National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology™

# Bladder Cancer

## Including Upper Tract Tumors and Urothelial Carcinoma of the Prostate

V.1.2009

Continue

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[NCCN Guidelines Panel Disclosures]

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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

# Summary of the Guidelines updates

**Summary of the changes in the v.1.2009 version of the Bladder Cancer guidelines from the v.2.2008 version include:**

**BL-1:**

- Clinical presentation was changed from "hematuria" to "suspicion of urothelial carcinoma."
- "Cytology" was added under initial evaluation.
- "ECG" was removed as an additional workup for metastatic disease.

**BL-2:**

- "Secondary surgical treatment" is a new heading.
  - cTa, high grade, secondary surgical treatment, "If lymphovascular invasion, or incomplete resection or no muscle in specimen, then reresect" was added.
  - cT1, low and high grade, secondary surgical treatment, "Strongly advise reresection or cystectomy (high grade)" was added.
- Footnote 'd' was modified to include, "The majority of grade 2 tumors are high-grade; some grade 2 tumors may be classified as low-grade by some pathologists ."
- cTa, low grade, adjuvant intravesical treatment, "induction intravesical chemotherapy" was added as an option.
- Footnote f, "See Follow-Up After Cystectomy (BL-E)" is new throughout the guidelines.
- Footnote h, "See Principles of Intravesical Treatment (BL-F)" is new throughout the guidelines.
- Follow-up, consider imaging of upper tract collecting system, "for high-grade tumors" was added for clarification.

**BL-3:**

- Maintenance BCG was changed from a "preferred " treatment to an "optional" treatment.
- For follow-up every 3 mo, "then at increasing intervals" was added.
- Recurrence post-intravesical treatment with BCG or mitomycin, "TURBT" was added as an evaluation.

**BL-4:**

- For primary treatment, radical cystectomy, "consider neoadjuvant *cisplatin-based combination*" chemotherapy and a category 2B designation were added.
- For primary treatment with segmental cystectomy, "consider neoadjuvant cisplatin-based combination chemotherapy" was added.
- For patients with cT2 with selective bladder sparing following maximal TUR or extensive comorbid disease or poor performance status, "at completion of RT or at 3 months" was added to "Evaluate after RT of 40-50 Gy" (Also for BL-5)
- For an unresectable tumor, "or not a surgical candidate" was added (Also for BL-5)

**BL-5:**

- For primary treatment, radical cystectomy, "***strongly*** consider neoadjuvant ***cisplatin-based combination*** chemotherapy" was added.

**BL-6:**

- Metastatic, "additional workup" was added to the page.
- Adjuvant treatment, tumor present, "surgery" was added as an adjuvant treatment option.

**BL-7**

- Muscle invasive, "and selected metastatic disease treated with curative intent" was added.

**BL-A**

- Radical cystectomy, "at a minimum including common, internal, and external iliac nodes, and obturator nodes" was added.

Continued on next page

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## Summary of the Guidelines updates (continued)

**BL-B**
- The two "Principles of Pathology Management" bullets are new to page.
- For urothelial carcinoma grade 2B, TCC grade 2, "or low" was added to "urothelial carcinoma high grade"

**BL-C**
- Pathology, "low grade" and "high grade" were added as appropriate.

**BL-D**
- Mixed histology, first bullet, "Urothelial carcinoma plus pure squamous, glandular adenocarcinoma, micropapillary, nested, plasmacytoid, sarcomatoid should be identified" is new.
- Any small-cell component, second bullet, "Chemotherapy regimens similar to small cell lung cancer. See Small Cell Lung Cancer Guidelines" is new.
- "Urachal carcinoma" and "primary bladder sarcoma" were added as new categories for non-urothelial cell carcinoma of the bladder.

**BL-E**
- "Follow-up After Cystectomy" is new to the guidelines.

**BL-F**
- "Principles of Intravesical Treatment" is new to the guidelines.

**BL-G**
- First line chemotherapy (neoadjuvant, adjuvant and metastatic), the third through sixth bullets are new.
- "First-line chemotherapy, alternative regimens (category 2A)" section is new.
- "Second-line chemotherapy (metastatic)" section is new.
- "Radiosensitizing chemotherapy agent" section is new.

**BL-H**
- "Consider low-dose pre-operative radiation therapy prior to segmental resection for invasive tumors (category 2B)" was added as a new principle of radiation therapy management of invasive disease.

**UTT-1**
- Primary treatment, high grade, "consider neoadjuvant therapy in selected patients" was added as an option.
- Footnote b is new to Upper GU tract Tumors.

**UTT-2**
- Primary treatment, nephroureterectomy with cuff of bladder, "consider neoadjuvant therapy in selected patients" was added to "upper, mid (high grade) and distal."

**UTT-3**:
- Adjuvant treatment, pT2, pT3, pT4, pN+ stage patients, "± radiation therapy" was added.
- Footnote a and footnote c are new to the page.

**UCP-1**
- Stromal invasion, primary treatment, "± neoadjuvant chemotherapy" was added.

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# Bladder Cancer

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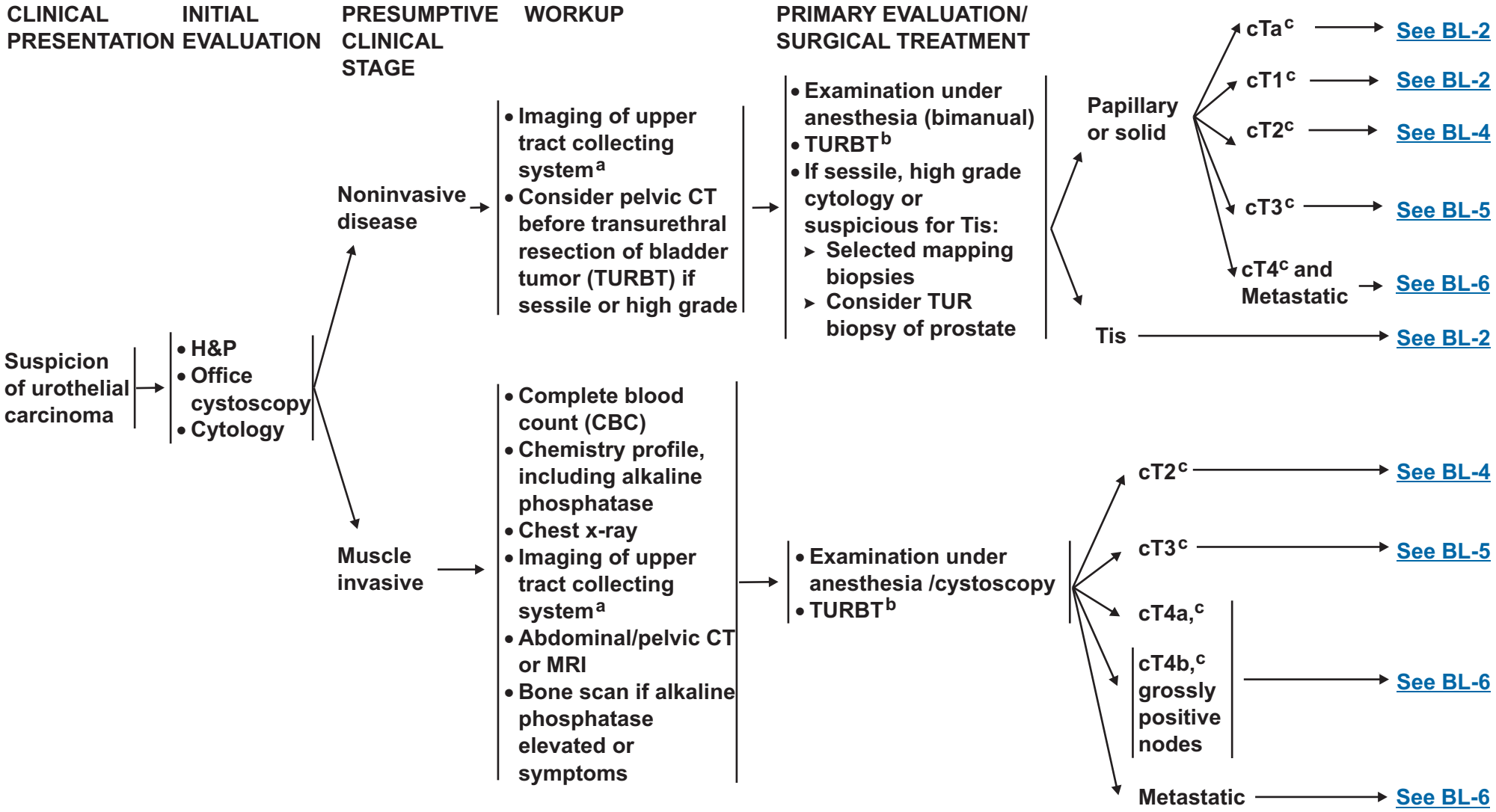


[a] Imaging may include IVP, CT urography, renal ultrasound with retrograde pyelogram, or MRI urogram.

