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Bladder Cancer

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Bladder Cancer

Clinical Practice Guidelines in Oncology

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Abstract

Bladder cancer is the fourth most common cancer in the United States. Urothelial carcinoma that originates from the urinary bladder is the most common subtype. These NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) provide recommendations on the diagnosis and management of non-muscle-invasive and muscle-invasive urothelial carcinoma of the bladder. This version of the guidelines provides extensive reorganization and updates on the principles of chemotherapy management. (*JNCCN* 2013;11:446–475)

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.

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

Overview

An estimated 73,510 new cases of urinary bladder cancer will be diagnosed in the United States (55,600 men and 17,910 women) in 2012.¹ Bladder cancer, the fourth most common cancer, is 3 times more common in men than in women in the United States. During the same period, approximately 14,880 deaths (10,510 men and 4,370 women) will result from bladder cancer. Bladder cancers are rarely diagnosed in individuals younger than 40 years. Because the median age of diagnosis is 65 years, medical comorbidities are a frequent consideration in patient management.

The clinical spectrum of bladder cancer can be divided into 3 categories that differ in prognosis, management, and therapeutic goals. The first category consists of non-muscle-invasive tumors, for

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Disclosures for the NCCN Bladder Cancer Panel

At the beginning of each NCCN Guidelines panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Bladder Cancer Panel members can be found on page 475. (The most recent version of these guidelines and accompanying disclosures are available on the NCCN Web site at NCCN.org.)

These guidelines are also available on the Internet. For the latest update, visit NCCN.org.

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 whether the bladder should be removed or can be preserved without compromising survival, and to determine whether the primary lesion can be managed independently or whether 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 in this disease. The issue has become how to use these agents to achieve the best possible outcome.

Histology

More than 90% of urothelial tumors originate in the urinary bladder, 8% originate in the renal pelvis, and the remaining 2% originate in the ureter and urethra. Urothelial (transitional cell) carcinomas, the most common histologic subtype in the United States, may develop anywhere transitional epithelium is present, from the renal pelvis to the ureter, bladder, and proximal two-thirds of the urethra. The distal third of the urethra is dominated by squamous epithelium. The diagnosis of squamous cell tumors, which constitute 3% of the urinary tumors diagnosed in the United States, requires the presence of keratinization in the pathologic specimen.²

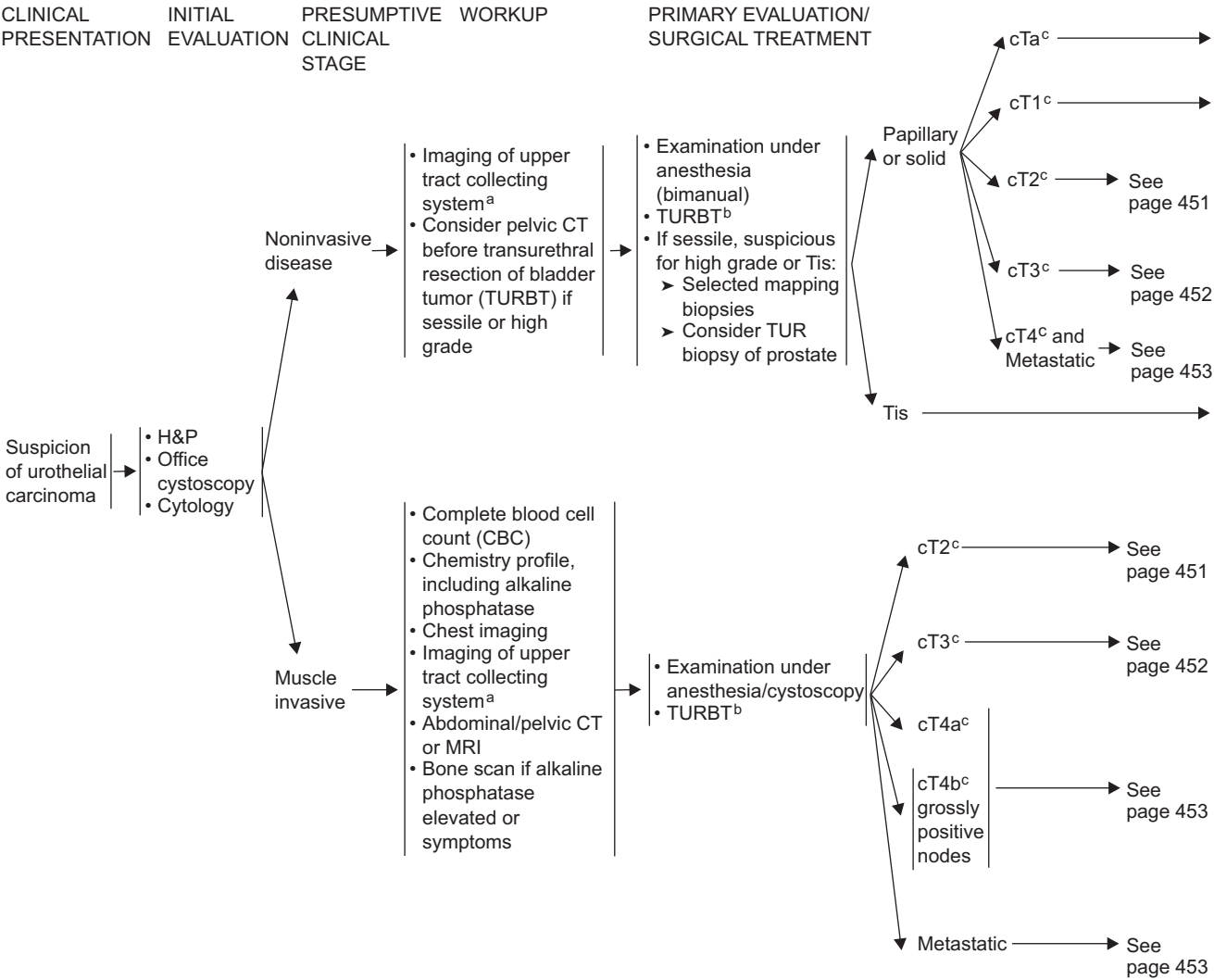
Of the other histologic subtypes, 1.4% are adenocarcinomas and 1.0% are small cell tumors (with

