, 8, 15 of 28-day cycle
	Cisplatin	70 mg/m <sup>2</sup> on day 2
<b>M-VAC</b> <sup>31, 51</sup>	Methotrexate	30 mg/m <sup>2</sup> on days 1, 15, 22
	Vinblastine	3 mg/m <sup>2</sup> on days 2, 15, 22
	Doxorubicin	30 mg/m <sup>2</sup> on day 2
	Cisplatin	70 mg/m <sup>2</sup> on day 2

\*This dose should not be combined with radiation.

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