[b] See Principles of Surgical Management (BL-A).

[c] 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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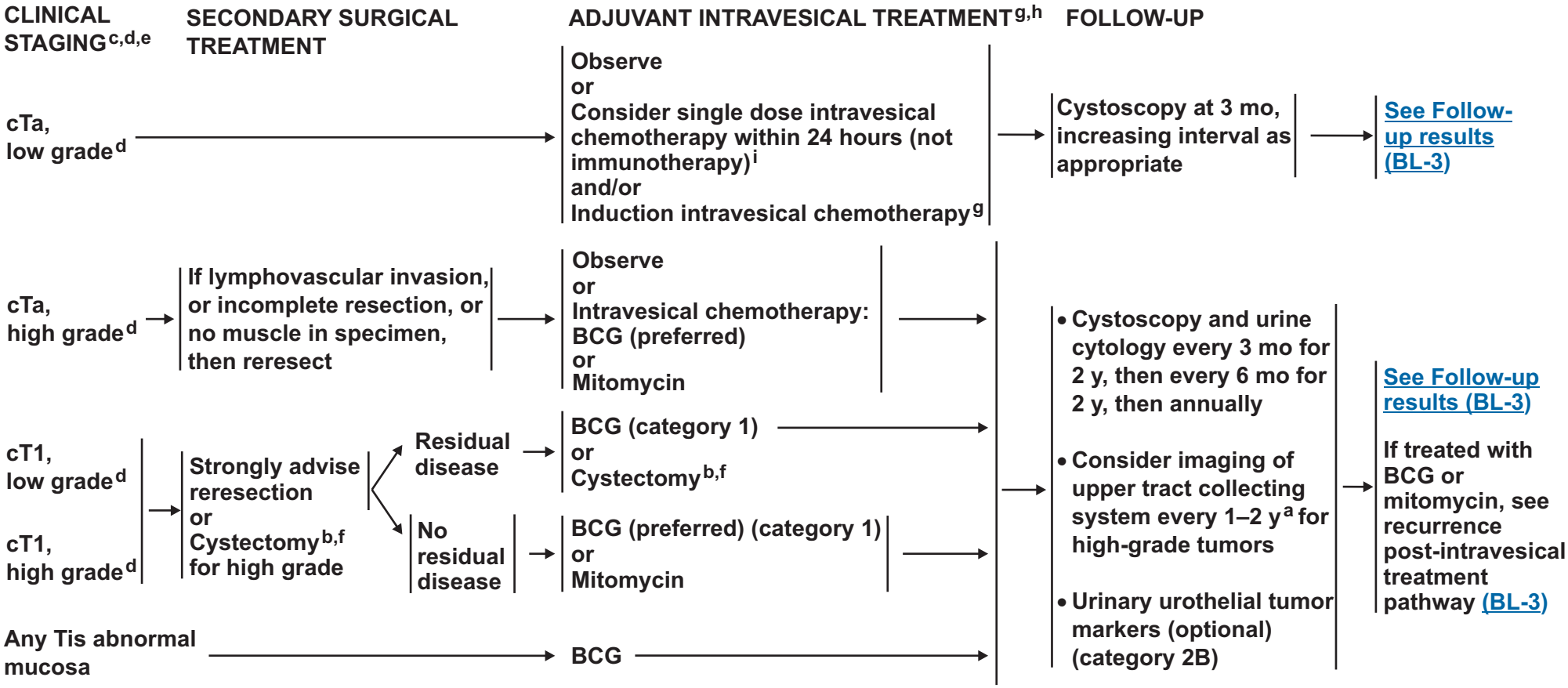


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[d] Grading of these protocols refers to the World Health Organization International Histological Classification of Tumours, Edition 1, published 1973. The majority of grade 2 tumors are high-grade; some grade 2 tumors may be classified as low-grade by some pathologists. See Principles of Pathology Management (BL-B) and manuscript (MS-3).

[e] See Probability of Recurrence and Progression (BL-C) and Non-Urothelial Cell Carcinoma of the Bladder (BL-D).

[f] See Follow-Up After Cystectomy (BL-E).

[g] Indications for adjuvant therapy: Based on probability of recurrence and progression to muscle invasive disease: (1) size; (2) number; (3) grade.

[h] See Principles of Intravesical Treatment (BL-F).

[i] Immediate intravesical chemotherapy, not immunotherapy, may decrease recurrence.

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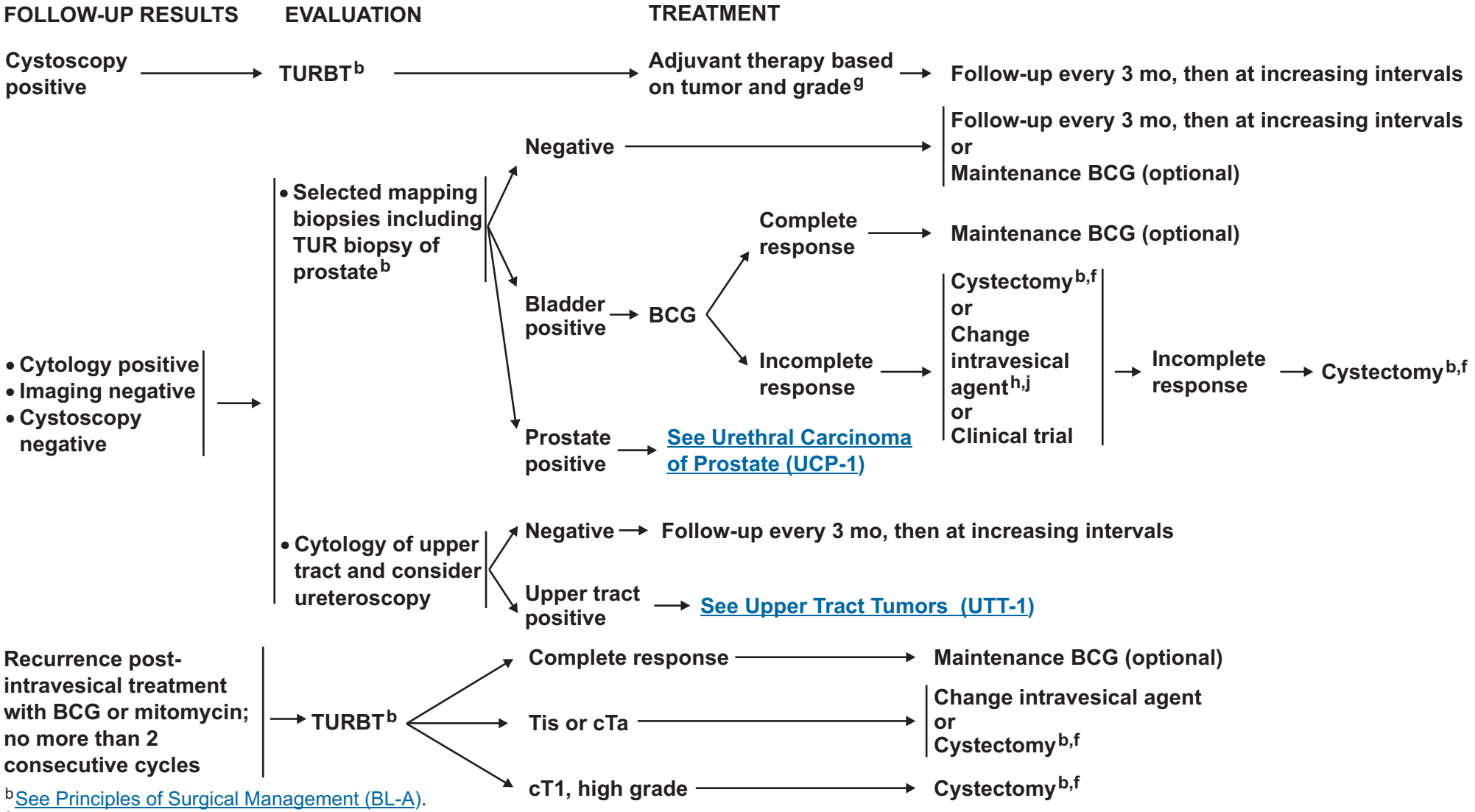
## POSTTREATMENT cTa, cT1, Tis RECURRENT OR PERSISTENT DISEASE




[b] See Principles of Surgical Management (BL-A).
[f] See Follow-Up After Cystectomy (BL-E).
[g] Indications for adjuvant therapy: Based on probability of recurrence and progression to muscle invasive disease: (1) size; (2) number; (3) grade.
[h] See Principles of Intravesical Treatment (BL-F).
[j] BCG + interferon has been reported to be effective, but data from phase III randomized trials is not yet available.