Text continues on p. 460

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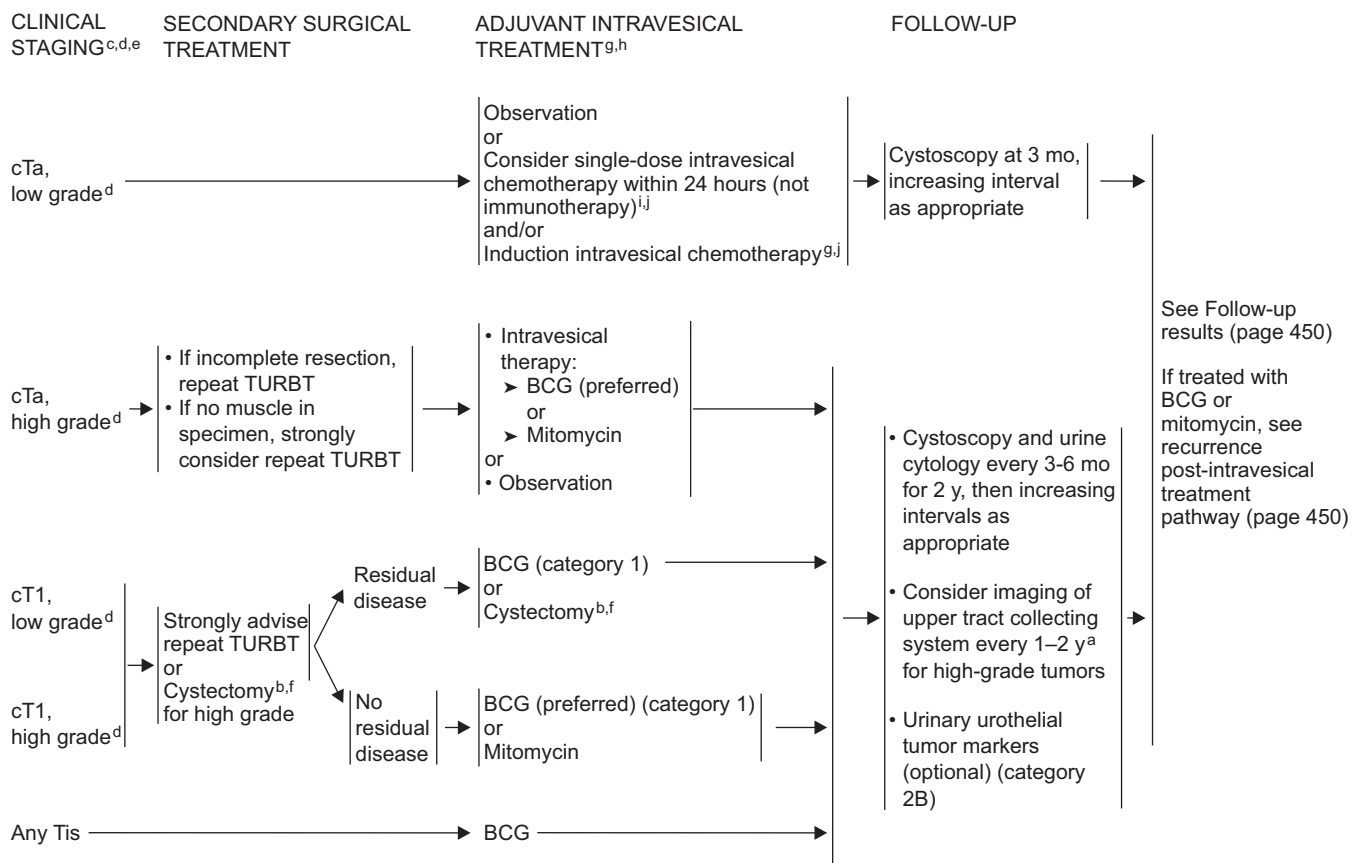
^aImaging may include one or more of the following: intravenous pyelogram (IVP), CT urography, renal ultrasound with retrograde pyelogram, ureteroscopy, or MRI urogram.

^bSee Principles of Surgical Management (page 455).

^cThe 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.

BL-1

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^aImaging may include one or more of the following: IVP, CT urography, renal ultrasound with retrograde pyelogram, ureteroscopy, or MRI urogram.

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^dMontironi 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 (page 455).

^eSee Approximate Probability of Recurrence and Progression (page 456) and Non-Urothelial Cell Carcinoma of the Bladder (page 456).

^fSee Follow-Up After Cystectomy and Bladder Preservation (page 457).

