National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Bladder Cancer

Version 2.2015

NCCN.org

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NCCN Guidelines Panel Disclosures

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Clinical Trials: 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.

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Updates in Version 2.2015 of the NCCN Guidelines for Bladder Cancer from Version 1.2015 include:

MS-1

- **The Discussion section was updated to reflect the changes in the algorithm.**

Updates in Version 1.2015 of the NCCN Guidelines for Bladder Cancer from Version 2.2014 include:

Bladder Cancer

BL-1

- **Workup, noninvasive disease, 2nd bullet was revised, "Consider pelvic CT *or MRI* before transurethral resection of bladder tumor (TURBT) if sessile or high grade."**
- **Footnote "a" was revised, "Imaging may include one or more of the following: ~~intravenous pyelogram (IVP),~~ CT urography, renal ultrasound *or CT without contrast* with retrograde pyelogram, ureteroscopy, or MRI urogram." Revision made throughout the guidelines.**

BL-2

- **For cT1, low and high grade, if no residual disease, the option "Observation in highly selected cases" with a corresponding footnote, "Highly selected cases with small-volume tumors with limited lamina propria invasion and no CIS" was added.**

BL-3

- **Maintenance BCG therapy was changed from "optional" to "preferred" when BCG has been previously given.**

BL-4

- **Primary treatment for patients with extensive comorbid disease, the option of chemotherapy alone was removed and RT was revised as, "RT *or* concurrent *chemoradiotherapy* ~~or Chemotherapy alone~~."**
- **Adjuvant treatment for patients with extensive comorbid disease,**
  - **Tumor unresectable or not a surgical candidate, the treatment was revised, "*Consider RT if not previously given* and/or Alternative chemotherapy *or TURBT and Best supportive care*." Also for BL-5.**

BL-6

- **Metastatic, additional workup**
  - **2nd bullet was revised by removing MRI, "Chest CT ~~or MRI.~~"**
  - **3rd bullet was revised by adding, "Creatinine clearance, *if calculated GFR <60 mL/min*."**

BL-7

- **Follow-up**
  - **Footnote "s" was added, "No single follow-up plan is appropriate for all patients. Follow-up should be individualized based on treatment schedules, side effects, comorbidities, and symptoms."**
- **Local recurrence or persistent disease; preserved bladder**
  - **For invasive disease, "RT (if not prior RT)" was changed to "*Chemoradiotherapy* (if not prior RT)."**

BL-A

- **Principles of Surgical Management**
  - **For both papillary appearing tumor and suspected or known carcinoma in situ, a new bullet was added, "Blue light cystoscopy may be helpful in identifying lesions not visible using white light cystoscopy."**

BL-C

- **Approximate Probablity of Recurrence**
  - **The "approximate probablity of progression to muscle invasion" column was removed from the table.**

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Updates in Version 2.2015 of the NCCN Guidelines for Bladder Cancer from Version 2.2014 include:

BL-D

- The corresponding bullets for pure squamous were extensively revised.
  - "Neoadjuvant/adjuvant chemotherapy should not be given for non-urothelial histologies
  - Local control with surgery or RT and best supportive care recommended.
  - For advanced disease, clinical trial preferred. For selected patients, combination chemotherapy with paclitaxel, ifosfamide, and cisplatin may be considered."
- The sections for adenocarcinoma and urachal carcinoma were combined as "pure adenocarcinoma including urachal" and the cooresponding bullets were extensively revised.
  - Neoadjuvant/adjuvant chemotherapy should not be given for non-urothelial histologies
  - Local control with surgery or RT and best supportive care recommended.
  - For localized disease, cystectomy or partial cystectomy with en block resection of the urachal ligament with umbilicus for Urachal Carcinoma
  - For advanced disease, clinical trial preferred. For selected patients, combination chemotherapy with a 5-FU–based regimen or combination paclitaxel, ifosfamide, and cisplatin may be considered.

BL-E

- Follow-up after a radical cystectomy
  - 3rd bullet was revised by adding, "*Consider* urethral wash cytology every 6 to 12 mo, particularly if Tis was found within the bladder or prostatic urethra."

BL-G 3 of 4

Principles of Chemotherapy Management

- Radiosensitizing chemotherapy regimens for bladder-preserving chemoradiation following a maximal TURBT
  - Low-dose gemcitabine was added as a category 2B recommendation.
- Radiosensitizing chemotherapy given concurrently with conventionally fractionated radiation for palliation of metastases or for pelvic recurrence after cystectomy
  - Low-dose gemcitabine was changed from a category 3 to a category 2B recommendation.
- Footnote "a" was added, "Carboplatin should not be substituted for cisplatin with radiation."

BL-H 1 of 2

- Principles of Radiation Management of Invasive Disease, Carcinoma of the Bladder
  - 8th bullet was added, "When irradiating the bladder only or bladder tumor boost, consider daily image guidance."

Primary Carcinoma of the Urethra

PCU-1

- Footnote "a" was added, "Referral to a specialized center is recommended."

PCU-2

- T2 disease
  - Male, pendulous urthera, adjuvant treatment option, "RT ± chemotherapy" was changed to "RT preferably with chemotherapy."
  - Male, bulbar urethra, adjuvant treatment option, "Consider adjuvant chemotherapy ± RT" was changed to "Consider adjuvant chemotherapy or chemoradiotherapy."
  - Female, therapy for recurrence, "or chemoradiotherapy" was added to "chemotherapy."
- T3,T4 disease and Palpable inguinal lymph nodes
  - cN0 and cN1/cN2, primary treatment option, "RT ± chemotherapy" was changed to "RT preferably with chemotherapy."
  - cN1/cN2, primary treatment, "or chemoradiotherapy" was added to "chemotherapy"
  - Therapy for recurrence, "or chemoradiotherapy" was added to "chemotherapy" with a categeory 2A recommendation.
- Distant metastasis
  - Primary treatment, "or chemoradiotherapy" was added.
- Footnote "c" was revised by adding, "Consider neoadjuvant chemotherapy (category 2B) *or chemoradiation.*"

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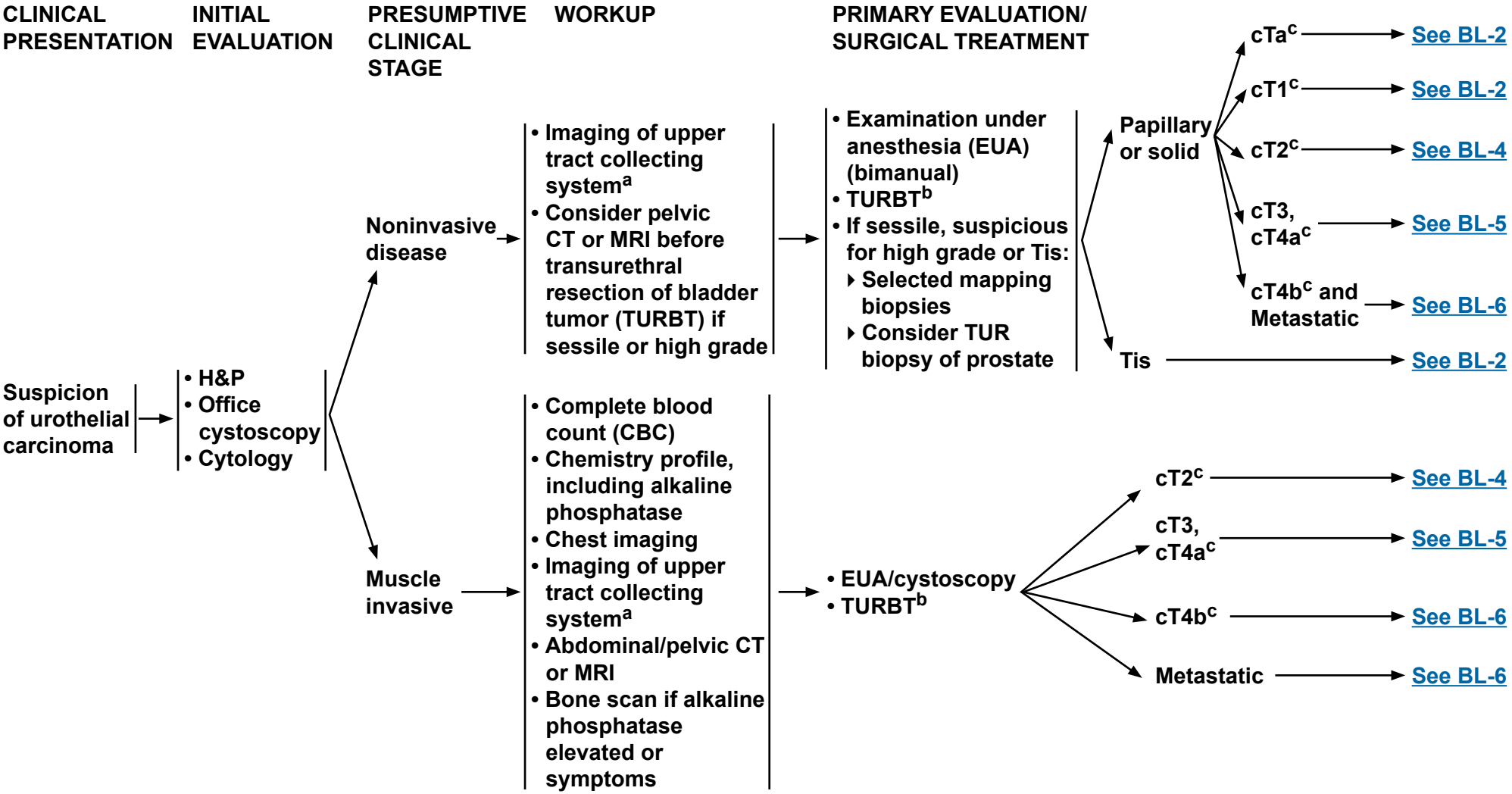

[a]Imaging may include one or more of the following: CT urography, renal ultrasound or CT without contrast with retrograde pyelogram, ureteroscopy, or MRI urogram.

[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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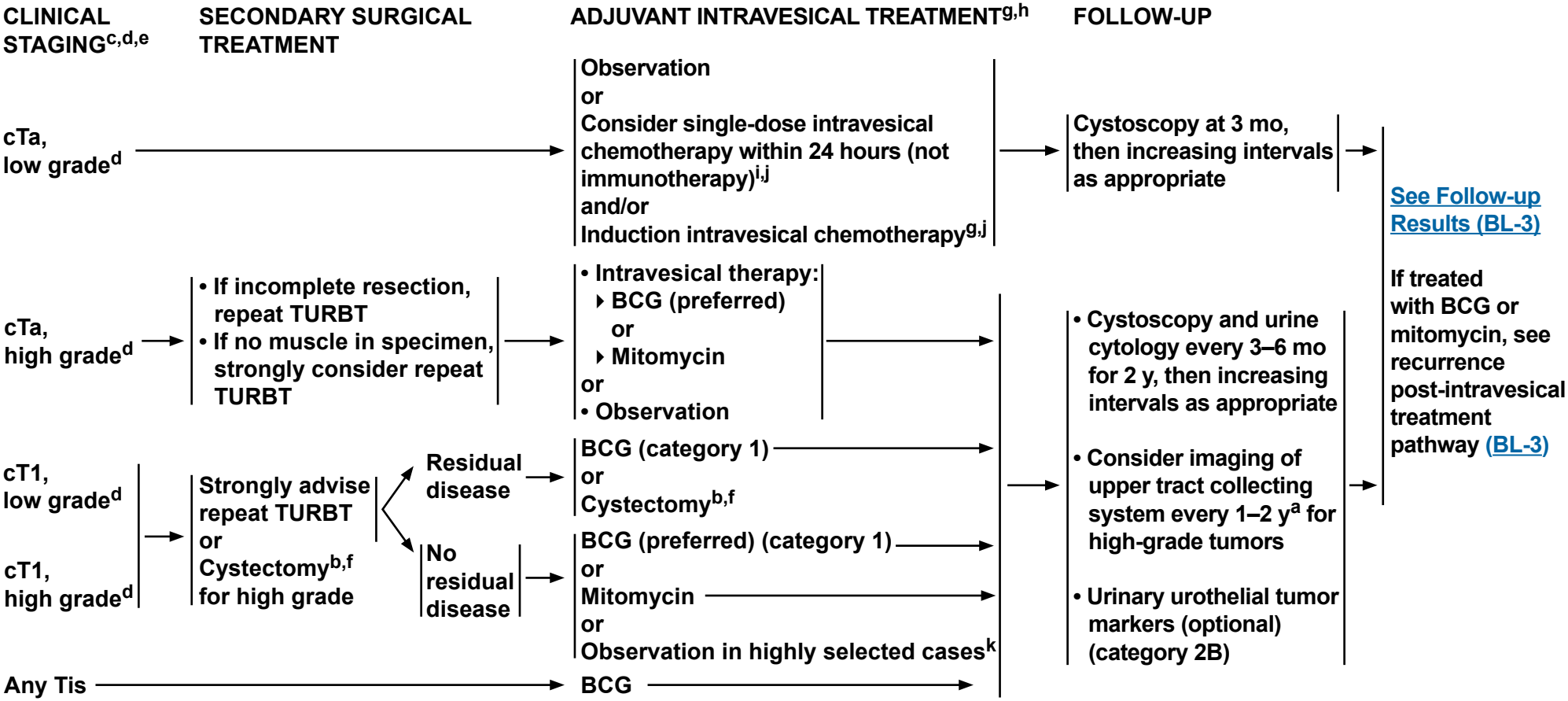

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[d]Montironi R, Lopez-Beltran A. The 2004 WHO classification of bladder tumors: A summary and commentary. Int J Surg Pathol 2005;13:143-153. See Principles of Pathology Management (BL-B).

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

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

[g]Indications for adjuvant therapy: Based on probability of recurrence and progression to muscle-invasive disease, such as size, number, and grade.

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

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

[j]Although there is no intravesical chemotherapy standard for cTa low grade, mitomycin is most commonly used.

[k]Highly selected cases with small-volume tumors with limited lamina propria invasion and no CIS.