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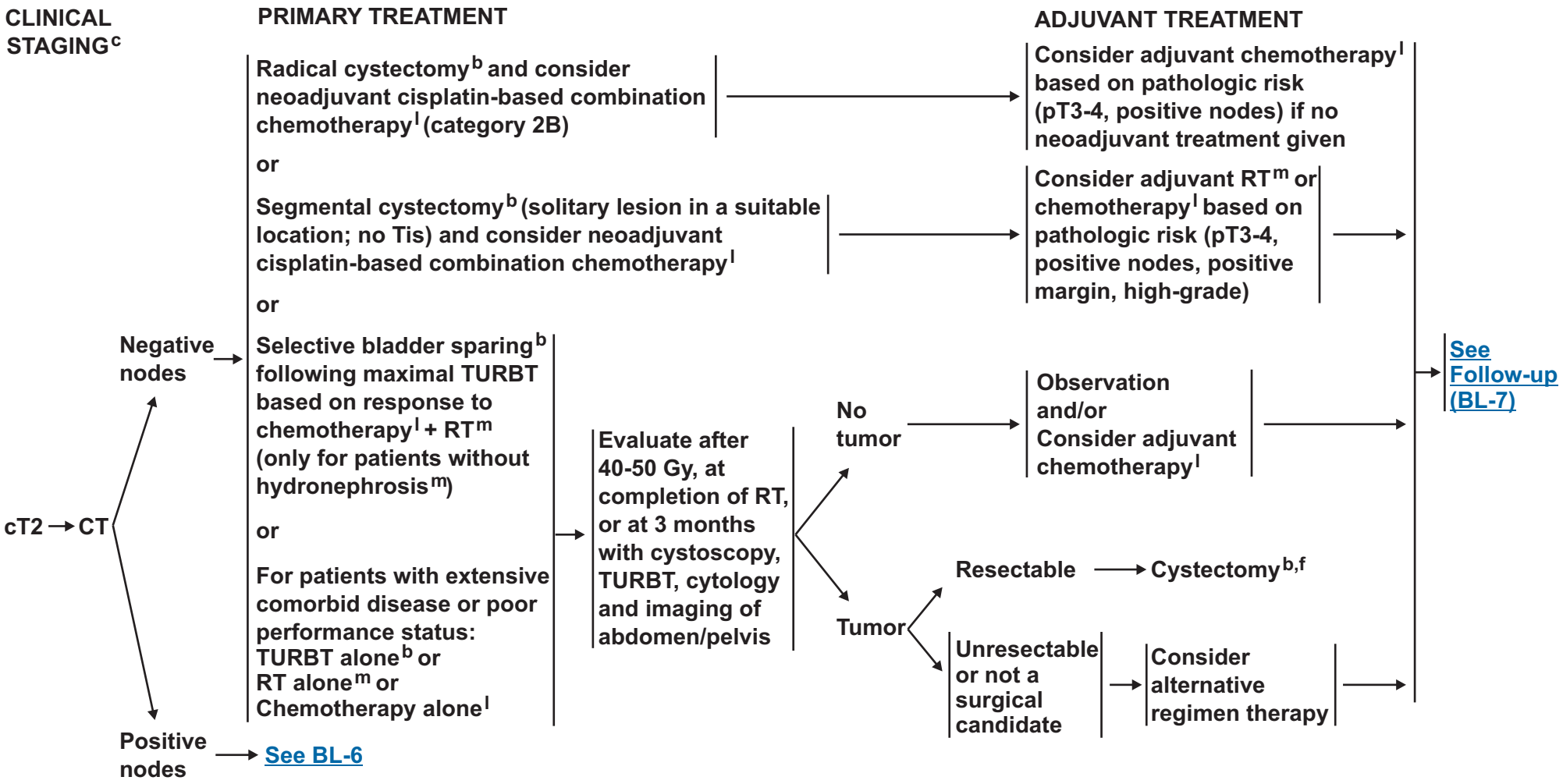


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[f] See Follow-Up After Cystectomy (BL-E).

[k] 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.

[l] See Principles of Chemotherapy Management (BL-G).

[m] See Principles of Radiation Management of Invasive Disease (BL-H).

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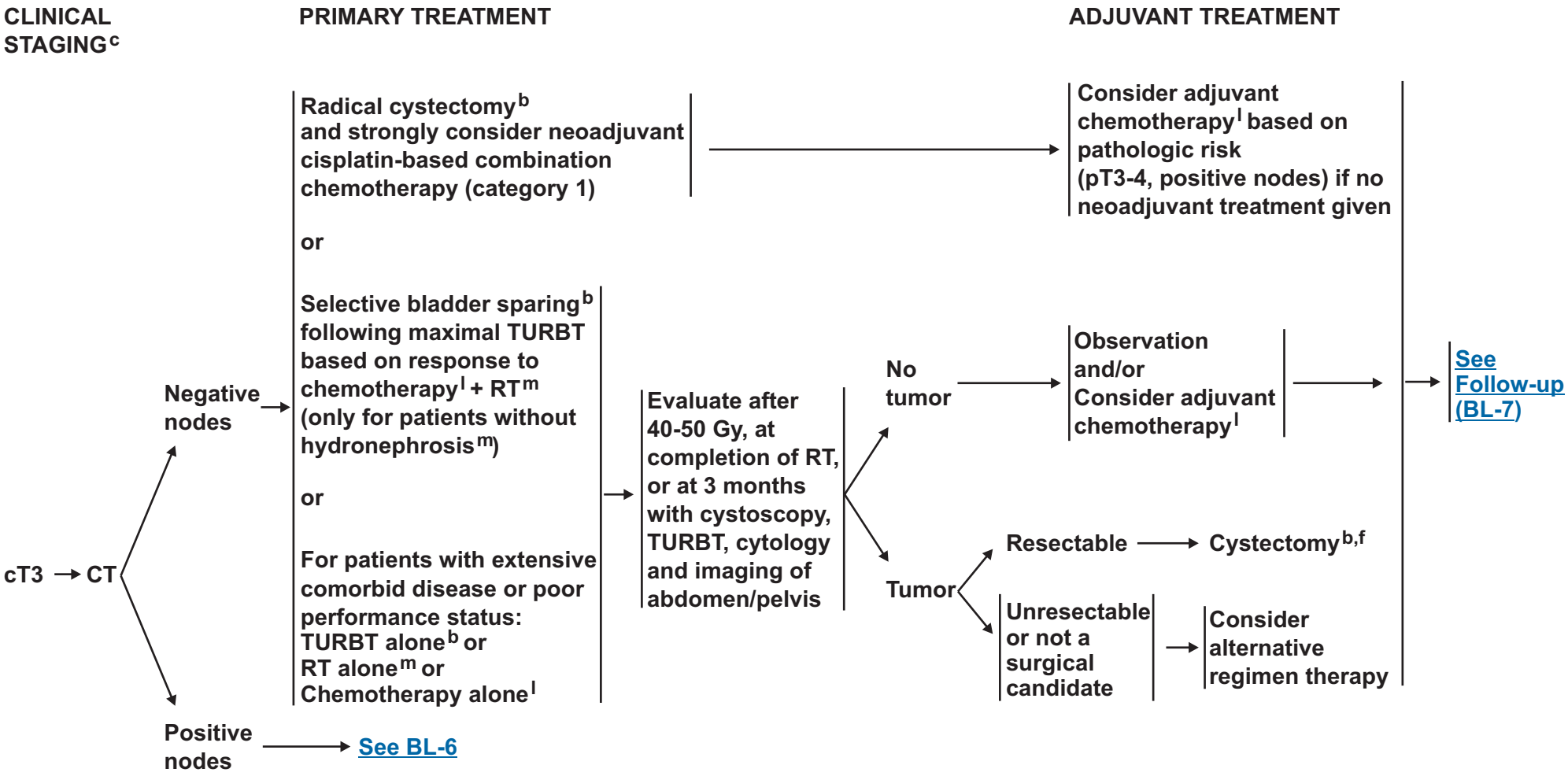