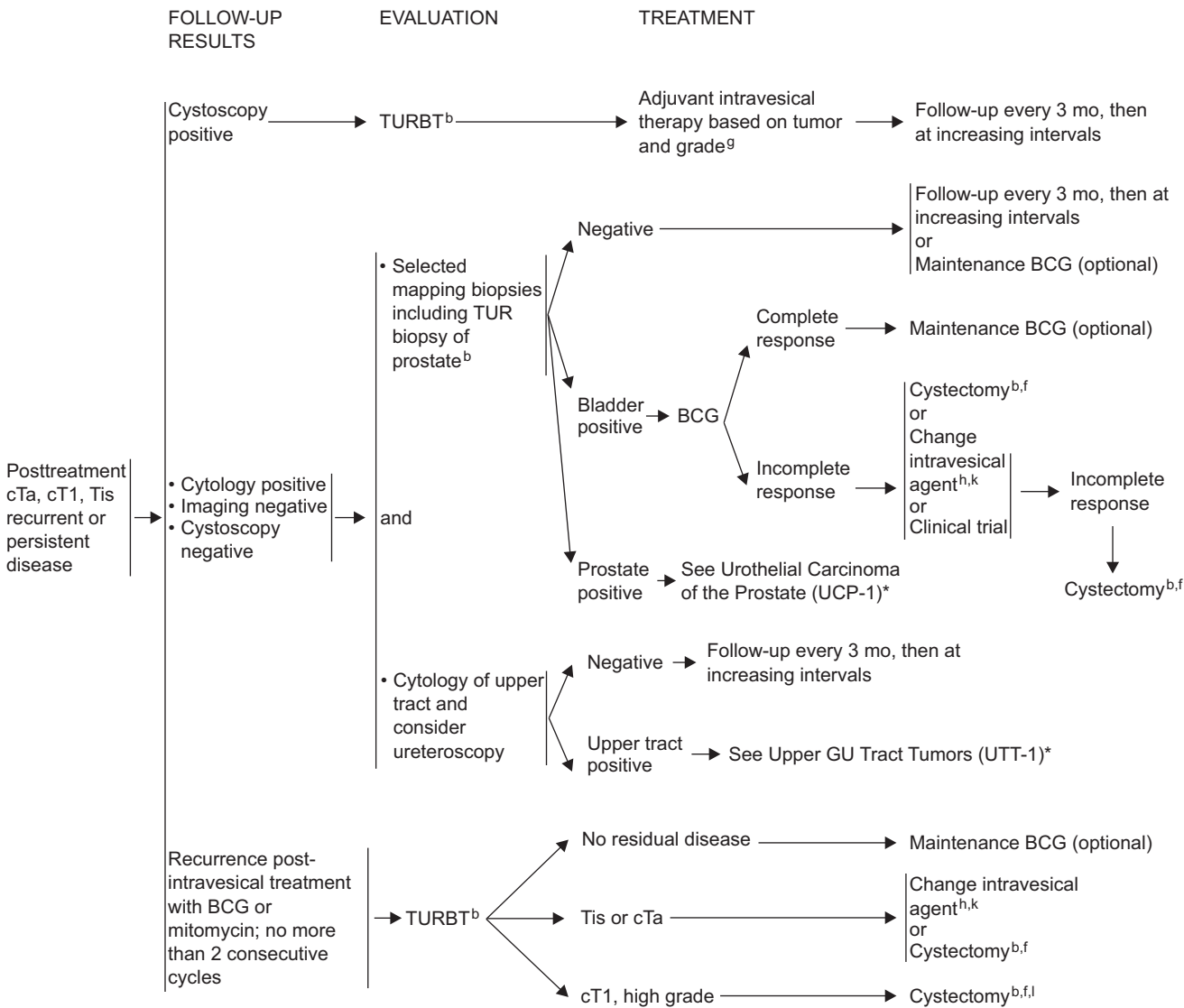
^gIndications for adjuvant therapy: Based on probability of recurrence and progression to muscle invasive disease, such as size, number, and grade.

^hSee Principles of Intravesical Treatment (page 457).

ⁱImmediate intravesical chemotherapy, not immunotherapy, may decrease recurrence.

^jAlthough there is no intravesical chemotherapy standard for cTa low grade, mitomycin is most commonly used.