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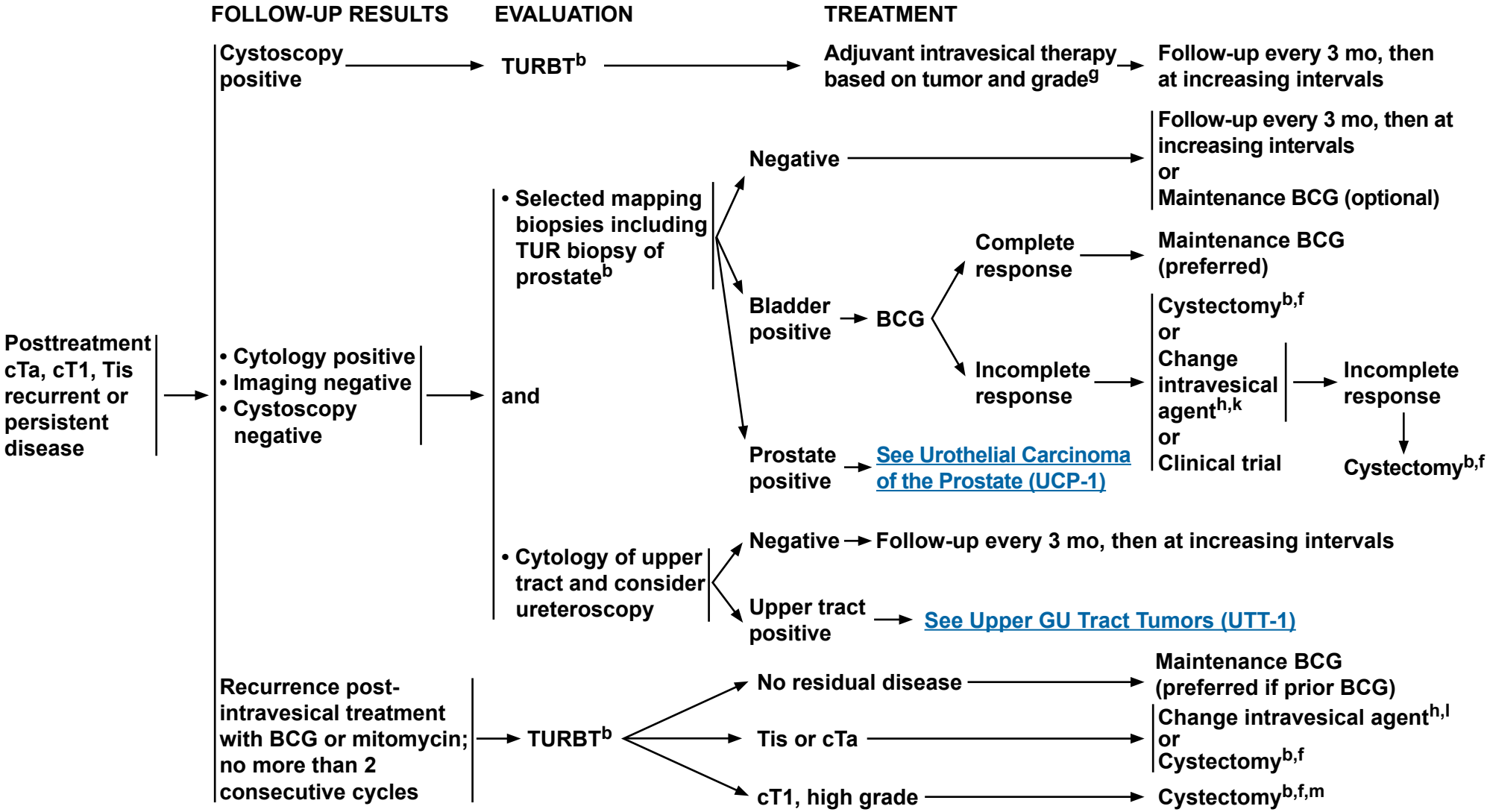

[b] See Principles of Surgical Management (BL-A).
[f] See Follow-Up After Cystectomy and Bladder Preservation (BL-E).
[g] Indications for adjuvant therapy: Based on probability of recurrence and progression to muscle-invasive disease, such as size, number, and grade.
[h] See Principles of Intravesical Treatment (BL-F).
[l] Valrubicin is approved for BCG-refractory carcinoma in situ.
[m] If not a cystectomy candidate, consider concurrent chemotherapy and radiation, change in intravesical agent, or a clinical trial.

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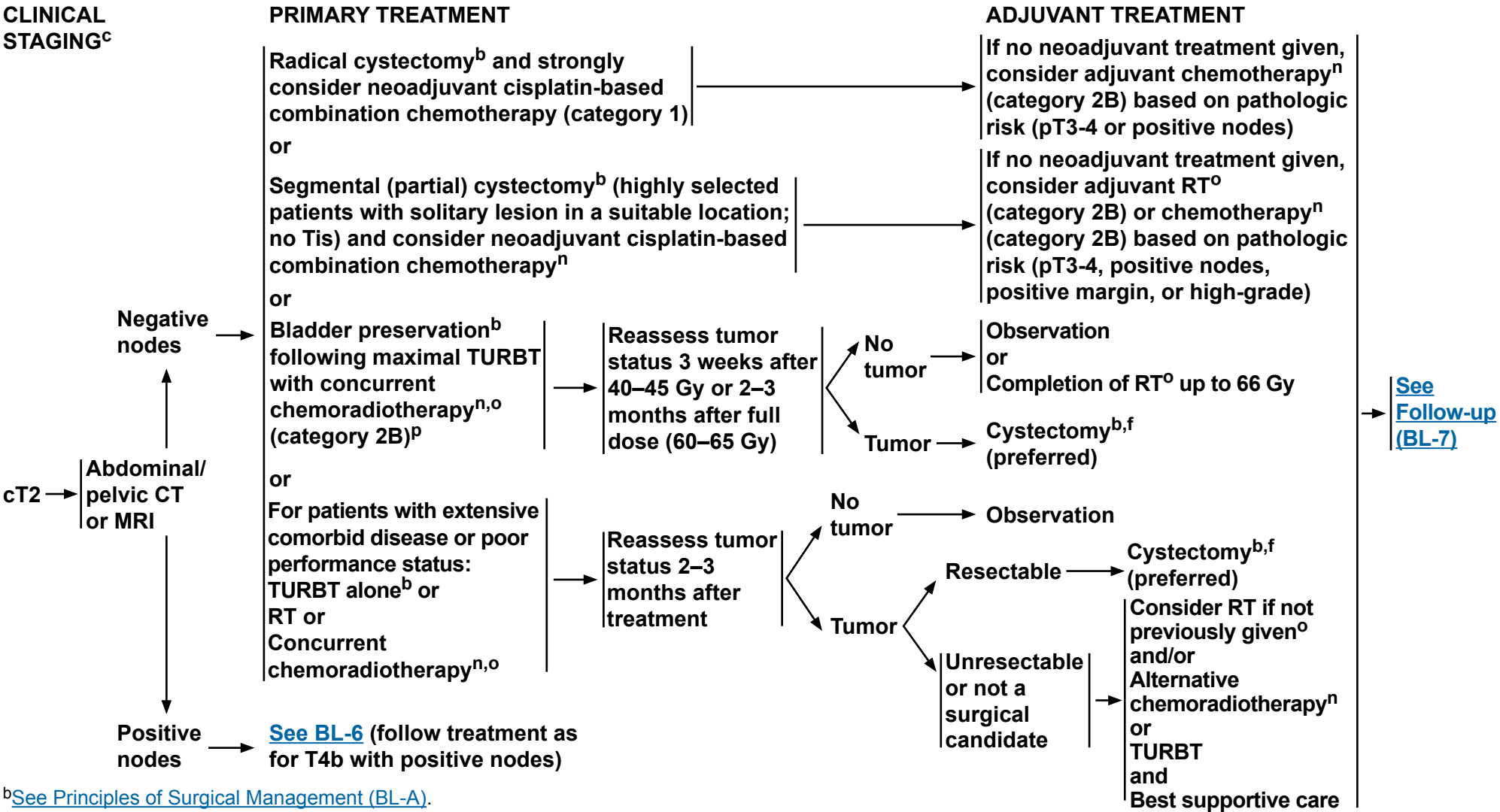

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[f] See Follow-Up After Cystectomy and Bladder Preservation (BL-E).

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

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

[p] 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.

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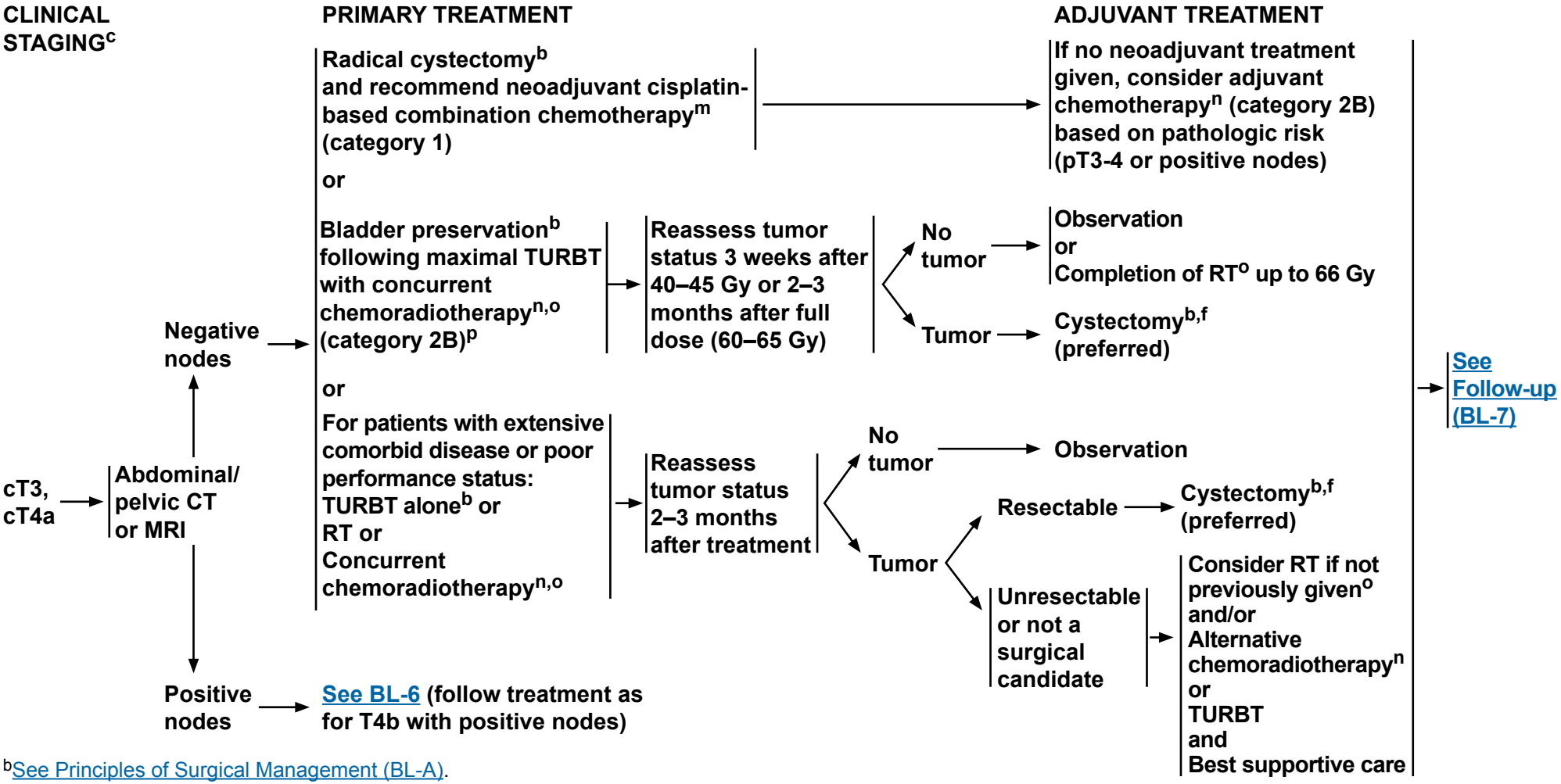

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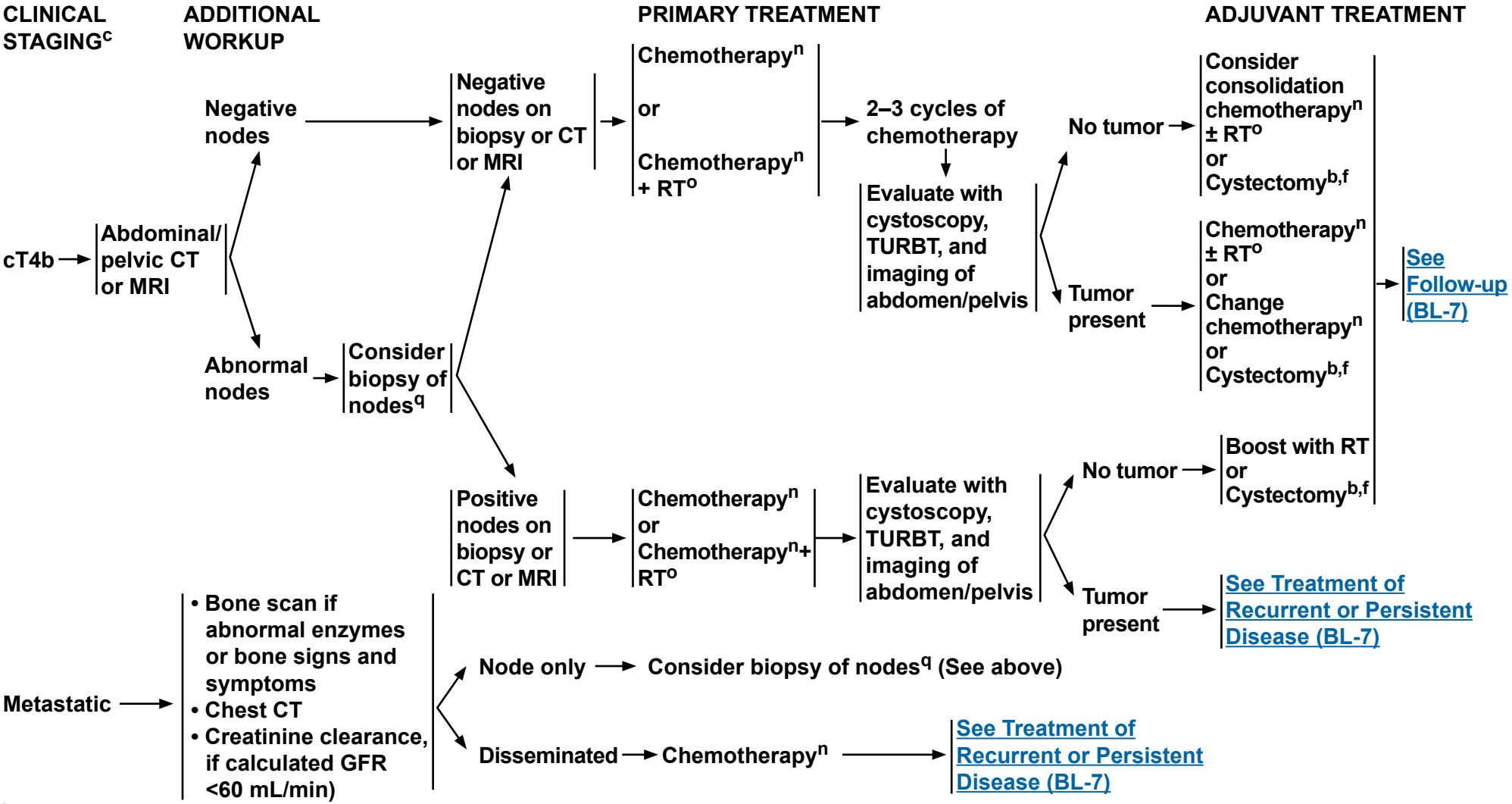

[b] See Principles of Surgical Management (BL-A).

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

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

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

[q] If technically possible.