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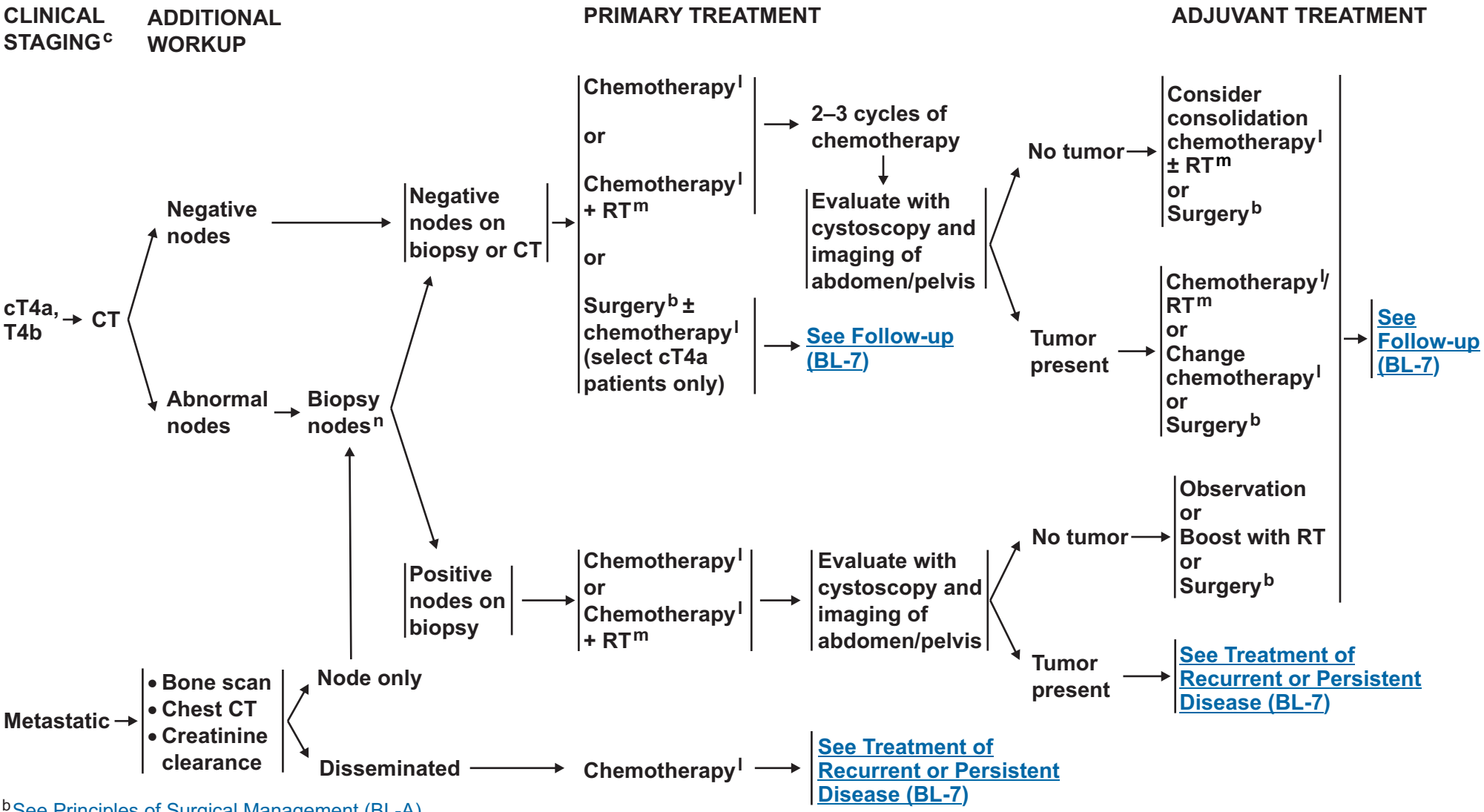


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[l] See Principles of Chemotherapy Management (BL-G).

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[n] If technically possible.

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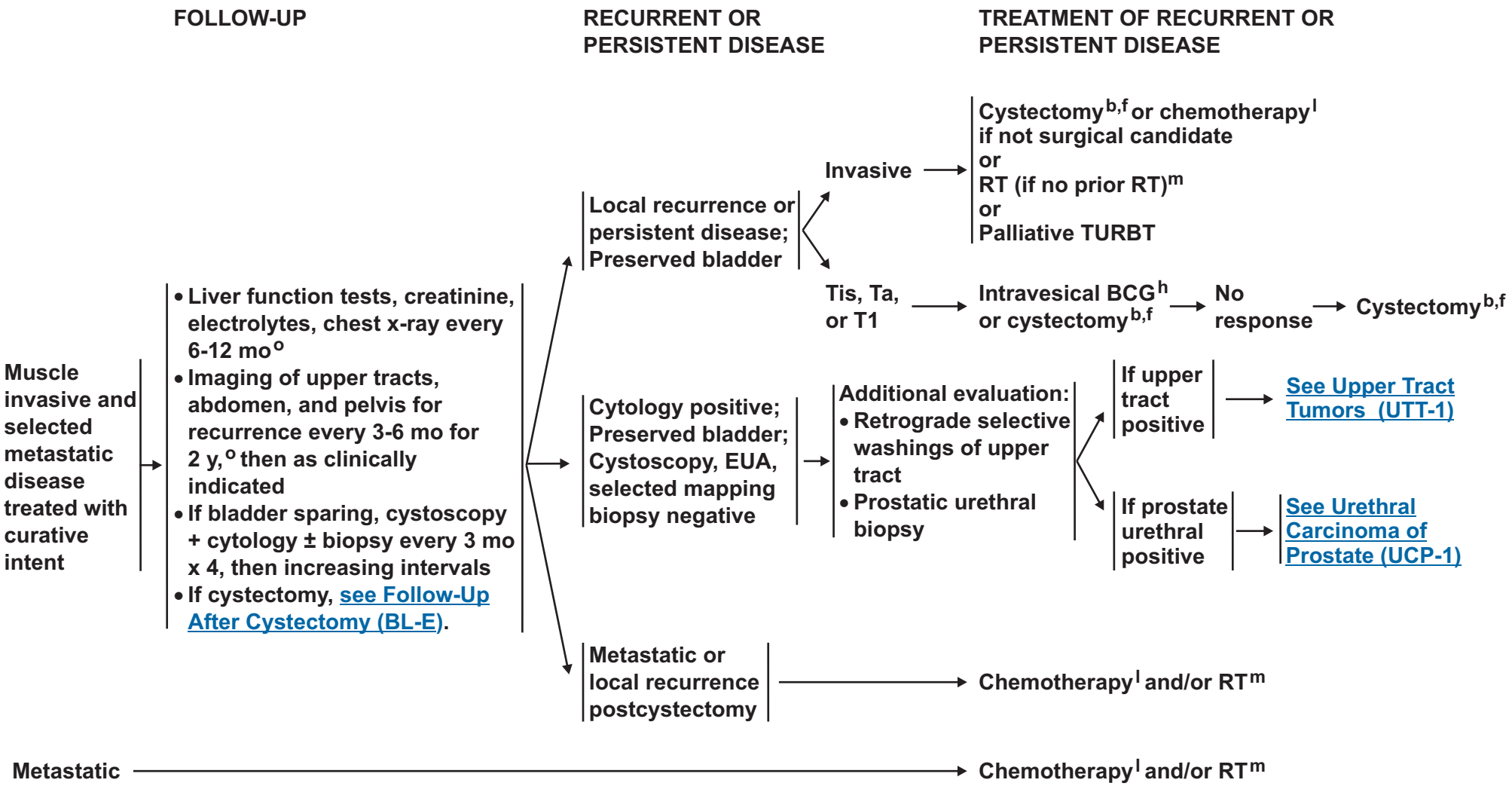


[b] See Principles of Surgical Management (BL-A).
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[h] See Principles of Intravesical Treatment (BL-F).
[l] See Principles of Chemotherapy Management (BL-G).
[m] See Principles of Radiation Management of Invasive Disease (BL-H).
[o] Depending on risk 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 biopsies

**TURBT: Invasive**

Repeat reresection:
- 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***

| 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 |

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

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## PROBABILITY OF RECURRENCE AND PROGRESSION

| Pathology | Probability of Recurrence in 5 years | Probability of Progression to Muscle Invasion |
|---|---|---|
| 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, glandular adenocarcinoma, micropapillary, nested, plasmacytoid, sarcomatoid should be identified.
- Follow Urothelial Carcinoma of the Bladder (BL-1) with complete response less likely if bladder sparing considered

**Pure Squamous:**
- Cystectomy or RT

**Adenocarcinoma:**
- MVAC (methotrexate, vinblastine, doxorubicin and cisplatin) ineffective
- Cystectomy or partial cystectomy
- Consider 5-FU-based therapy

**Any Small-cell component:**
- Neoadjuvant or adjuvant chemotherapy using small-cell regimens and local treatment (cystectomy or radiotherapy)
- Chemotherapy regimens similar to small cell lung cancer. See NCCN Small Cell Lung Cancer Guidelines

**Urachal Carcinoma:**
- Treatment as per NCCN Colon Cancer Guidelines
- Requires complete urachal resection

**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
- Chest x-ray, and imaging of the abdomen and pelvis every 3 to 6 months for 2 years 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
- Postoperative CT scan to define the revised anatomy of the pelvis, then every 3 to 6 months for 2 years if the risk for recurrence is high, and then every 12 months

**After a partial cystectomy**

- Same follow-up as above, in addition to the following:
  - ➤ Serial cytologic examinations and cystoscopies at 3-month intervals to monitoring for relapse in the bladder

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## PRINCIPLES OF INTRAVESICAL TREATMENT

**Indications: Based on probability of recurrence and progression to muscle invasive disease: (1) size; (2) number; (3) grade.**

**Immediate Intravesical Therapy**
- **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 loca,l 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$^2$ on days 1 and 2 or days 1 and 8). 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 ≥ 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 patients receiving 3 cycles prior to cystectomy but not radiotherapy, in randomized trials and meta-analyses performed.