BL-2



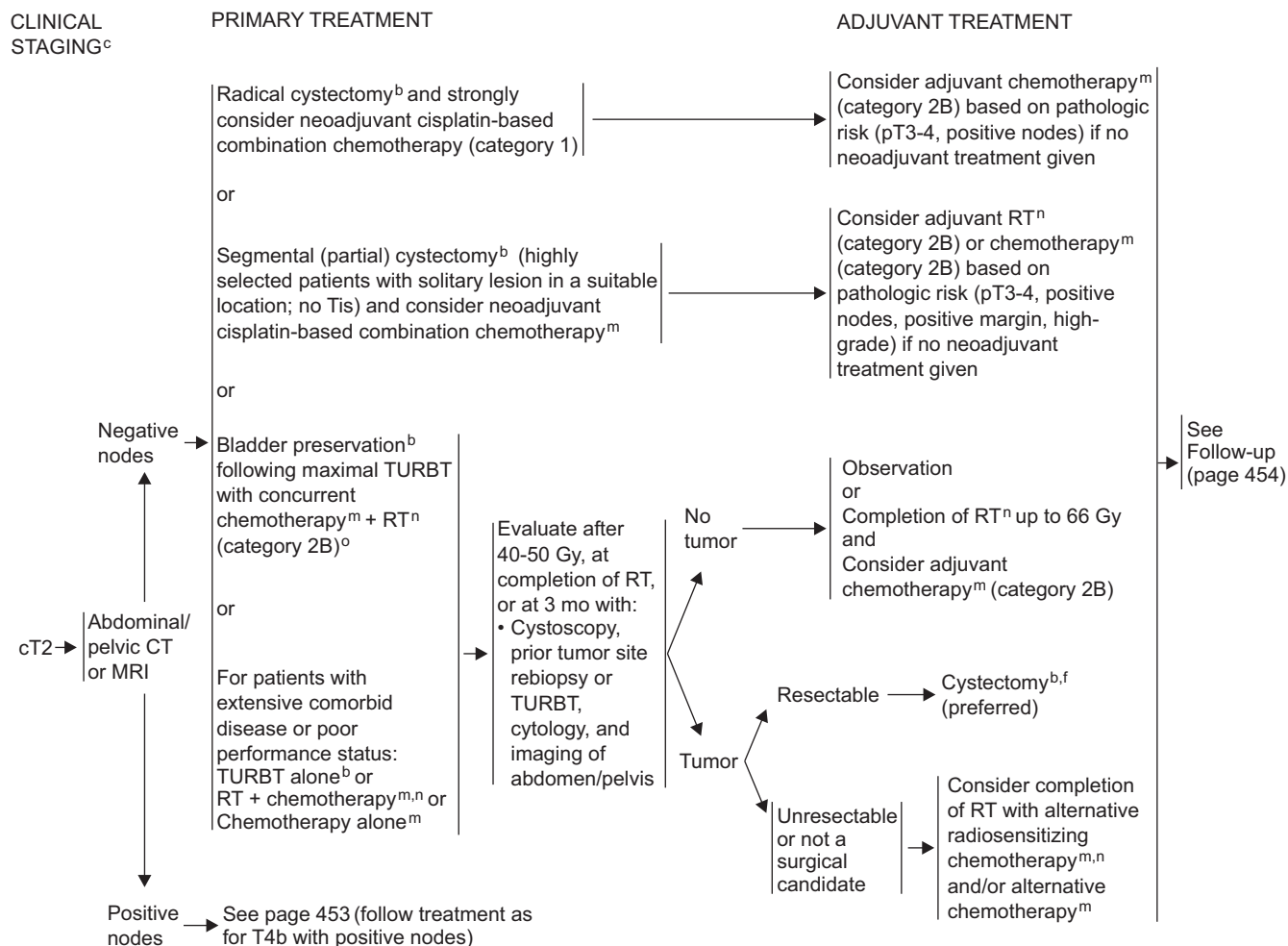
*Available online, in these guidelines, at NCCN.org

^bSee Principles of Surgical Management (page 455).
^fSee Follow-Up After Cystectomy and Bladder Preservation (page 457).
^gIndications for adjuvant therapy: Based on probability of recurrence and progression to muscle invasive disease, such as size, number, and grade.
^hSee Principles of Intravesical Treatment (page 457).
^kValrubicin is approved for BCG-refractory carcinoma in situ.
^lIf not a cystectomy candidate, consider concurrent chemotherapy and radiation on a clinical trial.

BL-3

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^bSee Principles of Surgical Management (page 455).

^cThe 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.

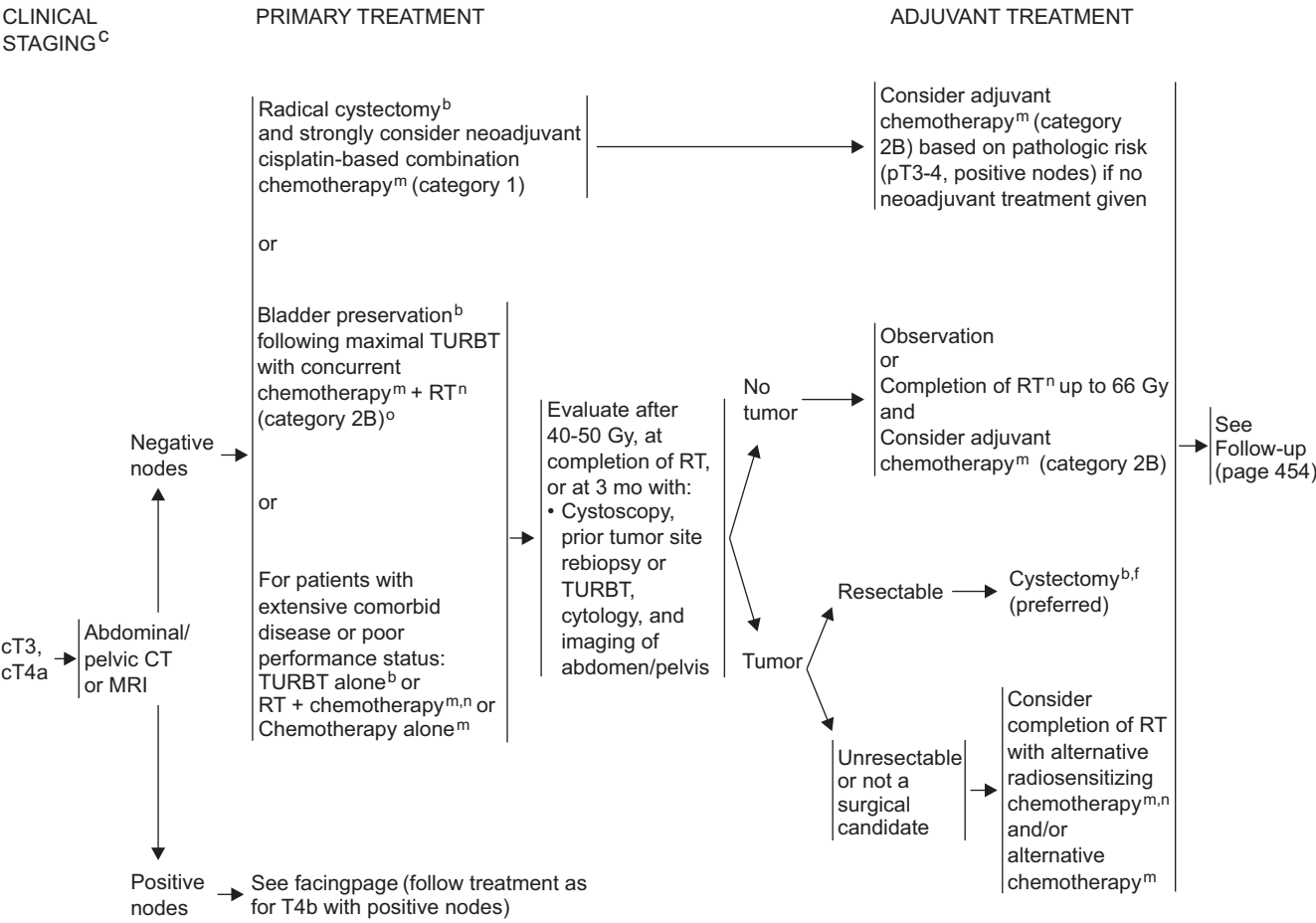
^fSee Follow-Up After Cystectomy and Bladder Preservation (page 457).