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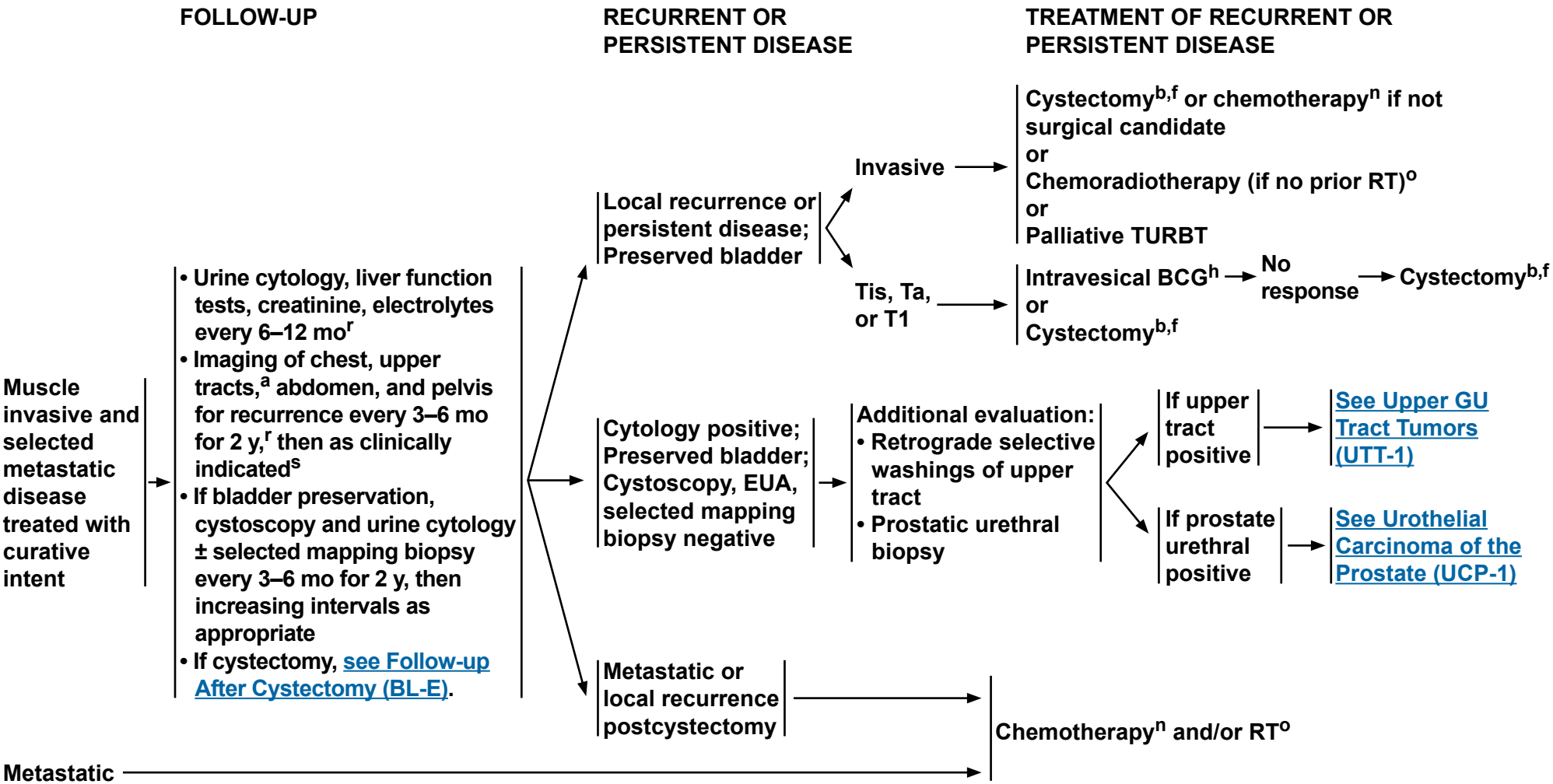

[a]Imaging may include one or more of the following: CT urography, renal ultrasound or CT without contrast with retrograde pyelogram, ureteroscopy, or MRI urogram.
[b]See Principles of Surgical Management (BL-A).
[f]See Follow-Up After Cystectomy and Bladder Preservation (BL-E).
[h]See Principles of Intravesical Treatment (BL-F).
[n]See Principles of Chemotherapy Management (BL-G).
[o]See Principles of Radiation Management of Invasive Disease (BL-H).
[r]Depending on risk of recurrence.
[s]No single follow-up plan is appropriate for all patients. Follow-up should be individualized based on treatment schedules, side effects, comorbidities, and symptoms.

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PRINCIPLES OF SURGICAL MANAGEMENT

Transurethral Resection for Papillary Appearing Tumor (likely non-muscle invasive)
- Adequate resection with muscle in specimen
- Early repeat TURBT (within six weeks) if
  - Incomplete initial resection
  - No muscle in original specimen for high-grade disease
  - Large or multi-focal lesions
  - Any T1 lesion
- Blue light cystoscopy may be helpful in identifying lesions not visible using white light cystoscopy

Transurethral Resection for Suspected or Known Carcinoma In Situ
- Multiple selective and/or random biopsies
- Additional biopsy adjacent to papillary tumor
- Consider prostate urethral biopsy
- Blue light cystoscopy may be helpful in identifying lesions not visible using white light cystoscopy

Transurethral Resection for Sessile or Invasive Appearing Tumor (likely muscle invasive)
- Perform EUA
- Repeat TURBT if
  - No muscle in specimen for high-grade disease
  - Any T1 lesion
  - First resection does not allow adequate staging/attribution of risk for treatment selection
  - Incomplete resection and considering tri-modality bladder preservation therapy

Segmental (Partial) Cystectomy
- Reserved for solitary lesion in location amenable to segmental resection with adequate margins
- No carcinoma in situ as determined by random biopsies
- Bilateral pelvic lymphadenectomy should be performed and include at a minimum common, internal iliac, external iliac, and obturator nodes.

Radical Cystectomy
- Bilateral pelvic lymphadenectomy should be performed and include at a minimum common, internal iliac, external iliac, 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, LLC.

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APPROXIMATE PROBABILITY OF RECURRENCE

Pathology	Approximate Probability of Recurrence in 5 years
Ta, low grade	50%
Ta, high grade	60%
T1, low grade (rare)	50%
T1, high grade	50%–70%
Tis	50%–90%

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NON-UROTHELIAL CELL CARCINOMA OF THE BLADDER

Mixed Histology:
- **Urothelial carcinoma plus squamous, adenocarcinoma, micropapillary, nested, plasmacytoid, and sarcomatoid should be identified because of the potential to have a more aggressive natural history.**
- **These are usually treated in a similar fashion to pure urothelial carcinoma of the bladder except their generally worse prognosis must be taken into consideration.**

Pure Squamous
- **Neoadjuvant/adjuvant chemotherapy should not be given for non-urothelial histologies.**
- **Local control with surgery or RT and best supportive care recommended.**
- **For advanced disease, clinical trial preferred. For selected patients, combination chemotherapy with paclitaxel, ifosfamide, and cisplatin may be considered.[1]**

Pure Adenocarcinoma including Urachal
- **Neoadjuvant/adjuvant chemotherapy should not be given for non-urothelial histologies.**
- **Local control with surgery or RT and best supportive care recommended.**
- **For localized disease, cystectomy or partial cystectomy with en block resection of the urachal ligament with umbilicus for Urachal carcinoma.**
- **For advanced disease, clinical trial preferred. For selected patients, combination chemotherapy with a 5-FU–based regimen or combination paclitaxel, ifosfamide, and cisplatin may be considered.[1,2]**

Any Small-Cell Component (or neuroendocrine features):
- **Neoadjuvant chemotherapy using small-cell regimens and local treatment (cystectomy or radiotherapy).**
- **Primary chemotherapy regimens similar to small cell lung cancer. See NCCN Guidelines for Small Cell Lung Cancer.**

Primary Bladder Sarcoma:
- **Treatment as per NCCN Guidelines for Soft Tissue Sarcoma.**

[1]Galsky M, Iasonos A, Mironov S, et al. Prospective trial of ifosfamide, paclitaxel, and cisplatin in patients with advanced non-transitional cell carcinoma of the urothelial tract. Urology 2007;69:255-259.
[2]Siefker-Radtke A, Gee J, Shen Y, et al. Multimodality management of urachal carcinoma: the M. D. Anderson Cancer Center experience. J Urol 2003;169:1295-1298.

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FOLLOW-UP AFTER CYSTECTOMY AND BLADDER PRESERVATION

After a radical cystectomy

- Urine cytology, liver function tests, creatinine, and electrolytes every 3 to 6 mo for 2 y and then as clinically indicated
- Imaging of the chest, upper tracts, abdomen, and pelvis every 3 to 6 mo for 2 y based on risk of recurrence and then as clinically indicated
- Consider urethral wash cytology every 6 to 12 mo, 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 or bladder preservation

- Same follow-up as above, in addition to the following:
  - Cystoscopy and urine cytology ± selected mapping biopsy every 3 to 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**

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

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PRINCIPLES OF CHEMOTHERAPY MANAGEMENT

Perioperative chemotherapy (neoadjuvant or adjuvant)

- **Regimens**
  - **DDMVAC (dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin) with growth factor support for 3 or 4 cycles[1,2]**
  - **Gemcitabine and cisplatin for 4 cycles[3,4]**
  - **CMV (cisplatin, methotrexate, and vinblastine) for 3 cycles[5]**

- **Randomized trials and meta-analyses show a survival benefit for cisplatin-based neoadjuvant chemotherapy in patients with muscle-invasive bladder cancer.[1,6,7]**
- **Meta-analysis suggests a survival benefit to adjuvant therapy for pathologic T3, T4 or N+ disease at cystectomy.[7]**
- **Neoadjuvant chemotherapy is preferred over adjuvant-based chemotherapy on a higher level of evidence data.**
- **DDMVAC is preferred over standard MVAC based on category 1 evidence showing DDMVAC to be better tolerated and more effective than conventional MVAC in advanced disease.[2,8] Based on these data, the traditional dose and schedule for MVAC is no longer recommended.**
- **Perioperative gemcitabine and cisplatin is a reasonable alternative to DDMVAC based on category 1 evidence showing equivalence to conventional MVAC in the setting of advanced disease.[4,9]**
- **For gemcitabine/cisplatin, both 21- and 28-day regimens are acceptable. Better dose compliance may be achieved with fewer delays in dosing using the 21-day schedule.[10]**
- **Neoadjuvant chemotherapy may be considered for select patients with upper tract urothelial carcinoma, particularly for higher stage and/or grade tumors, as renal function will decline after nephroureterectomy and may preclude adjuvant therapy.**
- **Carboplatin should not be substituted for cisplatin in the perioperative setting.**
  - **For patients with borderline renal function or minimal dysfunction, a split-dose administration of cisplatin may be considered (such as 35 mg/m^2 on days 1 and 2 or days 1 and 8) (category 2B). While safer, the relative efficacy of the cisplatin-containing combination administered with such modifications remains undefined.**
  - **For patients who are not candidates for cisplatin, there are no data to support a recommendation for perioperative chemotherapy.**

Continued on BL-G 2 of 4 and BL-G 3 of 4

References on BL-G 4 of 4

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PRINCIPLES OF CHEMOTHERAPY MANAGEMENT

First-line chemotherapy for metastatic disease

- **Regimens**
  - **Gemcitabine and cisplatin[4] (category 1)**
  - **DDMVAC[2,8] with growth factor support (category 1)**
- **Alternative regimens**
  - **Carboplatin- or taxane-based regimens, or single-agent chemotherapy (category 2B)**

- **The 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.**
- **For most patients, the risks of adding paclitaxel to gemcitabine and cisplatin outweigh the limited benefit seen in the randomized trial.[11]**
- **A substantial proportion of patients cannot receive cisplatin-based chemotherapy due to renal impairment or other comorbidities.**
  - **Participation in clinical trials of new or more tolerable therapy is recommended.**
  - **Carboplatin- or taxane-based regimens, or single-agent therapy can be considered for these patients (category 2B).**

Second-line chemotherapy for metastatic disease

- **No standard therapy exists in this setting; thus, participation in clinical trials of new agents is recommended.**
- **Depending on first-line treatment received, single-agent taxane or gemcitabine is preferred for palliation in this setting. Additional palliative options include single-agent cisplatin, carboplatin, doxorubicin, 5-FU, ifosfamide, pemetrexed, methotrexate, and vinblastine.**

Continued on BL-G 3 of 4

References on BL-G 4 of 4

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.

PRINCIPLES OF CHEMOTHERAPY MANAGEMENT

Radiosensitizing chemotherapy regimens for bladder-preserving chemoradiation following a maximal TURBT

- **First-line chemotherapy[a]**
  - **Cisplatin**
  - **Cisplatin and 5-FU[12]**
  - **5-FU and mitomycin C[13]**
  - **Cisplatin and paclitaxel[14] (category 2B)**
  - **Low-dose gemcitabine (category 2B)**
  - **Clinical trial**

Radiosensitizing chemotherapy given concurrently with conventionally fractionated radiation for palliation of metastases or for pelvic recurrence after cystectomy[a]

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

References on BL-G 4 of 4

[a]Carboplatin should not be substituted for cisplatin with radiation.

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.

PRINCIPLES OF CHEMOTHERAPY MANAGEMENT

REFERENCES

[1]Grossman HB, Natale RB, Tangen CM, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. N Engl J Med 2003;349:859-866.
[2]Sternberg CN, de Mulder PH, Schornagel JH, et al. Randomized phase III trial of high-dose-intensity methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) chemotherapy and recombinant human granulocyte colony-stimulating factor versus classic MVAC in advanced urothelial tract tumors: European Organization for Research and Treatment of Cancer Protocol no. 30924. J Clin Oncol 2001;19:2638-2646.
[3]Dash A, Pettus JA, Herr HW, et al. A role for neoadjuvant gemcitabine plus cisplatin in muscle-invasive urothelial carcinoma of the bladder: a retrospective experience. Cancer 2008;113:2471-2477.
[4]Von der Maase H, Hansen SW, Roberts JT, et al. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. J Clin Oncol 2000;18:3068-3077.
[5]Griffiths G, Hall R, Sylvester R, et al. International phase III trial assessing neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: long-term results of the BA06 30894 trial. J Clin Oncol 2011;29:2171-2177.
[6]Advanced Bladder Cancer Meta-analysis Collaboration. Neoadjuvant chemotherapy in invasive bladder cancer: update of a systematic review and meta-analysis of individual patient data advanced bladder cancer (ABC) meta-analysis collaboration. Eur Urol 2005;48:202-205; discussion 205-206.
[7]Advanced Bladder Cancer Meta-analysis Collaboration. Adjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis of individual patient data Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. Eur Urol 2005;48:189-199; discussion 199-201.
[8]Sternberg CN, de Mulder P, Schornagel JH, et al. Seven year update of an EORTC phase III trial of high-dose intensity M-VAC chemotherapy and G-CSF versus classic M-VAC in advanced urothelial tract tumours. Eur J Cancer 2006;42:50-54.
[9]von der Maase H, Sengelov L, Roberts JT, et al. Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. J Clin Oncol 2005;23:4602-4608.
[10]Soto Parra H, Cavina R, Latteri F, et al. Three-week versus four-week schedule of cisplatin and gemcitabine: results of a randomized phase II study. Ann Oncol 2002;13:1080-1086.
[11]Bellmunt J, von der Maase H, Mead GM, et al. Randomized phase III study comparing paclitaxel/cisplatin/gemcitabine and gemcitabine/cisplatin in patients with locally advanced or metastatic urothelial cancer without prior systemic therapy: EORTC Intergroup Study 30987. J Clin Oncol 2012;30:1107-1113.
[12]James ND, Hussain SA, Hall E, et al; BC2001 Investigators. Radiotherapy with or without chemotherapy in muscle-invasive bladder cancer. N Engl J Med 2012;366:1477-1488.
[13]Mitin T, Hunt D, Shipley W, et al. Transurethral surgery and twice-daily radiation plus paclitaxel-cisplatin or fluorouracil-cisplatin with selective bladder preservation and adjuvant chemotherapy for patients with muscle invasive bladder cancer (RTOG 0233): a randomized multicentre phase 2 trial. Lancet Oncol 2013;14:863-872.
[14]Efstathiou JA, Spiegel DY, Shipley WU, et al. Long-term outcomes of selective bladder preservation by combined-modality therapy for invasive bladder cancer: The MGH experience. Eur Urol 2012; 61:705-711.