**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. Options include single agent therapy with a taxane (paclitaxel, docetaxel) or pemetrexed in patients not previously treated with a taxane. Participation in clinical trials of new agents is recommended.

**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 trials

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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.
- 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 40-55 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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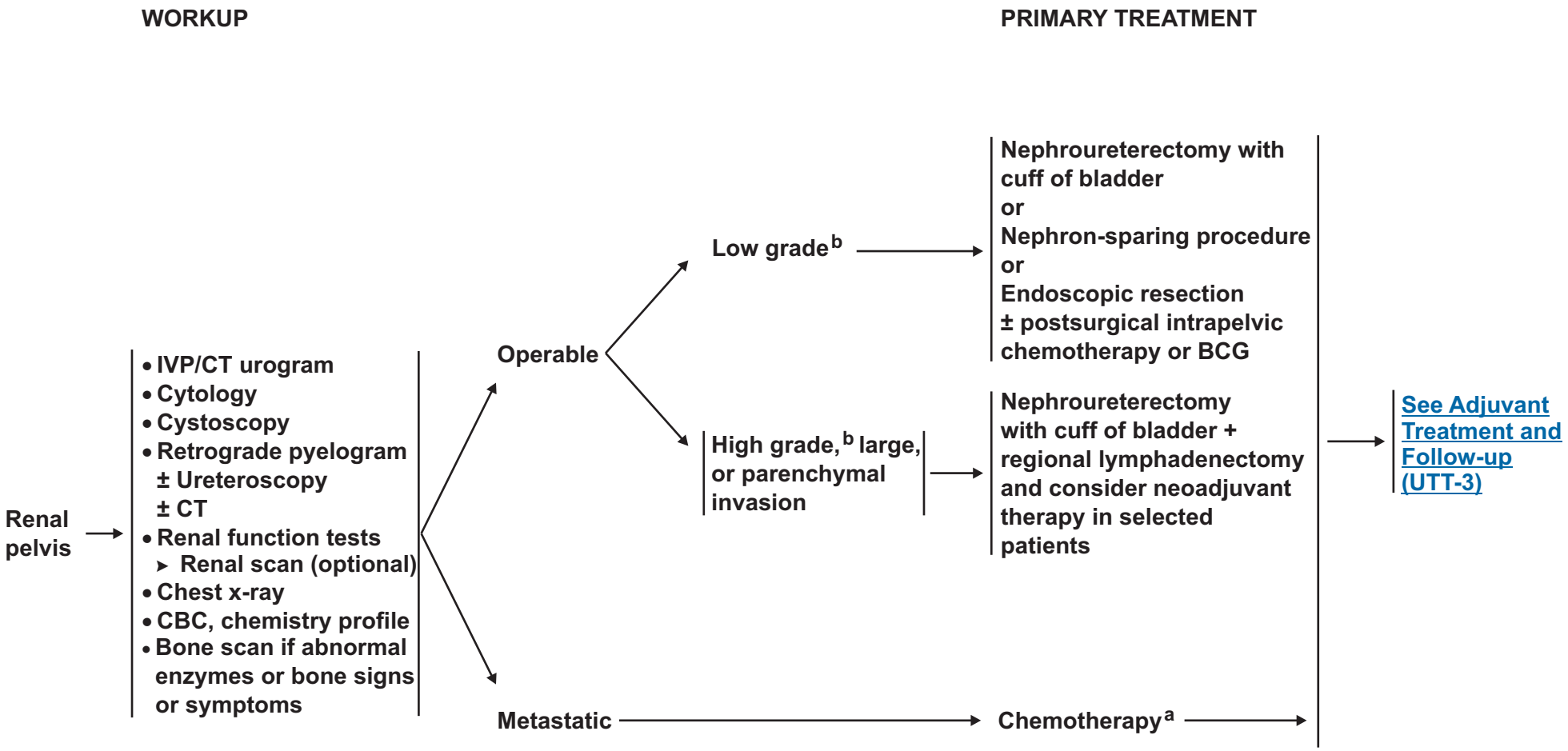
# Upper GU Tract Tumors






[a] See Principles of Chemotherapy Management (BL-G).

[b] Grading of these protocols refers to the World Health Organization International Histological Classification of Tumours, Edition 1, published 1973. The majority of grade 2 tumors are high-grade; some grade 2 tumors may be classified by some pathologists as low-grade. See Principles of Pathology Management (BL-B) and manuscript (MS-3).

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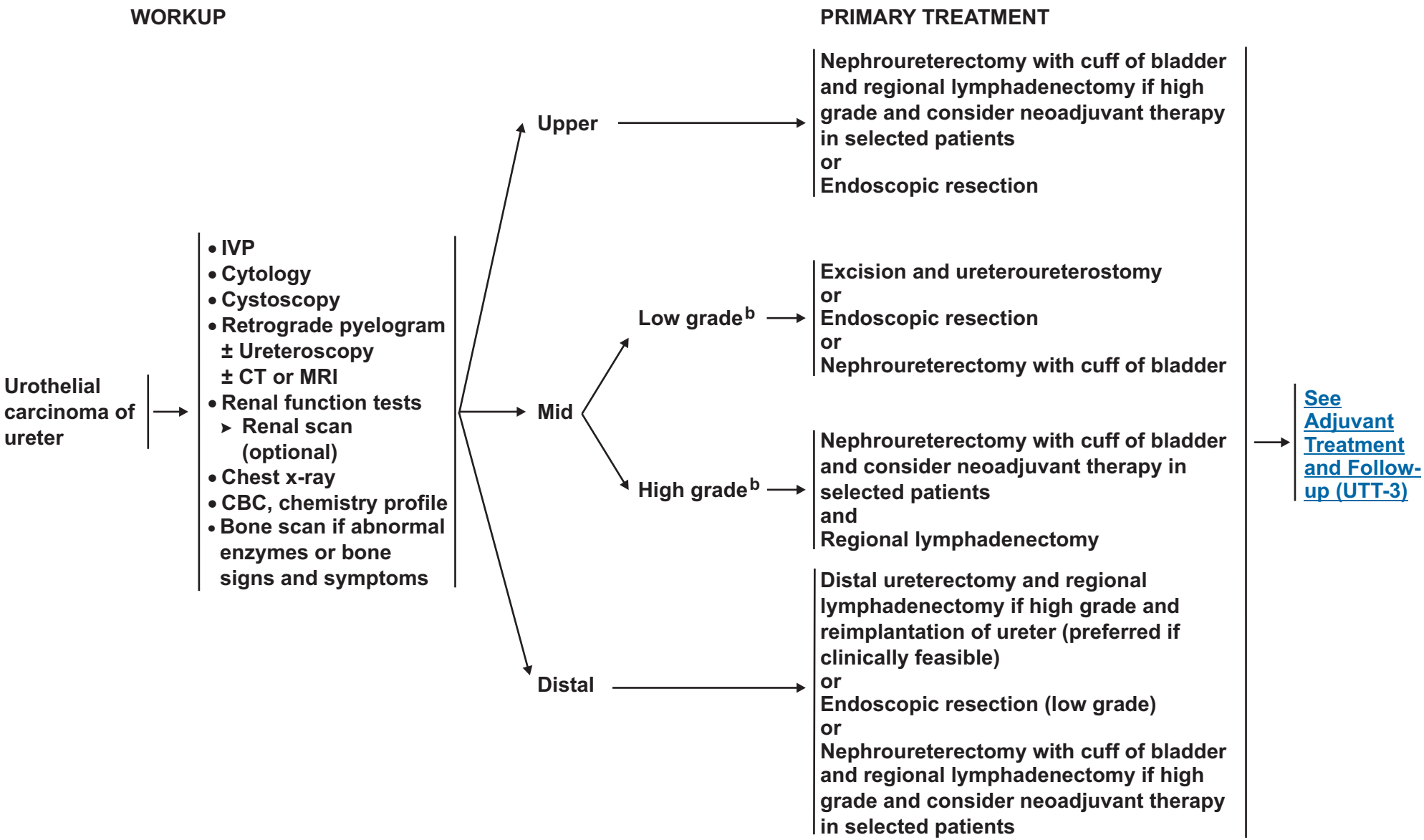