^mSee Principles of Chemotherapy Management (pages 458-459).

ⁿSee Principles of Radiation Management of Invasive Disease (page 459).

^oThere 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.

BL-4



^bSee Principles of Surgical Management (page 455).

^cThe 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.

^fSee Follow-Up After Cystectomy and Bladder Preservation (page 457).

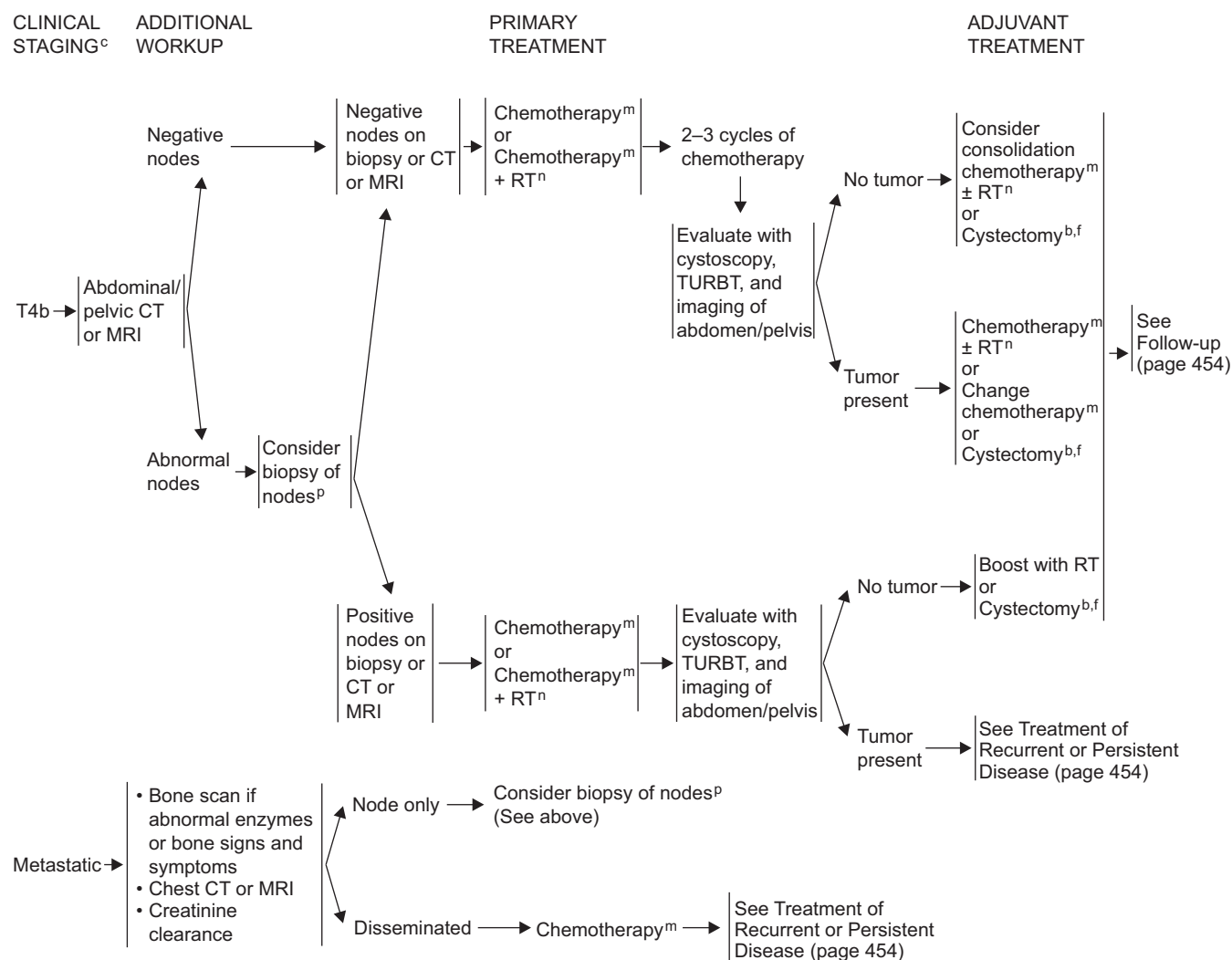
^mSee Principles of Chemotherapy Management (pages 458-459).