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

PRINCIPLES OF RADIATION MANAGEMENT OF INVASIVE DISEASE

Carcinoma of the Bladder

- **Precede radiation therapy alone or concurrent chemotherapy and radiation by maximal TUR of the tumor when safely possible.**
- **Simulate and treat patients when they have an empty bladder.**
- **Use multiple fields from high-energy linear accelerator beams.**
- **For invasive tumors, consider low-dose preoperative radiation therapy prior to segmental cystectomy (category 2B).**
- **Concurrent chemotherapy and radiation therapy or radiation therapy alone is most successful for patients without hydronephrosis and without extensive carcinoma in situ associated with their muscle-invading tumor.**
- **For patients with stage Ta, T1, or Tis, external beam radiation therapy (EBRT) alone is rarely appropriate. For patients with recurrent Ta-T1 disease usually following BCG therapy but without extensive Tis who are not candidates for cystectomy, concurrent chemotherapy and radiation therapy may be considered as a potentially curative alternative to radical cystectomy, which is the standard treatment by NCCN Guidelines.**
- **Treat the whole bladder with or without pelvic lymph nodes with 40 to 45 Gy and then boost the bladder tumor to a total dose up to 66 Gy excluding, if possible, normal areas of the bladder from the high-dose volume.**
- **When irradiating the bladder only or bladder tumor boost, consider daily image guidance.**
- **Concurrent chemotherapy with radiation therapy is encouraged for added tumor cytotoxicity, and can be given without increased toxicity over radiation therapy alone. Concurrent 5-FU and mitomycin C can be used instead of cisplatin in patients with low or moderate renal function. Such therapy is optimally given by dedicated multidisciplinary teams.**
- **Concurrent chemotherapy with radiation therapy or radiation therapy alone should be considered as potentially curative therapy for medically inoperable patients or for local palliation in patients with metastatic disease.**
- **When giving palliative radiation for metastatic bladder cancer or for recurrent pelvic tumor, combining radiation with radiosensitizing chemotherapy should be considered. See BL-G 3 of 4 for agents. Chemotherapy should not be used concurrently with high-dose (>3 Gy per fraction) palliative radiation.**

Continued on next page

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.

PRINCIPLES OF RADIATION MANAGEMENT OF INVASIVE DISEASE

Carcinoma of the Urethra:

- **Data support the use of radiation therapy for urothelial carcinoma and squamous cell carcinoma of the urethra (case series and experience treating these carcinomas arising from other disease sites); radiation can also be considered for adenocarcinomas of the urethra.**
- **Definitive Radiation Therapy (organ preservation)**
  - **cT2 cN0**
    - ◊ **66 to 70 Gy EBRT delivered to gross disease with a margin to encompass areas of potential microscopic spread. Concurrent chemotherapy is encouraged for added tumor cytotoxicity.**
    - ◊ **Strongly consider prophylactic radiation treatment of regional-nodal basins (inguinal and low pelvic nodes for female and distal male tumors; pelvic lymph nodes for proximal male tumors).**
  - **cT3-T4, or lymph node positive**
    - ◊ **45 to 50.4 Gy EBRT delivered to gross disease with a margin to encompass areas of microscopic spread and to regional-nodal basins (inguinal and low pelvic nodes for female and distal male tumors; pelvic lymph nodes for proximal male tumors). Boost gross primary disease to 66 to 70 Gy and gross nodal disease to 54 to 66 Gy, if feasible. Dose delivered to gross nodal disease may be limited secondary to normal tissue dose constraints. Concurrent chemotherapy should be administered for added tumor cytotoxicity.**
  - **Postoperative Adjuvant Radiation Therapy**
    - ◊ **Treatment field should encompass areas at risk for harboring residual microscopic disease based on pathologic findings at resection and may include resection bed, inguinal lymph nodes, and pelvic lymph nodes. Areas at risk for harboring residual microscopic disease should receive 45 to 50.4 Gy EBRT. Involved resection margins and areas of extranodal extension should be boosted to 54 to 60 Gy if feasible based on normal tissue constrains. Areas of gross residual disease should be boosted to 66 to 70 Gy, if feasible based on normal tissue constrains. Concurrent chemotherapy should be considered for added tumor cytotoxicity.**

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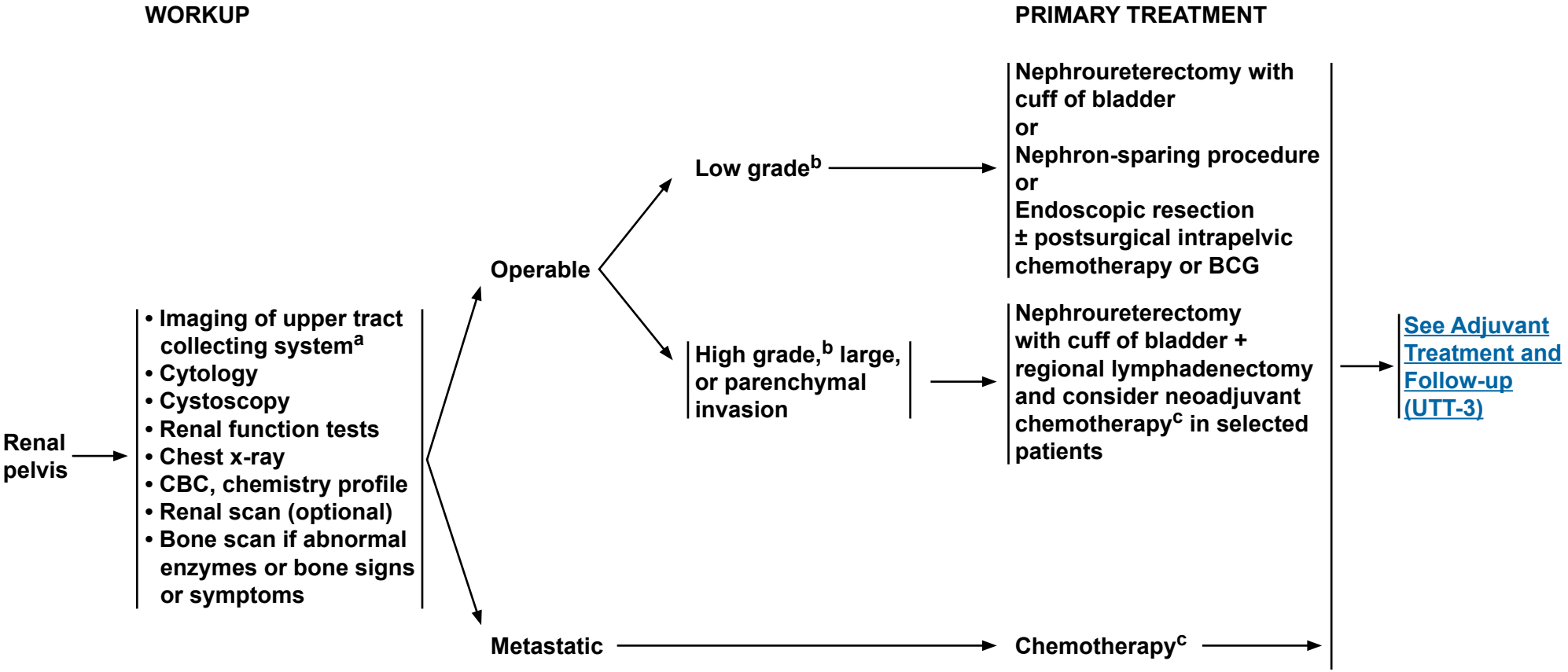
NCCN Guidelines Version 2.2015
Upper GU Tract Tumors

NCCN Guidelines Index
Bladder Cancer TOC
Discussion



[a]Imaging may include one or more of the following: CT urography, renal ultrasound or CT without contrast with retrograde pyelogram, ureteroscopy, or MRI urogram.
[b]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).
[c]See Principles of Chemotherapy Management (BL-G).

Note: All recommendations are category 2A unless otherwise indicated.
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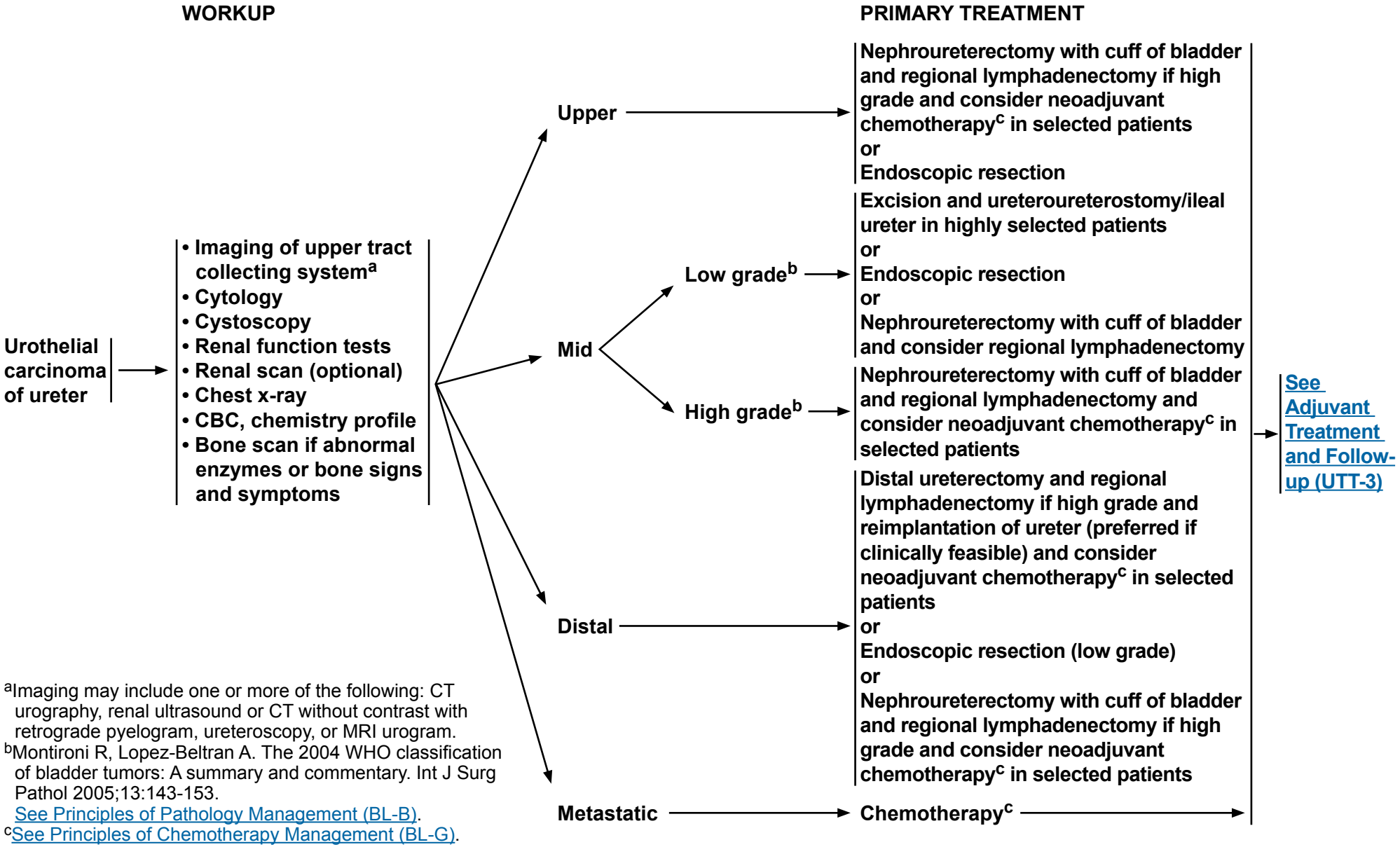
NCCN Guidelines Version 2.2015
Upper GU Tract Tumors

NCCN Guidelines Index
Bladder Cancer TOC
Discussion



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[b]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).

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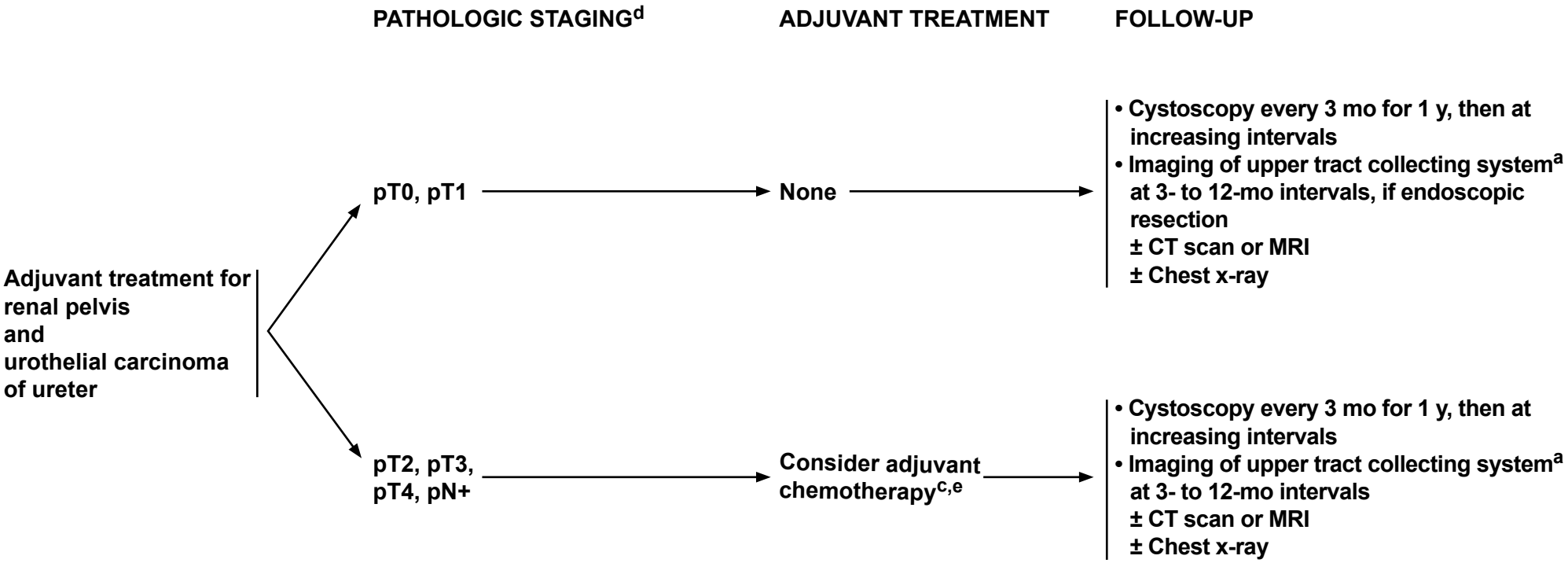

[a]Imaging may include one or more of the following: CT urography, renal ultrasound or CT without contrast with retrograde pyelogram, ureteroscopy, or MRI urogram.
[c]See Principles of Chemotherapy Management (BL-G).
[d]The modifier "p" refers to pathologic staging based on cystectomy and lymph node dissection.
[e]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.