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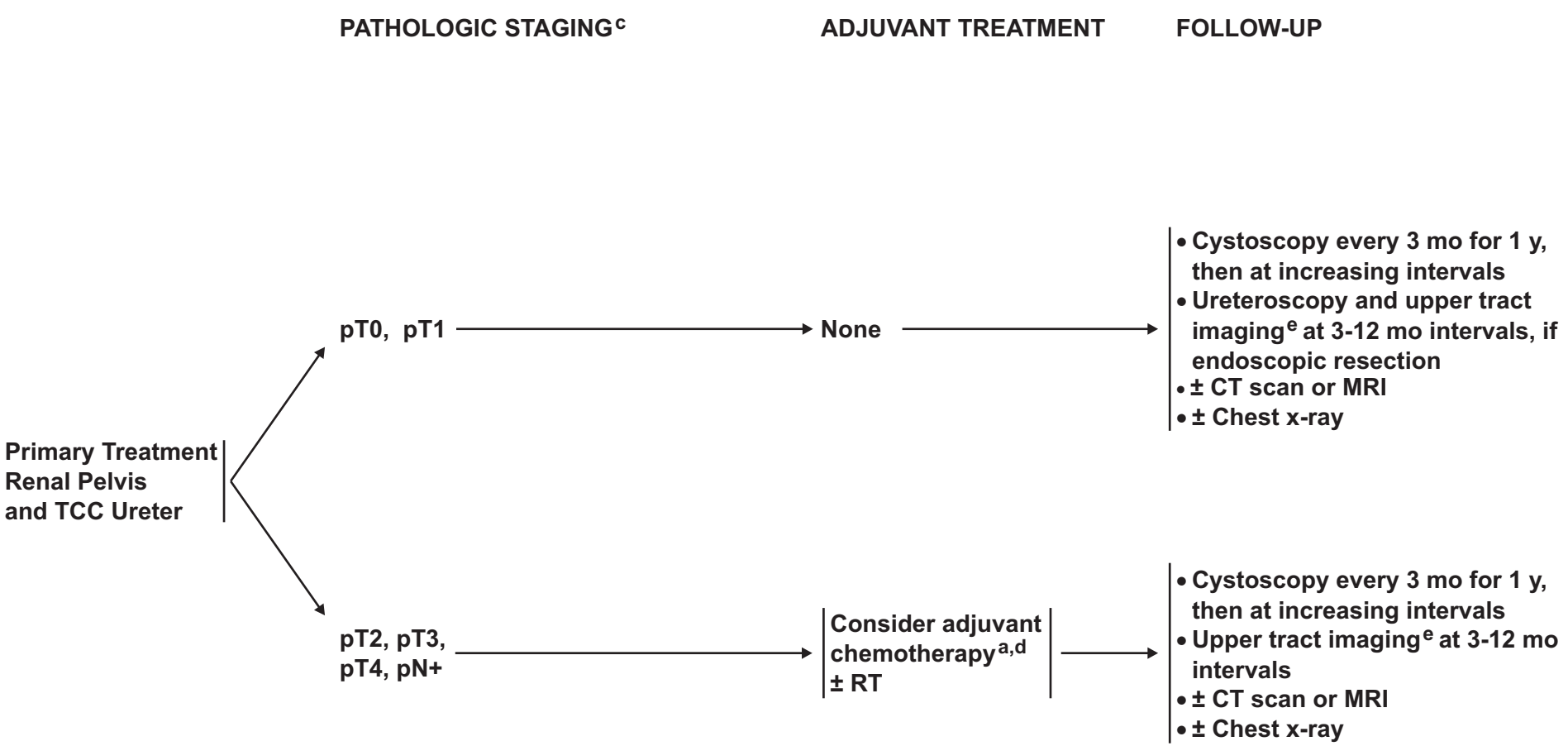


[a] See Principles of Chemotherapy Management (BL-G).
[c] The modifier "p" refers to pathologic staging based on cystectomy and lymph node dissection.
[d] Follow recommendations for adjuvant chemotherapy after ensuring that patient is fully staged to rule out metastatic disease.
[e] Imaging may include IVP, CT urography (if available), retrograde pyelogram, or MRI urogram.

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# Urothelial Carcinoma of the Prostate

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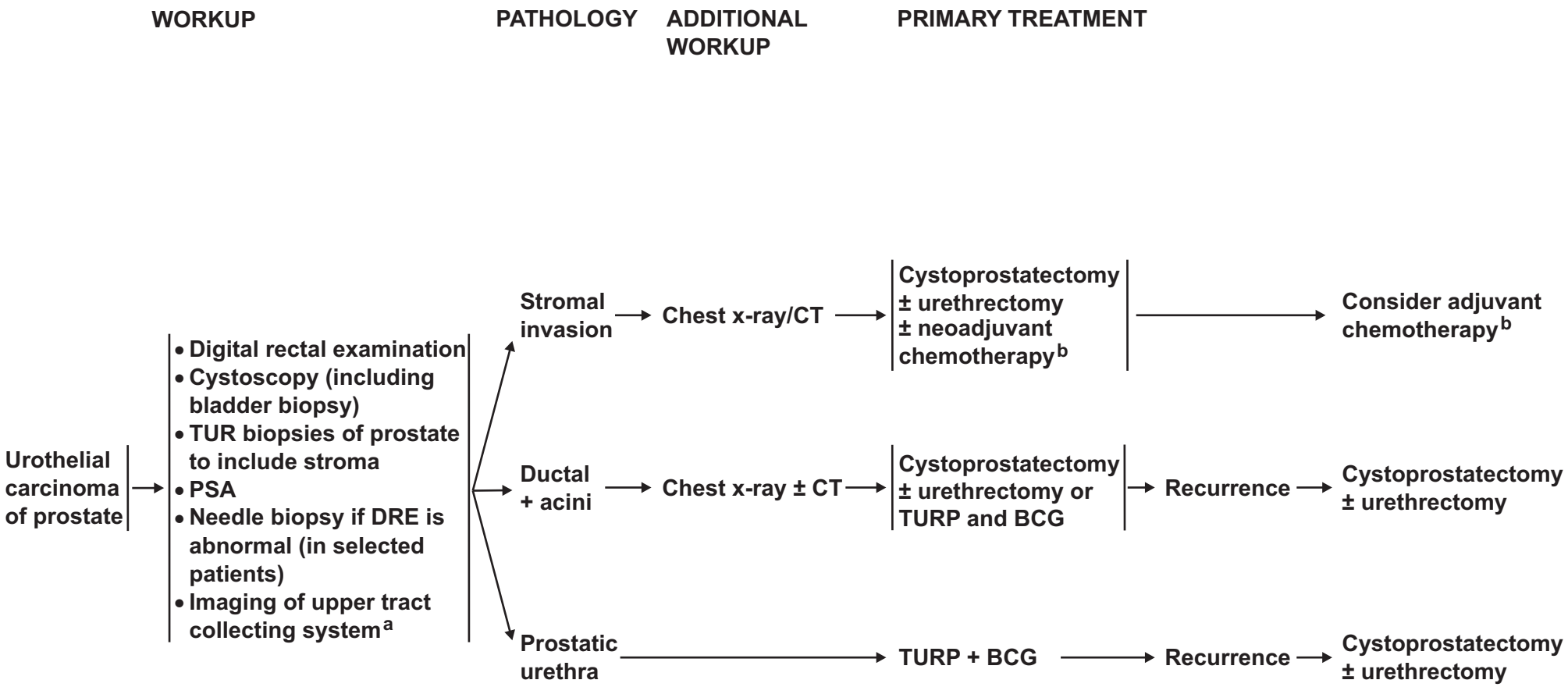
Staging, Discussion, References




[a] Imaging may include IVP, CT urography, renal ultrasound with retrograde pyelogram, or MRI urogram.

[b] 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.**

# Staging

***Table 1***
**American Joint Committee on Cancer (AJCC)**
**TNM Staging System For Bladder Cancer**

**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 muscle
- **T2a** Tumor invades superficial muscle (inner half)
- **T2b** Tumor invades deep muscle (outer half)

**T3** Tumor invades perivesical tissue
- **T3a** Microscopically
- **T3b** Macroscopically (extravesical mass)

**T4** Tumor invades any of the following: prostate, uterus, vagina, pelvic wall, abdominal wall
- **T4a** Tumor invades prostate, uterus, vagina
- **T4b** Tumor invades pelvic wall, abdominal wall

**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 T3a, T3b, and T4b disease, respectively. Appropriate imaging techniques for lymph node evaluation should be used. 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. Laterality does not affect the N classification.