ⁿSee Principles of Radiation Management of Invasive Disease (page 459).

^oThere 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.

BL-5

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^bSee Principles of Surgical Management (page 455).

^cThe 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.

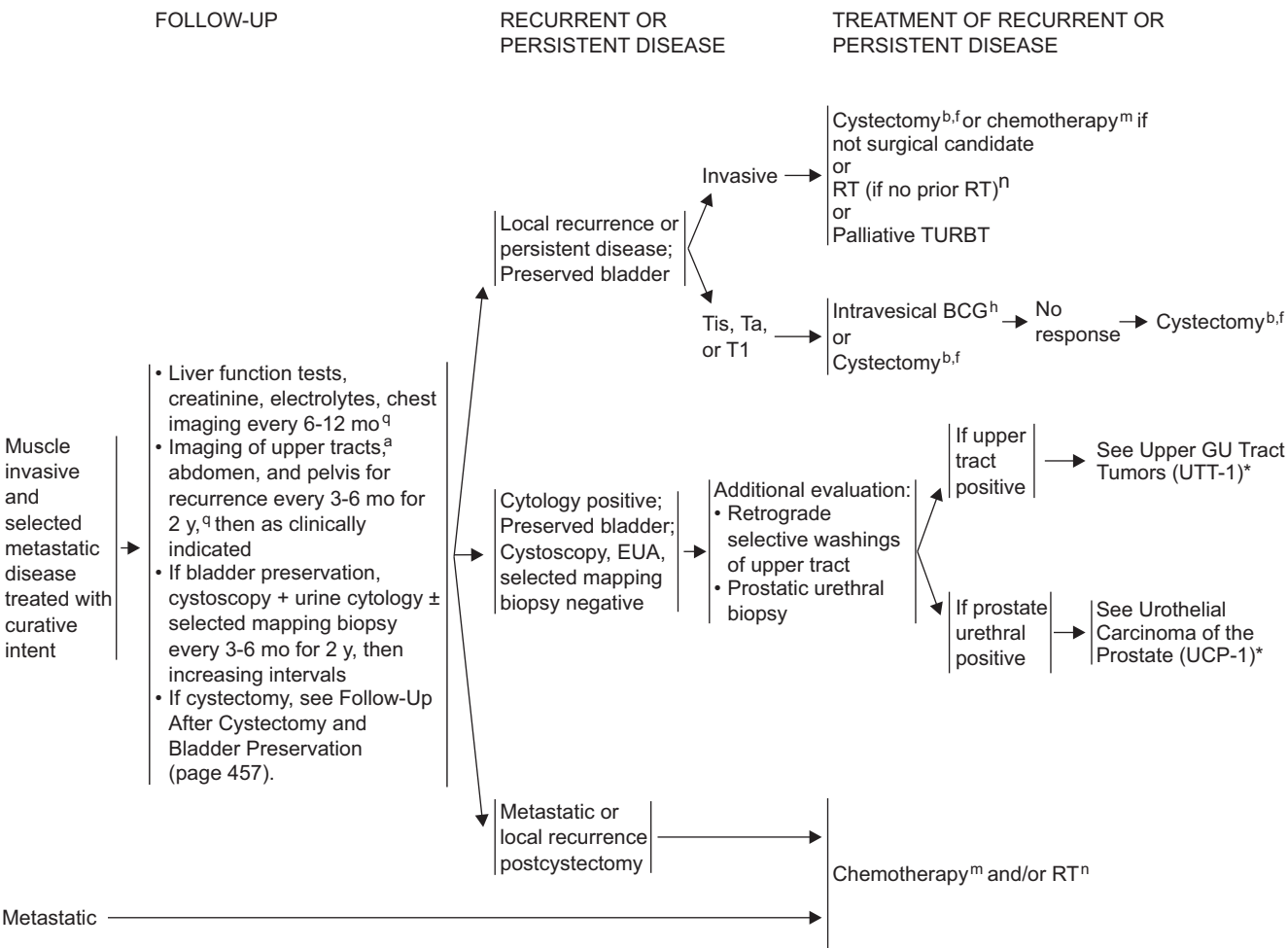
^fSee Follow-Up After Cystectomy and Bladder Preservation (page 457).

^mSee Principles of Chemotherapy Management (pages 458–459).

ⁿSee Principles of Radiation Management of Invasive Disease (page 459).

^pIf technically possible.

BL-6



*Available online, in these guidelines, at NCCN.org.

^aImaging may include one or more of the following: IVP, CT urography, renal ultrasound with retrograde pyelogram, ureteroscopy, or MRI urogram.
^bSee Principles of Surgical Management (page 455).
^fSee Follow-Up After Cystectomy and Bladder Preservation (page 457).
^hSee Principles of Intravesical Treatment (page 457).
^mSee Principles of Chemotherapy Management (pages 458-459).
ⁿSee Principles of Radiation Management of Invasive Disease (page 459).
^qDepending on risk of recurrence.