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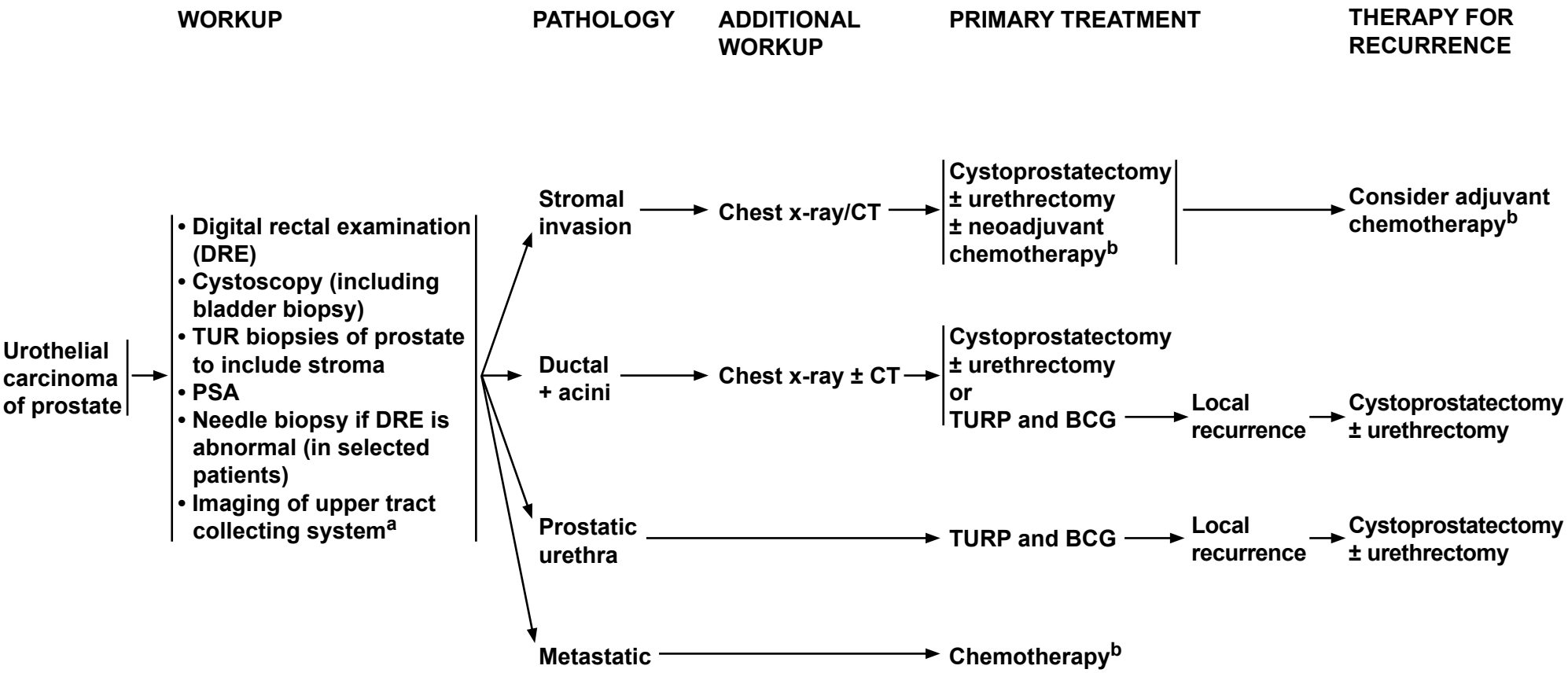
NCCN Guidelines Version 2.2015
Urothelial Carcinoma of the Prostate

NCCN Guidelines Index
Bladder Cancer TOC
Discussion



[a]Imaging may include one or more of the following: CT urography, renal ultrasound or CT without contrast with retrograde pyelogram, ureteroscopy, or MRI urogram.
[b]See Principles of Chemotherapy Management (BL-G).

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NCCN Guidelines Version 2.2015
Primary Carcinoma of the Urethra

NCCN Guidelines Index
Bladder Cancer TOC
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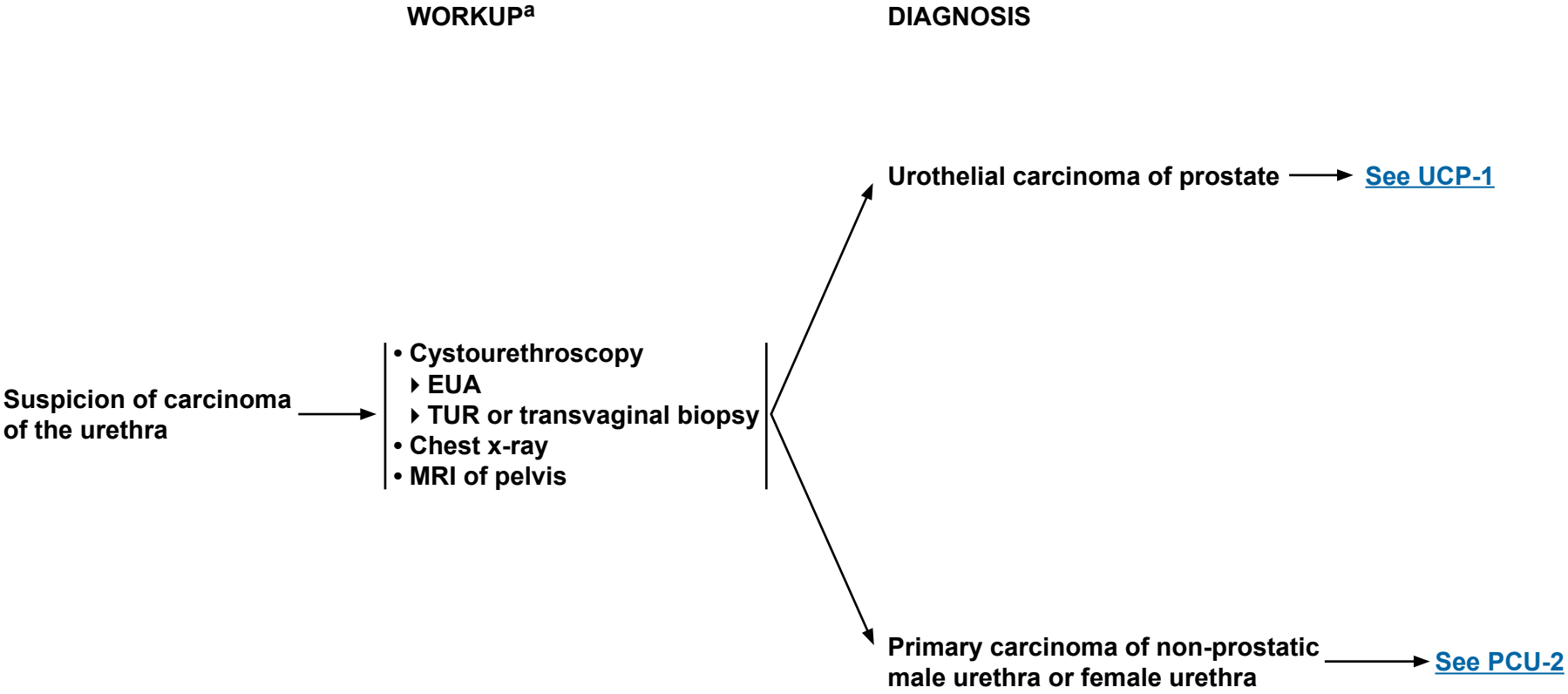

[a]Referral to a specialized center is recommended.

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.

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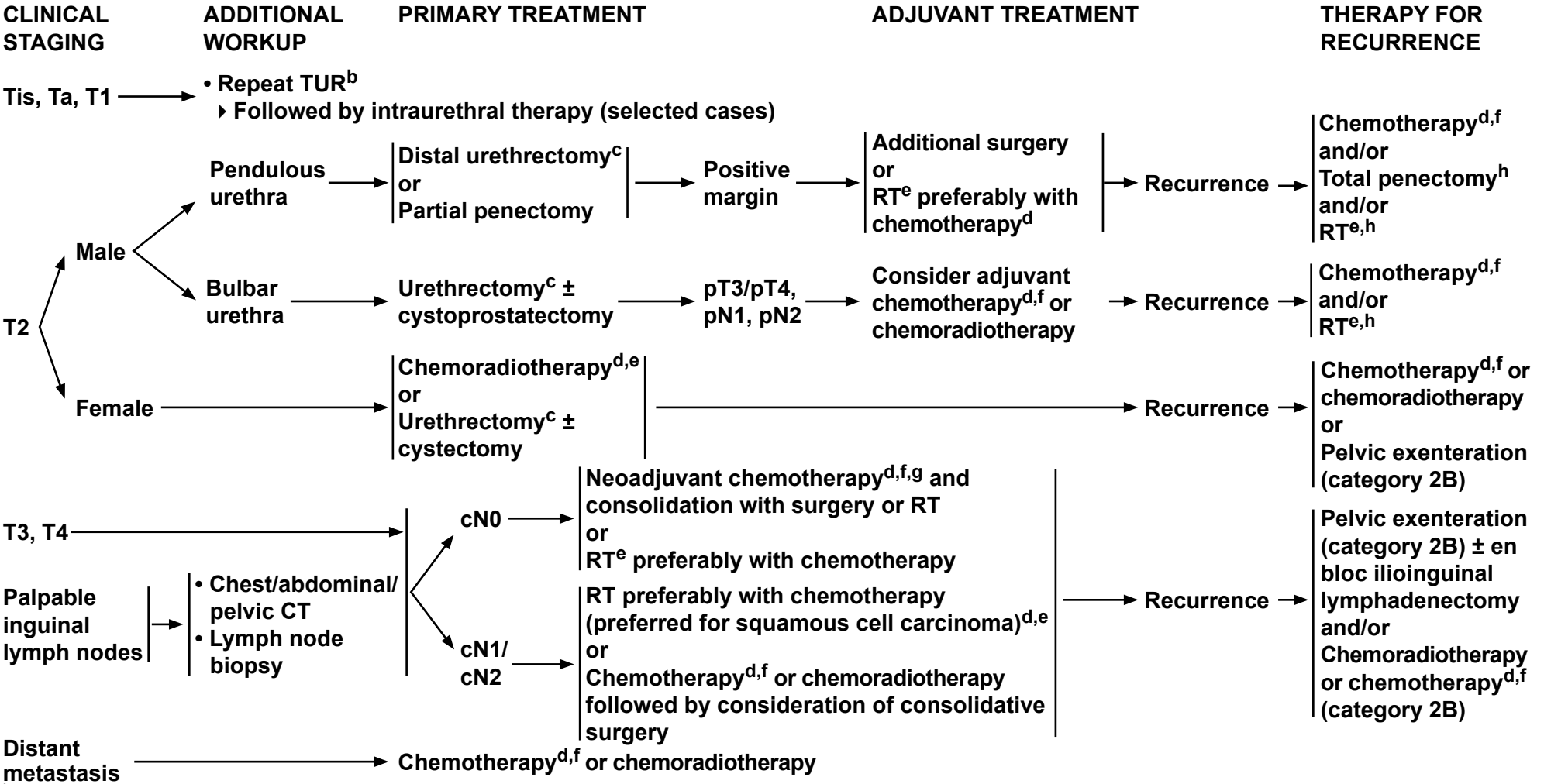
NCCN Guidelines Version 2.2015
Primary Carcinoma of the Urethra

NCCN Guidelines Index
Bladder Cancer TOC
Discussion



[b] In patients with a prior radical cystectomy or a cutaneous diversion, consider a total urethrectomy.

[c] Consider neoadjuvant chemotherapy (category 2B) or chemoradiation.

[d] See Principles of Chemotherapy Management (BL-G) and Non-Urothelial Cell Carcinoma of the Bladder (BL-D).

[e] See Principles of Radiation Management of Invasive Disease- Carcinoma of Urethra (BL-H 2 of 2).

[f] Chemotherapy regimen based on histology. (Dayyani F, Pettaway C, Kamat A, et al. Retrospective analysis of survival outcomes and the role of cisplatin-based chemotherapy in patients with urethral carcinomas referred to medical oncologists. Urol Oncol 2013;31:1171-1177.)

[g] Data support neoadjuvant chemotherapy only for urothelial carcinoma.

[h] Consider for local recurrence (± chemotherapy).

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

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

ANATOMIC STAGE/PROGNOSTIC GROUPS

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	N1-3	M0
	Any T	Any N	M1

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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 Urological 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.

Table 2

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

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Papillary noninvasive carcinoma
Tis	Carcinoma in situ
T1	Tumor invades subepithelial connective tissue
T2	Tumor invades the muscularis
T3	(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
T4	Tumor invades adjacent organs, or through the kidney into the perinephric fat.

Regional Lymph Nodes (N)*

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis 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

* Note: Laterality does not affect the N classification.

Distant Metastasis (M)

M0	No distant metastasis
M1	Distant metastasis

ANATOMIC STAGE/PROGNOSTIC GROUPS

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

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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 Urological 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.

Table 3

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

Primary Tumor (T) (Male and Female)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Noninvasive papillary, polypoid, or verrucous carcinoma
Tis	Carcinoma in situ
T1	Tumor invades subepithelial connective tissue
T2	Tumor invades any of the following: corpus spongiosum, prostate, periurethral muscle
T3	Tumor invades any of the following: corpus cavernosum, beyond prostatic capsule, anterior vagina, bladder neck
T4	Tumor invades other adjacent organs

Regional Lymph Nodes (N)

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 node more than 2 cm in greatest dimension, or in multiple nodes

Distant Metastasis (M)

M0	No distant metastasis
M1	Distant metastasis

Urothelial (Transitional Cell) Carcinoma of the Prostate

Tis pu	Carcinoma in situ, involvement of the prostatic urethra
Tis pd	Carcinoma in situ, involvement of the prostatic ducts
T1	Tumor invades urethral subepithelial connective tissue
T2	Tumor invades any of the following: prostatic stroma, corpus spongiosum, periurethral muscle
T3	Tumor invades any of the following: corpus cavernosum, beyond prostatic capsule, bladder neck (extraprostatic extension)
T4	Tumor invades other adjacent organs (invasion of the bladder)

ANATOMIC STAGE/PROGNOSTIC GROUPS

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

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Table 3 (Continued)

American Joint Committee on Cancer (AJCC)
TNM Staging System for Urethral Carcinoma (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 Urological 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 classification applies to urothelial (transitional cell), squamous, and glandular carcinomas of the urethra and to urothelial (transitional cell) carcinomas of the prostate and prostatic urethra. There should be histologic or cytologic confirmation of the disease.

Discussion

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Table of Contents

Overview

An estimated 74,000 new cases of urinary bladder cancer will be diagnosed in the United States (56,320 men and 17,680 women) in 2015.[1] Bladder cancer, the sixth most common cancer, is three times more prevalent in men than in women in the United States. During the same period, approximately 16,000 deaths (11,510 men and 4490 women) will result from bladder cancer. Bladder cancers are rarely diagnosed in individuals younger than 40 years of age. 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 non-muscle-invasive tumors, for which treatment is directed at reducing recurrences and preventing progression to a more advanced stage. The second group encompasses the muscle-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 quantity and quality of life. Numerous agents with different mechanisms of action have antitumor effects on this disease. The issue remains how to use these agents to achieve the best possible outcome.

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines for Bladder Cancer, an electronic search of the PubMed database was performed to obtain key literature published between August 20, 2013 and August 20, 2014**,** using the following search term: bladder cancer. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.[2]

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

The PubMed search resulted in 96 citations and their potential relevance was examined. The data from key PubMed articles as well as articles from additional sources deemed as relevant to these Guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

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

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.[3]

Of the other histologic subtypes, 1.4% are adenocarcinomas and 1% are 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 have been reclassified by WHO into 13 histologic variants based on differentiation patterns.[4] The most common variants are squamous, glandular, sarcomatoid, and micropapillary. Urothelial tumors often have a mixture of divergent histologic subtypes, such as urothelial and squamous, adenocarcinoma, and more recently appreciated nested micropapillary and sarcomatoid subtypes.[5] 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 component remains after systemic treatment.

Clinical Presentation and Workup

The most common presenting symptom in patients with bladder cancer is microscopic or gross hematuria, although urinary frequency from irritation or a reduced bladder capacity can also develop. Less commonly, a urinary tract infection is the presenting symptom, or upper tract obstruction or pain may occur in 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 around the time of cystoscopy.