**Regional Lymph Nodes (N)**
Regional lymph nodes are those within the true pelvis; all others are distant lymph nodes.
**NX** Regional lymph nodes cannot be assessed
**N0** No regional lymph node metastasis
**N1** Metastasis in a single lymph node, 2 cm or less in greatest dimension
**N2** Metastasis in a single lymph node, more than 2 cm but not more than 5 cm in greatest dimension; or multiple lymph nodes, none more than 5 cm in greatest dimension
**N3** Metastasis in a lymph node more than 5 cm in greatest dimension

**Distant Metastasis (M)**
**MX** Distant metastasis cannot be assessed
**M0** No distant metastasis
**M1** Distant metastasis

**Stage Grouping**

| | | | |
|---|---|---|---|
| **Stage 0a** | Ta | N0 | M0 |
| **Stage 0is** | Tis | N0 | M0 |
| **Stage I** | T1 | N0 | M0 |
| **Stage II** | T2a | N0 | M0 |
| | T2b | N0 | M0 |
| **Stage III** | T3a | N0 | M0 |
| | T3b | N0 | M0 |
| | T4a | N0 | M0 |
| **Stage IV** | T4b | N0 | M0 |
| | Any T | N1 | M0 |
| | Any T | N2 | M0 |
| | Any T | N3 | M0 |
| | Any T | Any N | M1 |

**Histopathologic Type**
The histologic types are the following:
**Urothelial (transitional cell) carcinoma**
**In situ**
- Papillary
- Flat
- With squamous metaplasia
- With glandular metaplasia
- With squamous and glandular metaplasia

**Squamous cell carcinoma**
**Adenocarcinoma**
**Undifferentiated carcinoma**
The predominant cancer is urothelial (transitional cell) carcinoma.

**Histopathologic Grade (G)**
**GX** Grade cannot be assessed
**G1** Well differentiated
**G2** Moderately differentiated
**G3-4** Poorly differentiated or undifferentiated

# 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 68,810 new cases of urinary bladder cancer will be diagnosed in the United States (51,230 men and 17,580 women) in 2008.[1] Bladder cancer the fourth most common cancer in men and is three times more common in men than in women in the United States During that same period, approximately 14,100 deaths (9,950 men and 4150 women) from bladder cancer are anticipated.[1] 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.

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 noninvasive 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.[2] 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.

If the cystoscopic appearance of the tumor is solid (sessile), high-grade, or suggests invasion into muscle, a computed tomographic (CT) scan 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 evaluation of the upper tracts with an intravenous pyelogram (IVP), retrograde pyelogram, CT urography, renal ultrasound, or MRI urogram, and urine cytology.

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: noninvasive, invasive, or metastatic.

Positive urinary cytology may indicate urothelial tumour anywhere in the urinary tract. 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%).[3] 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

over, 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. Refining these estimates for individual patients is an area of active research.[4]

## Staging and Grading

The most commonly used staging system is the tumor, node, metastasis (TNM) system,[5] as shown in Table 1 on page ST-1.

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 nonmuscle 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 Urologic Pathologists published and recommended a revised consensus classification for papillary neoplasms [6] 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.[6] 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 in the “Principles of Pathology Management” on page MS-18 (Table 2).

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 on BL-A, BL-E, BL-F, BL-G, and BL-H respectively.

## Treatment of Non–Muscle-Invasive Disease

Non–muscle-invasive tumors are divided into noninvasive papillomas or carcinomas (Ta), those invading the lamina propria (T1), and carcinoma in situ (CIS) or Tis.[7] 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). Standard treatment in these cases is repeat transurethral resection (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 2 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 low. Management of the different histologic subtypes of different grades is outlined in subsequent sections.

***Papilloma/cTa, low grade tumors:***
Transurethral resection without intravesical therapy is the standard treatment for cTa, low grade tumors. Because patients diagnosed with these tumors have a relatively high risk for recurrence, the panel recommends that, in addition to observation, experts consider administering a single dose of intravesicular chemotherapy (not immunotherapy) within 24 hours of resection. BCG has been shown to be effective as prophylaxis to prevent bladder cancer recurrences following TURBT.

Close follow-up 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. If no recurrences develop during the first year, the interval between evaluations can be increased.

***Post-treatment recurrence of Ta, low grade disease***
Patients with a documented recurrence by positive cystoscopy are treated with TURBT and adjuvant intravesical therapy based on the stage and grade of the recurrent lesion, and then followed-up at 3-month intervals. Intravesical therapy is recommended for patients with a history of recurrences.

***Ta, high grade:***
Tumors staged as Ta, high grade lesions are considered papillary tumors with a relatively high risk for recurrence and progression towards more invasiveness. In the absence of muscularis propria in the specimen, data suggests that 20% to 40% of patients will have either residual tumor and/or unrecognized muscle invasive disease.[8,9] Repeat resection is recommended if there is lymphovascular or incomplete resection, or there is no muscle in specimen.

Postoperatively, in addition to observation, they may be treated with intravesical bacillus Calmette-Guérin (BCG), or mitomycin C (MMC). 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 Ta and T1 tumors[10-13] 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-month intervals for the first 1-2 years, repeated at increasing intervals over the next 2 years, and annually 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.[14] 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.

***T1 tumors:***
T1 lesions, those invading lamina propria, are considered to be potentially dangerous (usually T1, high grade) and have a high 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 followed by intravesical therapy (this is optional for low grade lesions). Follow-up is similar to that for Ta disease.

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).

***High-Risk Disease (High-grade or multifocal lesions):***
In patients with high-risk disease (T1, high grade) 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 followed by intravesical therapy with BCG (category 1) or MMC is recommended (BL-2) or cystectomy. Some data suggest that early cystectomy may be preferred if residual disease is found, because of the high risk for progression to a more advanced stage.[15] If high-risk disease is managed conservatively and does not respond to BCG or MMC, a cystectomy should be performed.

**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-month intervals for the first 1-2 years, repeated at increasing intervals over the next 2 years, and annually thereafter. Imaging of the upper tract should be considered every 1-2 years for high-grade tumors. Urine molecular marker testing is optional (Category 2B recommendation).

***Post-treatment Tis or Ta Recurrent or Persistent Disease***
Patients with recurrent/persistent Tis or Ta tumors, after initial treatment, and 12-week (3-month) evaluation can be given a second induction course of BCG or MMC 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, a cystectomy should be strongly considered. Depending on prior treatment, extent of the disease, and frequency of recurrences, intravesical therapy with a different intravesical agent (mitomycin, or less commonly valrubicin; or BCG plus interferon-alpha) is an alternative to cystectomy. The combination of intravesical BCG and interferon alpha-2B has been shown to be potentially effective in this setting[16], 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.[13-21]

Regardless of whether maintenance therapy with BCG is administered, patients with Tis should be followed up at 3-month intervals with a urinary cytology and cystoscopy for the first 2 years, every 6 months in the third and fourth years if no recurrences are documented, and then annually. Imaging of the upper tract collecting system every 1 to 2 years is also recommended. Testing for urinary tumor markers is optional (Category 2B recommendation). 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.

***Post-treatment Recurrent or Persistent Disease Based on Cytology Only***

In patients with a documented recurrence (cytology positive, cystoscopy and imaging negative), transurethral resection (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 TUR biopsy of the bladder is positive, then the recommendation is to administer intravesical BCG treatment followed by maintenance BCG if a complete response is seen. For tumors that fail BCG[22] or show an incomplete response, the follow-up options include changing the intravesical agent to MMC or cystectomy or participation in a clinical trial. Available options for alternate intravesical agents include (Valrubicin, gemcitabine and BCG plus interferon). However further investigation and validation of results is warranted for establishing the efficacy of these agents in the second-line treatments.[22,23]

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 are positive then the treatment is described below under the section on Upper Tract Tumors.

## Treatment of Muscle-Invasive Disease

Before any treatment is advised, several workup procedures are recommended to 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, EUA/TURBT, chest radiograph, 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. Unfortunately, CT scans, ultrasound, and MRI cannot accurately predict the true depth of invasion.[24]

***Organ-Confined Disease (T2a, T2b):***

Surgical treatment with radical cystectomy is still the most effective local therapy in muscle-invasive bladder cancer. The critical issues in the management and prognosis of these patients are whether a palpable mass is appreciated at EUA and if the tumor has extended through the bladder wall. Tumors that are organ-confined (T2) have a better prognosis than those that have extended through the bladder wall to the perivesical fat (T3) and beyond.

Primary surgical treatment for T2 lesion is a radical cystectomy with the consideration of neoadjuvant chemotherapy (see section below on neoadjuvant chemotherapy). Segmental cystectomy can be considered only in 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. If no neoadjuvant chemotherapy was given, postoperative adjuvant chemotherapy is considered based on pathologic risk, such as positive nodes and pathologic T3 lesions. If segmental cystectomy was performed, adjuvant radiotherapy or chemotherapy based on pathologic risk, such as positive nodes, positive margin, high-grade, and pathologic T3 lesions, should be considered (BL-4).