BL-7

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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 6 weeks) if
 - Incomplete initial resection
 - No muscle in original specimen for high-grade disease
 - Large or multifocal lesions
 - Any T1 lesion

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

Transurethral Resection for Sessile or Invasive Appearing Tumor (likely muscle invasive)

- Perform exam under anesthesia
- 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 trimodality bladder preservation therapy

Segmental (Partial) Cystectomy

- Reserved for solitary lesion in location amenable to segmental resection with adequate margins
- No carcinoma in situ
- 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

PRINCIPLES OF PATHOLOGY MANAGEMENT

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

Malignancy Grading of Bladder Carcinoma: Old and New Systems*

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

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

BL-A

BL-B

APPROXIMATE PROBABILITY OF RECURRENCE AND PROGRESSION

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

NON-UROTHELIAL CELL CARCINOMA OF THE BLADDER

Same management as urothelial cell carcinoma with the following issues:

Mixed Histology:

- Urothelial carcinoma plus pure 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:

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

Adenocarcinoma:

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

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 Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Small Cell Lung Cancer*.

Urachal Carcinoma:

- Requires complete urachal resection.
- Conventional chemotherapy for urothelial carcinoma is not effective; however, the use of chemotherapy or RT should be individualized and may be of potential benefit in select patients.
- En-bloc resection of the urachal ligament with the umbilicus.

Primary Bladder Sarcoma:

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

*To view the most recent version of these guidelines, visit NCCN.org.

BL-C

BL-D

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FOLLOW-UP AFTER CYSTECTOMY AND BLADDER PRESERVATION

After a radical cystectomy

- Urine cytology, creatinine, and electrolytes, every 3 to 6 months for 2 years and then as clinically indicated
- Imaging of the chest, abdomen, and pelvis every 3 to 12 months for 2 years based on risk of recurrence and then as clinically indicated
- Urethral wash cytology, every 6 to 12 months; 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 3-6 mo for 2 y, then increasing intervals as appropriate

For Recurrent or Persistent Disease (see page 454)

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 h 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 wk after resection
- Maximum of 2 inductions without complete response
- Maintenance therapy is optional

Induction Intravesical Immunotherapy

- Initiated 3-4 wk 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

BL-E

BL-F

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 cycles⁵
- 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, because 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/m² on days 1 and 2 or days 1 and 8) (category 2B). Although safer, the relative efficacy of the cisplatin-containing combination administered with such modifications remains undefined.
 - For patients who are not candidates for cisplatin, no data support a recommendation for perioperative chemotherapy.

First-line chemotherapy for metastatic disease

- Regimens
 - Gemcitabine and cisplatin⁴ (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.

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

- First-line chemotherapy
 - Cisplatin alone or in combination with 5-FU
 - Mitomycin C in combination with 5-FU¹²
 - Clinical trial

BL-G
1 and 2 of 3

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PRINCIPLES OF CHEMOTHERAPY MANAGEMENT

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PRINCIPLES OF RADIATION MANAGEMENT OF INVASIVE DISEASE

- External-beam radiation alone is rarely appropriate for patients with stage Ta, T1, or Tis. For patients with recurrent Ta-T1 disease without extensive Tis who are not candidates for cystectomy, chemoradiation may be considered.
- External-beam radiation is most successful for patients without hydronephrosis or with extensive invasive tumor-associated Tis.
- External-beam radiation (with or without concurrent chemotherapy) can also be used as potentially curative therapy for medically inoperable patients or for local palliation in patients with metastatic disease.
- Precede radiation or concurrent chemotherapy and radiation by maximal TUR of the tumor when safely possible.
- Combining concurrent chemotherapy with radiation 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. This therapy is optimally given by dedicated multidisciplinary teams.
- Simulate and treat patients when they have an empty bladder.
- Use multiple fields from high-energy linear accelerator beams.
- Treat the whole bladder with or without pelvic lymph nodes with 40-45 Gy and then boost the bladder tumor to a total dose up to 66 Gy excluding, if possible, normal areas of the bladder from the high-dose volume.
- Consider low-dose preoperative radiation therapy before segmental resection for invasive tumors (category 2B).

BL-G 3
of 3
BL-H

Text continued from p. 447

or without an associated paraneoplastic syndrome). Adenocarcinomas often occur in the dome of the bladder in the embryonal remnant of the urachus, in the periurethral tissues, or with a “signet ring” cell histology. Urothelial tumors often have a mixture of divergent histologic subtypes, such as urothelial (transitional cell) and squamous, adenocarcinoma, and more recently appreciated nested micropapillary and sarcomatoid subtypes.³ 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 nonurothelial (non–transitional cell) histology, such as adenocarcinoma or squamous carcinoma. In some cases with a mixed histology, only the nonurothelial 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, whereas upper tract obstruction or pain may occur in a more advanced lesion. Patients presenting with these symptoms should be evaluated using office cystoscopy to determine whether 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) or 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 when 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 an intravenous pyelogram, renal ultrasound with retrograde pyelogram, CT urography, ureteroscopy, or MRI urogram. 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 resection (TUR) biopsy of the prostate may also be considered. Finally, if an invasive tumor is noted, an adequate sample of muscle must be obtained. A small fragment of tumor with few muscle fibers is inadequate for assessing the depth of invasion and guiding treatment recommendations.