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

TURBT with a bimanual examination under anesthesia (EUA) is performed to resect visible tumor and to sample muscle within the area of the tumor to assess 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 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-muscle-invasive, muscle-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 may 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. Consideration may be given to FDA-approved urinary biomarker testing by fluorescence in situ hybridization or nuclear matrix protein 22 in monitoring for recurrence.[6,7]

Pathology and Natural History

Approximately 70% of newly detected cases are non-muscle-invasive disease— exophytic papillary tumors confined largely to the mucosa (Ta) (70%–75%) or, less often, to the submucosa (T1) (20%–25%) or flat high-grade lesions (CIS, 5%–10%).[8,9] These tumors tend to be friable and have a high propensity for bleeding. Their natural history is characterized by a tendency to recur in the same portion or another part of the bladder, and these recurrences can be either at the same stage as the initial tumor or at a more advanced stage.

Papillary tumors confined to the mucosa or submucosa are generally managed endoscopically with complete resection. Progression to a more advanced stage may result in local symptoms or, less commonly, symptoms related to metastatic disease.

An estimated 31% to 78% of patients with a tumor confined to the mucosa or submucosa will experience a recurrence or new occurrence of urothelial carcinoma within 5 years.[10] These probabilities of recurrence vary as a function of the initial stage and grade, size, and multiplicity. Refining these estimates for individual patients is an area of active research.

Staging and Grading

The most commonly used staging system is the TNM staging system[11] by the 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 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.[12] 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 tumors, and others are classified as high-grade. 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, though the vast majority of clinicians now use the 2004 version. The different classification systems are compared in Table 1: *Principles of Pathology Management*. The 7th edition of the AJCC staging system has replaced the previous 4-grade system to match the current WHO/ISUP-recommended grading system.[11]

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

Non-Muscle-Invasive Disease

Workup and Primary Surgical Treatment

A physical examination usually does not reveal non-muscle-invasive disease. Non-muscle-invasive tumors are divided into noninvasive papillomas or carcinomas (Ta), tumors invading the lamina propria (T1), and noninvasive flat carcinoma (Tis), also termed CIS. 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).

Noninvasive disease may be diagnosed by initial cystoscopy and cytology. Once suspected, imaging of upper tract collecting systems is required. In addition, a pelvic CT or MRI scan should be considered before TURBT if sessile or high-grade disease is suspected.

Endoscopic evaluation has traditionally used white-light cystoscopy (WLC) as part of the diagnosis of non-muscle-invasive bladder cancer. More recently blue-light cystoscopy (BLC) has emerged as an adjunct for diagnosis. BLC identifies malignant cells through the absorption of the photosensitizing drug into the urothelial cytoplasm where it enters hem-biosynthesis metabolism. In normal cells, the photosensitizer is excreted; however, enzymatic abnormalities in malignant cells result in the formation of photoactive porphyrins that remain in the cell and fluorescence with a red emission in the presence of blue light. Earlier studies used the photosensitizer 5-aminolevulinic acid (5-ALA), although more recently hexyl-aminolevulinate (HAL) is the only approved agent.

Several prospective clinical studies have evaluated BLC in conjunction with WLC and found higher detection rates of non-muscle-invasive lesions compared to the use of WLC.[13-18] Particularly CIS, which is often missed by WLC, was detected at a higher rate. A meta-analysis of fluorescence cystoscopy TURBT in non-muscle-invasive bladder cancer included 12 randomized controlled trials with a total of 2258 patients.[19] A lower recurrence rate was observed (OR, 0.5; $P < .00001$) with a delayed time to first recurrence by 7.39 weeks ($P < .0001$). Recurrence-free survival was improved at 1 year (HR, 0.69; $P < .00001$) and at 2 years (HR, 0.65; $P = .0004$). However no significant reduction in the rate of progression to muscle-invasive bladder cancer was seen (OR, 0.85; $P = .39$).

In a meta-analysis from Burger et al, 1345 patients with Ta/T1 or CIS tumors showed improved detection of bladder tumors and a reduction in recurrence.[20] BLC compared to WLC detected more Ta tumors (14.7%; $P < .001$; OR, 4.898; 95% CI, 1.937–12.390) and CIS lesions (40.8%; $P < .001$; OR, 12.372; 95% CI, 6.343–0.924). Importantly 24.9% of patients had at least one additional Ta/T1 tumor detected ($P < .001$) and improved detection was seen in both primary (20.7%; $P < .001$) and recurrent cancer (27.7%; $P < .001$). Another review of the literature included 26 studies with 5-ALA, 15 studies with HAL, and 2 studies that used both methodologies. The results from this review also support improved detection and reduced recurrence but no reduction in disease progression.[21]

HAL-BLC was used in patients with non-muscle-invasive bladder cancer following TURBT plus single-dose intravesical mitomycin C and was compared to patients with WLC receiving mitomycin C.[22] There were no adverse events related to HAL and it was effective in diagnosing CIS (26% by HAL vs. 14% by WLC). However, no significant difference in recurrence was seen at 3 months (20% vs. 17% respectively; $P = .7$) or at 12 months (16% vs. 22%, respectively; $P = .4$) indicating that when best standard of care is used, the addition of HAL does not lower recurrence in newly presenting non-muscle-invasive bladder cancer.

Although data show improved detection and reduced recurrence, this technique does not prevent progression and there is no improvement in recurrence-free survival. Therefore, BLC may have the greatest advantage in detecting difficult-to-visualize tumors (eg, CIS tumors) that may be missed by WLC but has more limited applicability in disease monitoring. Other impediments to BLC include the need for appropriate expertise and equipment to employ this new technology. The limitations of BLC require judicious application of this additional diagnostic tool.

Standard treatment for Ta, T1, and Tis is TURBT.[23] It is used to diagnose, stage, and treat visible tumors. TURBT with a bimanual 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 the lesion is sessile or if Tis or high-grade disease is suspected, selected mapping biopsies and transurethral biopsy of prostate must be considered.

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

A second TURBT is performed when a high-grade, T1 tumor and possibly a Ta has been detected at the initial TURBT. This is especially critical in cases in which no muscularis propria was included in the resection.[24] However, depending on the depth of invasion and grade, intravesical therapy may be recommended based on the estimated probability of recurrence (ie, new tumor formation within the bladder) and progression to a more advanced, usually muscle-invasive stage; progression should be considered independently. Cystectomy is rarely considered for a Ta, low-grade lesion.

Intravesical Therapy

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 overused if given to patients who have a low probability of recurrence or progression. Bacillus Calmette-Guérin (BCG) has been shown to be as effective as prophylaxis to prevent bladder cancer recurrences following TURBT. A meta-analysis including 13 randomized controlled trials, totalling 2548 patients, showed that immediate intravesical chemotherapy prolonged the recurrence-free interval by 38% (HR, 0.62; 95% CI, 0.50–0.77; $P < .001$; I(2), 69%) and early recurrences were reduced by 12% (absolute risk reduction, 0.12; 95% CI, -0.18 to -0.06; $P < .001$; I(2), 0%).[25] However, the study acknowledges a low quality of evidence for these parameters and recommends further investigation. Management of the different histologic subtypes of noninvasive bladder tumors of different grades is outlined in subsequent sections.

Duration of maintenance BCG remains a question of debate. Most studies continue BCG maintenance for 3 years. In an evaluation of randomized controlled trials and meta-analyses, limited evidence was found for 1 year of BCG maintenance.[26] The data that were available suggest that 1 year may be suitable for patients at intermediate risk, but without more data, 3 years of BCG maintenance remains the

recommendation. Both intravesical gemcitabine and BCG have been used in patients with non-muscle-invasive bladder cancer as adjuvant therapies. A prospective, randomized phase II trial compared the quality of life in patients receiving either BCG (n = 59) or intravesical gemcitabine (n = 61) and found no significant difference as measured by the quality-of-life superficial bladder cancer–specific 24 Questionnaire or the EORTC Quality of Life Questionnaire Core 30.[27] There were more frequent local and systemic side effects in the BCG arm; however, they were mild to moderate and the treatment was well-tolerated in both groups.

Although BCG is effective, concerns remain regarding potential severe local and systemic side effects as well as the limited availability of BCG. In a phase III study, 1316 patients with intermediate- or high-risk Ta, T1 papillary carcinoma of the bladder were randomized to receive either reduced- (one-third) dose or full-dose BCG for either 1 or 3 years of maintenance.[28] Among all 4 groups, the percentage of patients with greater than or equal to 1 side effect was similar (P = .41). Studies using the one-third dose reduced BCG have shown that this is an effective alternative though side effects remain similar.

cTa, Low-Grade Tumors

TURBT is the standard treatment for cTa, low-grade tumors. Although a complete TURBT alone can eradicate cTa low-grade tumors, these tumors have a relatively high risk for recurrence. Therefore, after TURBT, the panel recommends observation and to strongly consider administering a single dose of immediate intravesicular chemotherapy (not immunotherapy) within 24 hours of resection. A meta-analysis of 7 randomized trials demonstrated a decreased risk of recurrence by 11% (from 48% down to 37%) following immediate intravesical therapy in patients having either single or multiple tumors.[29] Later studies had mixed results, with two reporting a decrease in recurrence and one finding no advantage.[30-32] The immediate intravesical chemotherapy may be followed by a 6-week induction of intravesical chemotherapy. Mitomycin C is the most commonly used agent. Immunotherapy is not recommended in these patients.

The need for adjuvant therapy depends on the patient prognosis. If the patient has a low risk for recurrence, a single immediate intravesical treatment may be sufficient. Factors to consider include the size, number, T category, and grade of the tumor(s), as well as concomitant CIS and prior recurrence.[10] Meta-analyses have confirmed the efficacy of adjuvant intravesical chemotherapy in reducing the risk of recurrence.[33,34] Immediate intravesical treatment should be avoided 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. Restaging TURBT detected residual disease in 27% of Ta patients when muscle was present in the original TURBT.[35] In the absence of muscularis propria in the initial TURBT specimen, 49% of patients with superficial disease will be understaged versus 14% if muscle was present.[24] Repeat resection is recommended if there is incomplete resection, or is strongly considered if there is no muscle in the specimen.

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

Follow-up is recommended, with a urinary cytology and cystoscopy at 3- to 6-month intervals for the first 2 years, and at increasing intervals as appropriate thereafter. Imaging of the upper tract should be considered every 1 to 2 years for high-grade tumors. Urine molecular tests for urothelial tumor markers are now available.[40] Most of these tests have a better sensitivity for detecting bladder cancer than urinary cytology, but specificity is lower. However, it remains unclear whether these tests offer additional information that is useful for detection and management of non-muscle-invasive bladder tumors. Therefore, the panel considers this to be a category 2B recommendation.

cT1 Tumors

T1 tumors are those that invade subepithelial connective tissue (also referred to as lamina propria). Based on the histologic differentiation, most cT1 lesions are high grade and considered to be potentially dangerous with a higher risk for recurrence and progression. These tumors may occur as solitary lesions or as multifocal tumors with or without an associated in situ component.

These tumors are also treated with a complete endoscopic resection. In patients with high-risk disease, especially if the complete resection is uncertain due to tumor size and location, lack of muscle in the specimen, presence of lymphovascular invasion, or inadequate staging, repeat TURBT is strongly advised.[41] This is supported by a trial that prospectively randomized 142 patients with pT1 tumors to a second TURBT within 2 to 6 weeks of the initial TURBT or no repeat TURBT.[42] All patients received adjuvant intravesical therapy. Although overall survival was similar, the 3-year recurrence-free survival was significantly higher in the repeat TURBT arm versus the control arm (69% vs. 37%, respectively), especially among patients with high-grade tumors.

Within the category of T1 disease, a particularly high-risk stratum can be identified: multifocal lesions, tumors associated with vascular invasion, or lesions that recur after BCG treatment. There are 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.[43] Therefore, cystectomy rather than repeat TURBT is recommended for high-risk tumors.

If residual disease is found after a second resection, immunotherapy with BCG (category 1 recommendation) or cystectomy is recommended. If no residual disease is found after the second resection, intravesical therapy with BCG (preferred; category 1 recommendation) or mitomycin C (category 2A) is recommended. Observation may be reasonable in very highly select cases where small-volume tumors had limited lamina propria invasion and no CIS.[44,45] Follow-up is similar to that for high-grade Ta disease.

Tis

Primary Tis (CIS) is a high-grade lesion that is believed to be a precursor of invasive bladder cancer. Standard therapy for this lesion is resection followed by intravesical therapy with BCG. 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 (ie, 3 months) after

the start of therapy. If the patient is unable to tolerate BCG, intravesical mitomycin C may be administered. Follow-up is similar to that for cT1 and cTa (high-grade) tumors.

Posttreatment Recurrent or Persistent cTa, cT1, and Tis Disease

Based on Cystoscopy Results

Patients under observation after initial TURBT, who show a documented recurrence by positive cystoscopy results, should undergo another TURBT followed by adjuvant intravesical therapy based on the stage and grade of the recurrent lesion, and then followed at 3-month intervals.

Recurrence Following Intravesical Treatment

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 two consecutive induction courses should be given. 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. For patients who have Tis or cTa disease after TURBT, 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.[46] In a recent phase II multicenter study of non-muscle-invasive bladder cancer that recurred following 2 courses of BCG, intravesical gemcitabine demonstrated activity that was relegated to high-risk non-muscle-invasive bladder cancer.[47] In the 47 patients with evaluable response, 47% had disease-free survival at 3 months. The 1-year RFS was 28% with all cases except for 2 attributed to the high-risk group. The 2-year RFS was 21%. Intravesical gemcitabine had some activity in the high-risk group, and may be an option if a candidate is not eligible for a cystectomy; however, the study results indicate that cystectomy is preferred when possible. Similarly, for patients with recurrence of high-grade cT1 disease after TURBT and induction BCG, cystectomy is the main option.[48] However, non-surgical candidates might consider concurrent chemoradiation, change of the intravesical agent, or a clinical trial.

For patients showing no residual disease at the follow-up cystoscopy, whether 1 or 2 courses of induction therapy were administered, maintenance therapy with BCG is optional. This recommendation is based on findings that an induction course of intravesical therapy followed by a maintenance regimen produced better outcomes than intravesical chemotherapy.[36,37,49-52] Malmstrom et al[53] performed a meta-analysis including 9 trials in 2820 patients with non-muscle-invasive bladder cancer. They report that mitomycin C is superior to BCG without maintenance in preventing recurrence, but inferior to BCG in trials with maintenance.

While the optimal maintenance regimen has not been established, most patients undergo maintenance for 1 to 3 years. The duration is often limited by toxicity. A study of 1355 patients with a median follow-up of 7.1 years found no benefit in 3 years of maintenance BCG compared to 1 year for intermediate-risk patients.[54] In high-risk patients, 3-year maintenance BCG reduced recurrence compared to 1-year maintenance, but did not impact progression or survival. Although a few NCCN Member Institutions do not routinely administer maintenance BCG, panelists agree that it should be an option.

Based on Cytology Results

In patients without a documented recurrence but with positive cytology and negative cystoscopy and imaging, TURBT must be performed with directed or selected mapping biopsies including transurethral biopsies of the prostate. In addition, cytology of the upper tract must be

evaluated and ureteroscopy may be considered for detecting tumors of the upper tract.

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

If transurethral biopsy of the prostate is positive, the treatment is described below under *Urothelial Carcinomas of the Prostate*. If cytology of the upper tract and/or ureteroscopy results is positive, then the treatment is described below in *Upper Genitourinary Tract Tumors*.

If the transurethral biopsies of the bladder and prostate are negative, then follow-up at 3-month intervals is recommended and maintenance therapy with BCG is preferred if prior BCG was given. If the cytology of the upper tract and uteroscopy is negative, follow-up at 3-month intervals is recommended.