***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 biopsy is modest in making these distinctions, 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, and is associated with better survival and lower pelvic recurrence rate. There are some patient factors which may preclude a PLND such as severe scaring 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, chest radiograph, and imaging of the abdomen and pelvis every 3 to 6 months for 2 years and then as clinically indicated. Patients should be monitored annually for vitamin $B_{12}$ 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. A postoperative CT scan is advised to define the revised anatomy of the pelvis and should be repeated every 3 to 6 months for 2 years if the risk for recurrence is high, and then every 12 months.

***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 (BL-7).

***Neoadjuvant Chemotherapy:***

Increasing data support the role of neoadjuvant chemotherapy before cystectomy for T2 and T3 lesions.[25–27] Two randomized trials show a survival benefit, particularly in patients with clinical T3 disease (palpable mass at EUA or unequivocal mass on CT).[25,26] 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.[25] 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).

***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.[28] Many trials showing a survival benefit were not randomized, raising the question of selection bias in the analysis of outcomes.

Two trials, [29] showed a survival advantage from therapy with cyclophosphamide, doxorubicin, and cisplatin (CAP) study and with MVAC or methotrexate, vinblastine, epirubicin, and cisplatin (MVEC).[30,31] 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[32], or more commonly now gemcitabine, cisplatin (GC)[33,34] may be used in patients undergoing adjuvant therapy. No data support the use of adjuvant chemotherapy for nonurothelial (nontransitional cell) carcinomas, regardless of stage (See Principles of Chemotherapy Management, BL-G).

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 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.[35] 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 with or without biopsy every 3 months within the first year, then at increased intervals thereafter. 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 at 3-month intervals, is a routine part of the management of all cases in which the bladder is preserved.

***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.[36]

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.

***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 complete pathologic response proportions in the bladder using neoadjuvant chemotherapy alone were only 20% to 30%.[25,26] 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***

These approaches use induction therapy with deferred management of the bladder pending the assessment of response in the primary tumor.

***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.[37] 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.[38] 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.[39] 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.[33-41] More recently, the concomitant use of cisplatin, 5-FU, and radiotherapy has been studied and the results have improved.[42– 44] 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 later. 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.

***Non–Organ-Confined Disease (T3a, T3b/T4a, T4b)***

***T3a, T3b Disease***
Primary surgical treatment for a tumor that extends beyond the confines of the bladder wall is radical cystectomy with consideration of cisplatin-based combination neoadjuvant chemotherapy, as outlined previously. Except in highly selected cases (described later), bladder preservation is not an option in these patients because the proportion rendered tumor-free is low. Tumors that are pathologic stage T3 or T4 with nodal involvement or vascular invasion have a high risk (> 50%) for systemic relapse and, therefore, may be considered for treatment with adjuvant chemotherapy or radiotherapy. The follow-up schema is the same as previously outlined for high-risk patients.

In patients with extensive comorbid disease or poor performance status, chemotherapy alone, radiotherapy plus chemotherapy, or radiotherapy alone, or TURBT is recommended. For patients not undergoing cystectomy, evaluation with cystoscopy and tumor site re-biopsy is necessary after primary treatment.

***T4a, T4b Disease***
Patients with unresectable disease, defined as a fixed bladder mass, or those with positive nodes evident before laparotomy are considered for chemotherapy alone or chemotherapy with radiotherapy. An initial stratification is based on the results of transaxial imaging. For patients who show no nodal disease on CT scans, the treatment recommendation includes 2 to 3 courses of chemotherapy with or without radiotherapy followed by cystoscopy and CT scan. If the tumor responds, options include cystectomy or consolidation chemotherapy with or without radiotherapy. If no response is noted, chemotherapy with radiotherapy or a new chemotherapy regimen can be used. In

highly selected T4a node-negative patients, surgery with or without chemotherapy is another treatment option.

If pelvic lymph nodes larger than 2 cm are documented on imaging, a biopsy is advised to confirm nodal spread. Baseline renal function, the presence or absence of cardiac disease, and overall performance status must also be considered when making a treatment recommendation. Patients with a good performance status and no significant comorbid disease may be considered for chemotherapy with or without radiotherapy if the nodes are positive. If they experience complete response, patients may undergo observation, receive a boost with radiotherapy, or be considered for cystectomy or lymphadenectomy.

Chemotherapy options are discussed under "Metastatic Disease," whereas combined modality approaches using chemotherapy and radiotherapy are discussed previously. For patients who cannot tolerate multidrug combinations with radiotherapy, an alternative is to use radiotherapy with a radiation sensitizer, such as cisplatin administered starting on day 1 and day 21 or 5-FU with various schedules. Patients are initially treated with 45 Gy of radiation to the pelvis and bladder, with a boost of approximately 20 Gy to sites of disease within the bladder.

In highly selected patients with metastatic disease who experience a complete systemic response to chemotherapy, surgery may be performed in an attempt to render the patient disease-free. Data from several groups show that this aggressive approach can result in long-term survival.

***Metastatic Disease***

Patients who present with unresectable or metastatic disease or who subsequently develop metastatic disease are generally treated with systemic chemotherapy and/or radiotherapy. These patients should undergo a staging evaluation that includes a chest CT, bone scan, and determination of creatinine clearance.

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 3). A commonly used combination is cisplatin and gemcitabine (GC)[45] or a multidrug cisplatin-based regimen, such as MVAC[46]. 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, [47] which showed that although cisplatin/gemcitabine was not inferior to MVAC in terms of survival. GC has demonstrated similar activity and somewhat less toxicity when compared to MVAC.[48]

Some combination regimens, including cisplatin/paclitaxel, gemcitabine/paclitaxel,[49] gemcitabine/docetaxel,[50] cisplatin/gemcitabine/paclitaxel,[51] or carboplatin/gemcitabine/paclitaxel, [52] and cisplatin/gemcitabine/docetaxel, have also shown activity in bladder cancer. They are considered for patients with locally advanced disease or limited metastatic recurrence who may be candidates for

consolidation surgery. Pemetrexed may be used in patients refractory to platinum containing agents.[53]

In patients with glomerular filtration rate (GFR) < 60 mL/min, carboplatin maybe substituted for cisplatin in all 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, and both gemcitabine and ifosfamide have shown efficacy as palliative therapy. Based on these results, several groups are exploring 2- and 3-drug combinations using these agents, with and without cisplatin, as initial therapy. 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.

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 with regimens typically used for colon cancers, and squamous tumors with regimens typically used for tumors originating in the head and neck). 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. Patients who cannot tolerate cisplatin-based therapy because of medical comorbidities may be considered for treatment with a carboplatin-based regimen

## 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 an IVP, CT urogram, or a retrograde pyelogram with or without ureteroscopy. A CT scan is useful for determining the location of the mass and whether any nodal spread has occurred, and 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 cytoscopy may help identify carcinoma cells. Hematologic, renal, and hepatic function should also be evaluated. Additional imaging studies, such as 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 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 therapy may be considered based on extrapolation of data from bladder cancer series.[25-27] 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 an upper tract imaging study. These studies should include IVP, retrograde pyelogram, or CT or MRI urography, if available, at 1- to 2-year intervals. Other follow-up options may include ureteroscopy 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, 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.

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. 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 transurethral resection (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 ductal 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.[25-27] Alternatively, TURP and BCG may be offered to patients with only ductal 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 nonurothelial (nontransitional cell) carcinoma. These pathologic entities include mixed histology, pure

squamous, adenocarcinoma, and small cell tumors. Depending on the pathologic findings, adjuvant chemotherapy may or may not be recommended. Patients with nonurothelial 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 nonurothelial 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 on BL-D.

## 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 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 2. Principles of Pathology Management: Malignancy Grading of Bladder Carcinoma: Old and New Systems[a,b]

| 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 |

[a]From Droller MJ. Bladder Cancer, Current Diagnosis and Treatment. Totowa (NJ): Humana Press, 2001.

[b]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, noninvasive 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 3. Combination Chemotherapy Regimens

| Regimen | Dosage | |
|---|---|---|
| **Gemcitabine/ Cisplatin**[33,34] | Gemcitabine* | 1000 mg/m$^2$ on days 1, 8, 15 of 28-day cycle |
| | Cisplatin | 70 mg/m$^2$ on day 2 |
| **M-VAC**[32,54] | Methotrexate | 30 mg/m$^2$ on days 1, 15, 22 |
| | Vinblastine | 3 mg/m$^2$ on days 2, 15, 22 |
| | Doxorubicin | 30 mg/m$^2$ on day 2 |
| | Cisplatin | 70 mg/m$^2$ on day 2 |

*This dose should not be combined with radiation.

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