Muscle-Invasive Disease

Workup and Primary Surgical Treatment

Before any treatment is advised, several workup procedures are recommended to accurately determine clinical staging. Laboratory studies, such as a complete blood cell count and chemistry profile, including alkaline phosphatase, 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 phosphatase; and imaging of the upper tracts with a CT or MRI scan of the abdomen and pelvis. Imaging studies help assess the extent of local tumor invasion and the spread to lymph nodes or distant organs.[55] CT and MRI may be used to assess local invasion. Unfortunately, CT scans, ultrasound, and MRI cannot accurately predict the true depth of invasion.

TURBT is the initial treatment for all muscle-invasive disease. The goal of the TURBT is to correctly identify the stage; therefore, bladder muscle must be included in the resection biopsies. The overwhelming majority of muscle-invasive tumors are high-grade urothelial carcinomas. Further treatment following initial TURBT is required for muscle-invasive tumors. Different treatment modalities are discussed below. These include radical cystectomy, partial cystectomy, neoadjuvant or adjuvant therapy, bladder-preserving approaches, and chemotherapy for advanced disease.

Radical Cystectomy

The appropriate surgical procedure involves a cystoprostatectomy in men and a cystectomy and commonly a hysterectomy in women, 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.

Unfortunately, the accuracy of the staging cystoscopy and TURBT is modest, with under-staging frequently encountered. 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 a lower pelvic recurrence rate.[56-60] Patient factors that may preclude a PLND include severe scarring secondary to previous treatments or surgery, advanced age, or severe comorbidities.

Partial Cystectomy

In fewer than 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 (ie, positive nodes or perivesical tissue involvement), similar to that for patients who undergo a radical cystectomy.

Neoadjuvant Chemotherapy

Increasing data support the role of neoadjuvant chemotherapy before cystectomy for T2 and T3 lesions.[61-63] Two randomized trials showed a survival benefit with neoadjuvant chemotherapy, particularly in patients with clinical T3 disease (palpable mass during EUA or unequivocal mass on CT).[61,62] Grossman et al[61] randomized 307 patients with muscle-invasive bladder cancer to radical cystectomy alone or 3 cycles of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) followed by radical cystectomy. Neoadjuvant chemotherapy increased median survival (77 months vs. 46 months, $P = .06$) and lowered the rate of residual disease (15% vs. 38%, $P < .001$) with no apparent increase in treatment-related morbidity or mortality. Another trial randomized 196 patients with invasive bladder cancer to 2 cycles of neoadjuvant MVAC before radical cystectomy or cystectomy only.[64] Neoadjuvant chemotherapy resulted in more patients achieving pT0 than cystectomy alone (34% vs. 9%; $P < .01$). Overall survival favored the neoadjuvant group, although it did not reach statistical significance. In a meta-analysis of 11 trials involving 3005 patients, platinum-based neoadjuvant chemotherapy was associated with improved 5-year overall and disease-free survivals (5% and 9% absolute improvement, respectively).[65]

In a multicenter prospective phase II trial, patients with cT2 to cT4a and N0 or N1 muscle-invasive bladder cancer were given 3 cycles of dose-dense MVAC (ddMVAC) with pegfilgrastim followed by radical cystectomy and lymph node dissection.[66] ddMVAC was anticipated to have a safer profile, a shorter time to surgery, and a similar pathologic CR rate compared to historical control data for neoadjuvant cisplatin-based chemotherapy. Patients receiving ddVAC had no grade 3 or 4 renal toxicities and no toxicity-related deaths. Grade 1 or 2 treatment-related toxicities were seen in 82% of patients. Additionally, the median time to cystectomy was 9.7 weeks. Early study data support the value of ddVAC as neoadjuvant treatment in muscle-invasive bladder cancer, though data should be interpreted cautiously due to the small sample size (n=44).[66]

Another alternative neoadjuvant chemotherapy regimen was evaluated in an international, multicenter, randomized trial (BA06 30894) that investigated the effectiveness of neoadjuvant cisplatin, methotrexate, and vinblastine (CMV) in 976 patients.[67] At a median follow-up of 8 years, patients receiving CMV before surgery had a 16% reduction in mortality risk (HR, 0.84; 95% CI, 0.72–0.99; *P* = .037).

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.[68] Many trials showing a survival benefit were not randomized, raising the question of selection bias in the analysis of outcomes. A meta-analysis of 6 trials found a 25% mortality reduction with adjuvant chemotherapy, but the authors pointed out several limitations of the data and concluded that evidence is insufficient for treatment decisions.[69] Studies showed a survival advantage from therapy with cyclophosphamide, doxorubicin, and cisplatin (CAP) and with MVAC or methotrexate, vinblastine, epirubicin, and cisplatin (MVEC).[70-72] However, methodologic issues question the applicability of these studies to all patients with urothelial tumors. In the MVEC trial, patients who experienced relapse in the control arm did not undergo chemotherapy, which is not typical of more contemporary series. A randomized phase III study in 194 patients reported no difference in overall or disease-free survival between patients receiving adjuvant gemcitabine and cisplatin (GC) and those receiving chemotherapy at relapse.[73]

Although evidence for adjuvant therapy is not as strong as for neoadjuvant therapy, current data suggest that adjuvant chemotherapy may delay recurrences, which may justify the administration of chemotherapy in those at a high risk for relapse.[74] A minimum of three cycles of a cisplatin-based combination, such as MVAC, or more commonly now GC, may be used in patients undergoing adjuvant therapy. Regimen and dosing recommendations are mainly based on studies in advanced disease. Carboplatin should not be substituted for cisplatin in the perioperative setting. No data support the use of adjuvant chemotherapy for non-urothelial carcinomas, regardless of stage.

Patients with tumors that are pT2 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% 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.

Adjuvant Radiation

Data on radiation or chemoradiation following cystectomy are scarce and further prospective studies are needed to evaluate their efficacy and potential toxicity. One older randomized study of 236 patients with pT3a to pT4a bladder cancer demonstrated improvement in 5-year disease-free survival and local control compared to surgery alone.[75] A retrospective series similarly demonstrated improved cancer-specific survival with adjuvant radiotherapy for patients with pT2 to T4a disease.[76] Because local recurrence rates are high for some patients after cystectomy (32% for pT3-T4 patients and 68% for patients with positive surgical margins),[58] adjuvant radiation therapy is reasonable to consider in these patients. Radiotherapy to 40 to 45 Gy, with or without concurrent cisplatin, could be used.

A phase III, multicenter, randomized trial evaluated the safety and non-inferiority of reduced high-dose volume radiation to standard volume radiation.[77] A radiation dose equivalent to 80% of the standard dose (standard dose defined as either 55 Gy/20 fractions over 4 weeks or 64 Gy/32 fractions over 6.5 weeks) was given to the uninvolved areas. Patients receiving concurrent chemotherapy received 5-FU (500 mg/m^2/24 hours continuous infusion during fractions 1 through 5 and fractions 16 through 20 of radiation therapy) and MMC (12 mg/m^2 intravenous bolus dose on day 1). Primary endpoints of late toxicity and time to locoregional recurrence were measured. No statistical difference between groups was seen in late side effects; non-inferiority could not be concluded, but the low rates of relapse and toxicity suggest that reduced radiation may be a treatment option. The safety of radiation doses, especially in the setting of a neobladder, needs to be further studied.

Since pT3a to pT4a patients are also at high risk of developing metastatic disease, they are also treated with first-line multidrug chemotherapy if their renal function is adequate for cisplatin. Radiation and multidrug chemotherapy should not be given concurrently.

Bladder-Preserving Options

Within the categories of T2 and T3a urothelial carcinomas, selected patients may be considered for bladder-preserving approaches.[78] Options include aggressive endoscopic TURBT alone, TURBT followed by chemotherapy alone, radiotherapy alone, or a combination of chemotherapy and radiotherapy. Partial cystectomy, also a form of bladder preservation, has been discussed above. No uniform consensus has been 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 to radical cystectomy. It is also endorsed by the International Consultation on Urologic Diseases-European Association of Urology evidence-based guidelines.[79] There is an apparent underutilization of aggressive bladder-preserving therapies for non-cystectomy candidates, especially the elderly and racial minorities.[80] Between 23% and 50% of patients with muscle-invasive bladder cancer who are 65 years of age and older receive no treatment or non-aggressive therapy.

The decision to use a bladder-preserving approach is partially based on the location of the lesion, depth of invasion, size of the tumor, status of the “uninvolved” urothelium, and status of the patient (eg, bladder capacity, bladder function, comorbidities). Patients who are medically fit for radical cystectomy but with hydronephrosis are poor candidates for bladder-sparing procedures.[81,82] If a bladder-sparing approach is considered, the patient should undergo as complete a TURBT of the tumor as possible, an EUA, and a metastatic workup before therapy is initiated.

With any of the alternatives to cystectomy, bladders that appear to be endoscopically free of tumor based on a clinical assessment (cT0) that includes a repeat TURBT are difficult to determine with certainty whether they are in fact pathologically free of tumor (pT0). Up to a third of bladders believed to be free of disease preoperatively after chemotherapy can have residual disease at cystectomy.[83] Conversely, one series reported that all patients who achieved a complete response after radiotherapy with concurrent cisplatin and 5-FU were pT0 on immediate cystectomy.[84] The frequency of residual disease after cytotoxic agents (either radiation or chemotherapy) is lower for patients who present with T2 disease than with T3 disease, which must be

considered when proposing a bladder-sparing approach. When possible, bladder-sparing options should be chosen in the context of clinical trials. After maximal TURBT, close cystoscopic observation alone, chemotherapy alone, radiotherapy alone, or chemotherapy combined with radiotherapy (all also followed by close cystoscopic observation and further treatment, if necessary) are potential treatment options. However, only chemotherapy combined with radiotherapy has been formally evaluated in prospective randomized comparisons[85,86]; the other treatment options are still considered to be investigational.

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

TURBT Alone

TURBT alone may be curative in selected cases that include solitary lesions less than 2 cm in size that have minimally invaded the muscle. These cases should also have no associated in situ component, palpable mass, or associated hydronephrosis.[87]

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

Chemotherapy Following TURBT

Chemotherapy alone is considered to be inadequate without additional treatment to the bladder and remains investigational. Studies showed that the proportions of complete pathologic response in the bladder using neoadjuvant chemotherapy alone were only up to 38%.[61] A higher proportion of bladders can be rendered tumor-free and therefore preserved when chemotherapy is combined with concurrent radiotherapy.

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.[88] Non-randomized studies reported 5- to 10-year overall survival of 69% to 73%; however, the rate of invasive recurrence was 23% to 33%.[83,89] This approach is currently not widely used, but it has the advantages of surgically removing the diseased portion of the bladder and allowing for definitive lymph node staging.

Radiotherapy Following TURBT

Radiotherapy alone is inferior to radiotherapy combined with chemotherapy for patients with an invasive bladder tumor, and is not considered standard for patients who can tolerate combined therapy.[85,86] In a randomized trial of 360 patients, radiotherapy with concurrent mitomycin C and 5-FU improved 2-year locoregional disease-free survival from 54% (radiotherapy alone) to 67% (P = .01), and 5-year overall survival from 35% to 48% (P = .16), without increasing grade 3-4 acute or late toxicity.[86] Hence, radiotherapy alone is only indicated for

those who cannot tolerate a cystectomy or chemotherapy because of medical comorbidities.

Radiotherapy with Concurrent Chemotherapy Following TURBT

Several groups have investigated the combination of concurrent or sequential chemotherapy and radiotherapy after TURBT. First, an endoscopic resection that is as complete as possible is performed. Incomplete resection is an unfavorable prognostic factor for the ability to preserve the bladder and for survival.[90,91]

Radiation Therapy Oncology Group protocol 89-03 compared concurrent cisplatin and radiotherapy with versus without 2 cycles of induction MCV (methotrexate, cisplatin, and vinblastine) chemotherapy.[82] No difference in complete clinical response or 5-year overall survival was observed between the treatment arms. Other studies also reported no significant survival benefit for neoadjuvant chemotherapy before bladder-preserving chemotherapy with radiation therapy.[91,92]

Radiotherapy with concurrent cisplatin-based chemotherapy as a radiosensitizer is the most common and well-studied chemoradiation method used to treat muscle-invasive bladder cancer.[78,81,82,84-86,90,91] 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 re-evaluation 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 consolidation 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 previously outlined.

Results from several prospective trials have demonstrated the effectiveness of this approach. In RTOG 89-03 in which 123 patients with clinical stage T2-T4a were treated with radiotherapy plus concurrent cisplatin, with or without induction MCV chemotherapy, 5-year overall survival was approximately 49% in both arms.[82] RTOG 95-06 treated 34 patients with twice-daily irradiation and concurrent cisplatin and 5-FU. Three-year overall survival was 83%.[93] RTOG 97-06 treated 47 patients with twice-daily irradiation and concurrent cisplatin; patients also received adjuvant chemotherapy with CMV.[94] Three-year overall survival was 61%. RTOG 99-06 treated 80 patients using twice-daily irradiation plus cisplatin and paclitaxel, followed by adjuvant cisplatin and gemcitabine. Five-year overall survival was 56%.[95] In these trials, the complete response rate achieved ranged from 59% to 81%. An alternative approach involves twice-daily radiation with concurrent paclitaxel plus cisplatin or 5-FU plus cisplatin.[96]

Currently, the following radiosensitizing regimens are reasonable for bladder-preserving chemoradiation following a maximal TURBT: cisplatin (category 2A); cisplatin plus 5-FU (category 2A); 5-FU plus mitomycin C (category 2A); cisplatin plus paclitaxel (category 2B); and low-dose gemcitabine (category 2B). Enrollment in a clinical trial is appropriate if available.

Up to about 80% of long-term survivors maintain an intact bladder, while other patients ultimately require radical cystectomy.[81,82,90-95] A combined analysis of survivors from these 4 trials, with median follow-up of 5.4 years, showed that combined-modality therapy was associated with low rates of late grade 3 toxicity (5.7% genitourinary and 1.9% gastrointestinal).[97] No late grade 4 toxicities or treatment-related deaths were recorded.

Chemotherapy for Advanced Disease

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

Cisplatin, the taxanes, and gemcitabine are first-line chemotherapy options for metastatic disease. GC[98,99] and ddMVAC[100,101] are commonly used in combinations that have shown clinical benefit. A large, international, phase III study randomized 405 patients with locally advanced or metastatic disease to GC or standard MVAC.[102] At a median follow-up of 19 months, overall survival and time to progression were similar in the two arms. Less toxic deaths were recorded among patients receiving GC compared to MVAC (1% vs. 3%), although this did not reach statistical significance. A 5-year update analysis confirmed that GC was not inferior to MVAC in terms of survival (overall survival, 13.0% vs. 15.3%; progression-free survival, 9.8% vs. 11.3%, respectively).[99] Another large, randomized, phase III trial compared ddMVAC to standard MVAC.[100,101] At a median follow-up of 7.3 years, 24.6% of patients were alive in the ddMVAC cohort compared with 13.2% in the standard MVAC cohort. There was one toxic death in each arm, but less overall toxicity was seen in the dose-dense group. From these data, standard MVAC is inferior to ddMVAC in terms of toxicity and efficacy, and is inferior to GC in terms of toxicity; therefore standard MVAC is no longer used. Both GC and ddMVAC with growth factor support are category 1 recommendations for metastatic disease. Alternative first-line regimens also include carboplatin or taxane-based regimens (category 2B) or single agent chemotherapy (category 2B)

The performance status of the patient is a major determinant in the selection of a regimen. Regimens with lower toxicity profiles are recommended in patients with compromised liver or renal status or serious comorbid conditions. In patients with a glomerular filtration rate (GFR) less than 60 mL/min, carboplatin may be substituted for cisplatin. A phase II/III study assessed 2 carboplatin-containing regimens in medically unfit patients (performance status 2).[103] The overall response rate was 42% for gemcitabine plus carboplatin and 30% for methotrexate, carboplatin, and vinblastine. However, the response rates dropped to 26% and 20%, respectively, with increased toxicity among patients who were both unfit and had renal impairment (GFR <60 mL/min).

Taxanes have been shown to be active as both front-line and palliative therapies. Based on these results, several groups are exploring 2- and 3-drug combinations using these agents, with and without cisplatin, as initial therapy. The alternative regimens, including cisplatin/paclitaxel,[104] gemcitabine/paclitaxel,[105] cisplatin/gemcitabine/paclitaxel,[106] carboplatin/gemcitabine/paclitaxel,[107] and cisplatin/gemcitabine/docetaxel,[108] have shown modest activity in patients with bladder cancer in phase I-II trials. A randomized phase III trial was conducted to compare GC and GC plus paclitaxel in 626 patients with locally advanced or metastatic urothelial cancer.[109] The addition of paclitaxel to GC resulted in higher response rates and a borderline overall survival advantage, which was not statistically significant in the intent-to-treat analysis. Analysis of eligible patients only (92%) resulted in a small (3.2 months) but statistically significant

survival advantage in favor of the 3-drug regimen (*P* = .03). There was no difference in progression-free survival. The incidence of neutropenic fever was substantially higher with the 3-drug combination (13.2% vs. 4.3%; *P* < .001). Panelists feel that the risk of adding paclitaxel outweighs the limited benefit reported from the trial.

Although current data are insufficient to recommend the above alternative regimens as routine first-line options, non-cisplatin-containing regimens may be considered in patients who cannot tolerate cisplatin because of renal impairment or other comorbidities (category 2B). The NCCN Panel recommends enrollment in clinical trials of potentially less toxic therapies.

The regimens effective for urothelial carcinoma histologies have limited efficacy for patients with non-urothelial carcinomas. These individuals are often treated based on the identified histology. For example, adenocarcinomas are managed surgically with radical or segmental cystectomy and with individualized adjuvant chemotherapy and radiotherapy for maximum benefit. Pure squamous cell tumors are treated by cystectomy, radiation therapy, or agents commonly used for squamous cell carcinoma of other sites such as 5-FU or taxanes. However, overall experience with chemotherapy in non-urothelial carcinomas is limited.

Independent of the specific regimen used, patients with metastatic disease are re-evaluated after 2 to 3 cycles of chemotherapy, and treatment is continued for 2 more cycles in patients whose disease responds or remains stable. Surgery or radiotherapy may be considered in patients who show a major partial response in an unresectable primary tumor or who have a solitary site of residual disease that is resectable after chemotherapy. In selected series, this approach has been shown to afford a survival benefit. If disease is completely resected, 2 additional cycles of chemotherapy can be considered, depending on patient tolerance. 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. A change in therapy is also advised for 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 depend on what was offered as first line. Docetaxel, paclitaxel, or gemcitabine monotherapy is preferred.[110-113] Other options include: cisplatin, carboplatin, doxorubicin, 5-FU, ifosfamide, pemetrexed, methotrexate, and vinblastine—with modest benefit limited to small phase II trials.[114-118]

Chemoradiation for Advanced Disease

Chemotherapy is sometimes combined with palliative radiation to treat metastases or pelvic recurrence after cystectomy. However, concurrent chemotherapy is inappropriate if high-dose radiation (>3 Gy fractions) is used. The radiosensitizing chemotherapy regimen remains controversial in this setting. Possible options include cisplatin (category 2A); docetaxel or paclitaxel (category 2B); 5-FU with or without mitomycin C (category 2B); capecitabine (category 3); and low-dose gemcitabine (category 2B).

T2, T3, and T4a Tumors

The critical issues in the management and prognosis of these patients are whether a palpable mass is appreciated at EUA and if the tumor has

extended through the bladder wall. Tumors that are organ-confined (T2) have a better prognosis than those that have extended through the bladder wall into the perivesical fat (T3) and beyond. T4a tumors involve the prostatic stroma, uterus, or vagina and are typically surgically managed similar to T3 tumors.

Primary surgical treatment for cT2, cT3, and cT4a lesions with no nodal disease seen on abdominal/pelvic CT or MRI scan is a radical cystectomy and pelvic lymphadenectomy. Based on results from two randomized trials,[61,62] NCCN panelists agree that there is stronger evidence to support neoadjuvant chemotherapy for cT3 disease than for cT2 disease. Therefore, neoadjuvant chemotherapy is recommended for patients with cT3 tumors (category 1) and should be strongly considered for those with cT2 tumors (category 1). If no neoadjuvant chemotherapy was given, postoperative adjuvant chemotherapy is considered based on pathologic risk, such as positive nodes or pT3-T4 lesions (category 2B recommendation).

Partial cystectomy along with neoadjuvant chemotherapy can be considered only in T2 patients with a single tumor in a suitable location and no presence of Tis. Partial cystectomy is not an option for T3 or T4a patients. If no neoadjuvant therapy is given, adjuvant radiotherapy or chemotherapy based on pathologic risk (ie, positive nodes, positive margin, high-grade lesions, pT3-T4 lesions) may be considered (category 2B recommendation).

Bladder preservation strategy with concurrent chemoradiotherapy (category 2B recommendation) is an option in highly selected patients. Candidates for bladder-sparing approaches include patients with tumors present without hydronephrosis and tumors that allow a visibly complete or a maximally debulking TURBT. The overall tumor status should be reassessed 3 weeks after radiation if 40 to 45 Gy was initially administered or 2 to 3 months after if the full dose of 60 to 65 Gy was delivered. If no residual tumor is detected, appropriate options include observation or completion of radiation up to 66 Gy. If tumor is present, cystectomy is the preferred option.

In patients with extensive comorbid disease or poor performance status, treatment options include TURBT alone, concurrent chemoradiation, or radiotherapy alone. Based on high-level evidence, only cisplatin alone or 5-FU and mitomycin C together have shown radiosensitizing with radiation to be superior to radiation alone.[85,86] The overall tumor status should be reassessed 2 to 3 months after treatment. If no tumor is evident, the patient should be observed. If tumor remains, cystectomy is the preferred choice if feasible. Patients who are not surgical candidates should consider completion of radiation with alternative radiosensitizing chemotherapy and/or alternative chemotherapy.

T4b Disease or Positive Nodes

For patients who show no nodal disease on abdominal/pelvic CT or MRI scans or biopsy, the primary treatment recommendation includes 2 to 3 courses of chemotherapy with or without radiotherapy followed by evaluation with TURBT, cystoscopy, and CT scan of the abdomen and pelvis. In highly selected T4a node-negative patients, cystectomy with or without chemotherapy is another primary treatment option. If no evidence of tumor is present after primary chemotherapy, a consolidation chemotherapy regimen with or without radiation may be considered. Alternatively, cystectomy may be a subsequent management option for these patients. If residual disease is noted upon evaluation after primary therapy, chemotherapy with or without radiation can be used. A change in chemotherapy regimen is reasonable. Cystectomy, if feasible, is again an option for patients regardless of their response to primary therapy.

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

Follow-up After Surgery

Results from a meta-analysis of 13,185 patients who have undergone cystectomy reported 0.75% to 6.4% prevalence of upper tract recurrence in these patients.[119] Surveillance by urine cytology detected 7% and upper urinary tract imaging detected 30% of these recurrences.

Follow-up after a cystectomy should include urine cytology, liver function tests, creatinine, and electrolytes every 6 to 12 months for 2 years and then as clinically indicated. Imaging of the chest, upper tracts, abdomen, and pelvis should be conducted every 3 to 6 months for 2 years based on the risk of recurrence and then as clinically indicated. Patients should be monitored annually for vitamin B_{12} deficiency if a continent urinary diversion was created. Consider urethral wash cytology every 6 to 12 months, particularly if Tis was found within the bladder or prostatic urethra.

Follow-up after a partial cystectomy is similar to that for a radical cystectomy, with the addition of monitoring for relapse in the bladder by serial cytologic examinations and cystoscopies (may include selected mapping biopsy) at 3- to 6-month intervals for the first 2 years, then at increasing intervals according to clinician discretion.

For patients who have undergone bladder preservation, there is a risk for recurrence in the bladder or elsewhere in the urothelial tract and distantly. Imaging studies and laboratory testing should be performed as outlined under post-cystectomy follow-up. Additionally, continued monitoring of the urothelium with cystoscopy and urinary cytologies with or without mapping biopsy is a routine part of the management of all cases in which the bladder is preserved. Follow-up intervals are typically every 3 to 6 months for the first 2 years, and then at increasing intervals as appropriate.

Recurrence or Persistent Disease After Surgery

Metastatic disease or local recurrence following cystectomy may be managed with palliative chemotherapy, radiation, or a combination of the two.

A positive cytology with no evidence of disease in the bladder should prompt selective washings of the upper tracts and a biopsy of the prostatic urethra. If the results are positive, patients are managed as described in the sections below.

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

has not undergone radiotherapy, a course of chemoradiotherapy is an alternative. Palliative TURBT is also an option.

Metastatic Disease

About half of all patients relapse after cystectomy depending on the pathologic stage of the tumor and nodal status. Local recurrences account for about 10% to 30% of relapses, whereas distant metastases are more common.

If metastasis is suspected, additional workup to evaluate the extent of the disease is necessary. This includes a chest CT and a bone scan if enzyme levels are abnormal or the patient shows signs or symptoms of skeletal involvement.

If the evidence of spread is limited to nodes, nodal biopsy should be considered and patients should be managed as in the case for T4 disease. Patients who present with disseminated metastatic disease are generally treated with systemic chemotherapy. Management of persistent disseminated disease may involve chemotherapy, radiation, or a combination of the two. Details on the choice of regimens have been discussed above.

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 CT urography, renal ultrasound or CT without contrast with retrograde pyelogram, ureteroscopy, 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 a renal scan or bone scan, may be needed if indicated by the test results or by the presence of specific symptoms.

Primary Treatment

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

Well-differentiated tumors of low grade may be managed with a nephroureterectomy with a bladder cuff, a nephron-sparing procedure through a transureteroscopic approach, or a percutaneous approach with or without postsurgical intrapelvic chemotherapy or BCG. High-grade tumors or those that are large and invade the renal parenchyma are managed through nephroureterectomy with a bladder cuff and regional lymphadenectomy. Decline in renal function following surgery may preclude adjuvant therapy. Hence, in selected patients, neoadjuvant chemotherapy may be considered based on extrapolation of data from bladder cancer series.[61-63] If metastatic disease is documented or associated comorbid conditions are present, treatment

should include systemic chemotherapy with regimens similar to those used for urothelial bladder tumors.

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

Follow-up

Subsequent management is dictated by the extent of disease at surgery. Tumors that are pT0 or pT1 should be followed up with serial cystoscopies at 3-month intervals for the first year and, if negative, every 6 months thereafter. Such tumors should also be followed up with ureteroscopy and upper tract imaging (eg, renal ultrasound or CT without contrast with retrograde pyelogram; CT urography; ureteroscopy; MRI urogram) at 3- to 12-month intervals if endoscopic resection is considered.

Patients with pT2, pT3, pT4, or nodal disease should be considered for adjuvant chemotherapy. 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 resectable ureteral tumors, the primary management is surgery. The specific procedure required varies depending on the location of the tumor (upper, mid, or distal location) and disease extent. Neoadjuvant chemotherapy may be considered in selected patients, such as when the degree of invasiveness is established before definitive surgery.[120]

Tumors that originate in the upper ureter occasionally can be managed endoscopically but more commonly are treated with nephroureterectomy with a bladder cuff plus regional lymphadenectomy for high-grade tumors. 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 or complete ureterectomy and ileal ureter in highly selected patients, endoscopic resection, or nephroureterectomy with a bladder cuff and consideration of regional lymphadenectomy. Larger, high-grade lesions are managed with nephroureterectomy with a bladder cuff 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 bladder cuff, 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 Tumors*) is recommended.

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

Urothelial Carcinomas of the Prostate

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

Workup

The evaluation of a suspected urothelial carcinoma of the prostate includes a digital rectal examination (DRE), cystoscopy with bladder biopsy, and a transurethral biopsy of the prostate that includes the prostatic stroma. Multiple stromal biopsies are 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. Based on data extrapolated from bladder cancer therapy, neoadjuvant chemotherapy may be considered in patients with stromal invasion.[61-63] 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. Local recurrences in patients undergoing TURP and BCG therapy are treated with cystoprostatectomy with or without urethrectomy.

Primary Carcinoma of the Urethra

Primary carcinoma that arises in the urethra is rare. Unlike for bladder cancer, squamous cell carcinoma is the most common histologic subtype for urethral cancer.[121] The 5-year overall survival is 42%.[122,123] Stage and disease location are the most important prognostic factors for male patients, while tumor size and histology are prognostically significant for female patients.[121,123] Unfortunately, there is a lack of robust, prospective data to support treatment decisions due to disease rarity.

Workup

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

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

Treatment

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

Treatment for T2 disease is based on patient gender and tumor location. For male patients with pendulous urethra, a distal urethrectomy or partial penectomy are viable options. Patients may consider neoadjuvant chemotherapy (category 2B) or chemoradiation (category 2B) before a urethrectomy. Patients who have positive margins may undergo additional surgery or radiation preferably with chemotherapy. At recurrence, options include chemotherapy, total penectomy, radiation, or a combination.

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

Initial treatment options for female patients with T2 tumors include chemoradiation or urethrectomy with or without cystectomy. Partial urethrectomy was associated with a high urethral recurrence rate.[124] At recurrence, the patient may receive chemotherapy or chemoradiotherapy (both category 2A) or pelvic exenteration (category 2B).

A multimodal treatment approach (ie, surgery, chemotherapy, radiation) is common for advanced disease. If chemotherapy is used, the choice of regimen should be based on histology. A cohort study reported a 72% response rate with the following treatment scheme before surgery: cisplatin, gemcitabine, and ifosfamide for squamous cell carcinoma; 5-FU, gemcitabine, and cisplatin-based regimens for adenocarcinoma; and MVAC for urothelial tumors.[125] Combined chemoradiation with 5-FU and mitomycin C has shown efficacy in a series of male patients with squamous cell carcinoma of the urethra.[126] Patients receiving salvage surgery after chemoradiation had a higher 5-year disease-free survival rate (72%) than those receiving chemoradiation alone (54%).

Patients with T3 or T4 disease but no clinical nodes should either receive neoadjuvant chemotherapy followed by consolidative surgery or radiation, or radiation preferably with chemotherapy. If positive nodes are present, radiation preferably with chemotherapy is the preferred treatment for squamous cell carcinoma. An alternative option is chemotherapy followed by consideration of consolidative surgery. At recurrence, the patient may undergo pelvic exenteration (category 2B) with or without en bloc ilioinguinal lymphadenectomy. Chemotherapy or chemoradiotherapy, in addition to surgery, is a category 2B option.

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

Non-Urothelial Carcinomas of the Bladder

Approximately 10% of bladder tumors are non-urothelial (non-transitional cell) carcinoma. These pathologic entities include mixed histology, pure squamous, adenocarcinoma, small cell tumors, urachal carcinoma, or primary bladder sarcoma. Depending on the pathologic findings, adjuvant chemotherapy may or may not be recommended. Patients with non-urothelial invasive disease are generally treated with cystectomy, although those with certain urachal tumors require complete urachal resection (en bloc resection of the urachal ligament

with the umbilicus) or may be appropriately treated with partial cystectomy. In patients with non-urothelial carcinomas of any stage, no data support the use of adjuvant chemotherapy, although the risk for relapse may be high. Some of the general principles of management applicable to urothelial carcinomas are appropriate with minor variations. These variations are documented in the algorithm.

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

Summary

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

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

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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