Additional diagnostic tests, such as a bone scan, should be performed if elevated levels of alkaline phosphatase are seen in the blood. Treatment decisions are then based on disease extent within the 3 general categories: non–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 using fluorescence in situ hybridization or nuclear matrix protein 22 in the monitoring for recurrence.^{4,5}

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%) or, less often, to the submucosa (T1; 25%), or flat high-grade lesions (CIS, 5%).⁶ 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 (transitional cell) carcinoma within 5 years.⁷ 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 system⁸ by the AJCC, as shown in the algorithm (available online, in these guidelines, at NCCN.org [ST-1]).

Tumor grade has been recognized as an important prognostic indicator with regard to the potential for disease recurrence and progression. The most widely used classification for grading of 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.⁹ 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. According to the WHO 2004 system, some grade 2 lesions are classified as low-grade tumors, and others as high-grade. This new system potentially allows for enhanced prognostic significance but depends on the pathologist to make these distinctions. The 2004 WHO classification is yet to be validated by clinical trials; therefore, tumors are graded using both the 1973 and 2004 WHO classifications. The different classification systems are compared in Table 1 ("Principles of Pathology Management: Malignancy Grad-

ing of Bladder Carcinoma: Old and New Systems," available online, in these guidelines, at NCCN.org [MS-21]). The 7th edition of the AJCC staging system has replaced the previous 4 grade system to match the current WHO/ISUP recommended grading system.⁸

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 CIS or Tis. These tumors were previously 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 using initial cystoscopy and cytology. Once suspected, imaging of upper tract collecting systems is required. In addition, a pelvic CT scan must be performed before TURBT if sessile or high-grade disease is suspected.

Standard treatment for Ta, T1, and Tis is TURBT.¹⁰ 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 TUR biopsy of prostate must be considered.

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

A second TUR is performed when a high-grade T1 tumor and possibly a Ta has been detected at

Bladder Cancer

the initial TUR. This is especially critical when no muscularis propria was included in the resection.¹¹ However, depending on the depth of invasion and grade, intravesical therapy may be recommended. This suggestion is based on the estimated probability of recurrence (ie, new tumor formation within the bladder) and progression to a more advanced, usually muscle-invasive stage, which are events that should be considered independently. Cystectomy is rarely considered for a Ta, low-grade lesion.

Intravesical Therapy

Intravesical therapy is used in 2 general settings: as prophylactic or adjuvant therapy after a complete endoscopic resection or, rarely, as therapy with the goal of eradicating residual disease that could not be completely resected. This distinction is important, because most published data reflect prophylactic or adjuvant use with the goal of preventing recurrence or delaying progression to a higher grade or stage. In many cases, intravesical therapy may be overused if given to patients who have a low probability of recurrence or progression. Bacillus Calmette-Guérin (BCG) has been shown to be effective as prophylaxis in preventing bladder cancer recurrences after TURBT. Management of the different histologic subtypes of noninvasive bladder tumors of different grades is outlined in subsequent sections.

cTa, Low-Grade Tumors

TUR is the standard treatment for cTa, low-grade tumors. Although a complete TUR by itself can eradicate cTa, low-grade tumors, these tumors have a relatively high risk for recurrence. Therefore, after TUR, the panel recommends that, in addition to observation, clinicians consider administering a single dose of immediate intravesicular chemotherapy (not immunotherapy) within 24 hours of resection. A meta-analysis of 7 randomized trials confirmed that immediate intravesical therapy decreased the risk of recurrence by 11% (from 48% to 37%) in patients with either single or multiple tumors.¹² Later studies had mixed results, with 2 reporting a decrease in recurrence and 1 finding no advantage.^{13–15} The immediate intravesical chemotherapy may be followed by a 6-week induction of intravesical chemotherapy. Mitomycin C is the agent most commonly used. Immunotherapy is not recommended in these patients.

The need for adjuvant therapy depends on patient prognosis. If the patient has a low risk of recur-

rence, a single immediate intravesical treatment may be sufficient. Factors to consider include the size, number, T category, and grade of the tumors; concomitant CIS; and prior recurrence.⁷ Meta-analyses have confirmed the efficacy of adjuvant intravesical chemotherapy in reducing the risk of recurrence.^{16,17} Immediate intravesical treatment should be avoided if TURBT was extensive or bladder perforation is suspected.

Close followup 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 thereafter.

cTa, High-Grade Tumors

Tumors staged as cTa, high-grade lesions are papillary tumors with a relatively high risk for recurrence and progression toward more invasiveness. Restaging TUR detected residual disease in 27% of patients with Ta tumors when muscle was present in the original TUR.¹⁸ In the absence of muscularis propria in the initial TUR specimen, 49% of patients with superficial disease will be understaged, versus 14% if muscle was present.¹¹ Repeat resection is recommended in patients with incomplete resection, or should be strongly considered if the specimen contains no muscle.

After TUR, in addition to observation, patients with Ta, high-grade tumors may be treated with intravesical BCG or mitomycin C. In the literature, 4 meta-analyses confirm that BCG after TUR is superior to TUR alone or TUR and chemotherapy in preventing recurrences of high-grade Ta and T1 tumors.^{19–22} The NCCN Bladder Cancer Panel recommends BCG as the preferred option over mitomycin 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.²³ Most of these tests have a better sensitivity for detecting bladder cancer than urinary cytology, but specificity is lower. However, whether these tests offer additional information that is useful for detection and management of non-muscle-invasive bladder tumors remains unclear. Therefore, the panel considers this a category 2B recommendation.

cT1 Tumors

T1 tumors are those that invade subepithelial connective tissue (also referred to as *lamina propria*). Based on the 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 are also treated with a complete endoscopic resection. In patients with high-risk disease, especially if the complete resection is uncertain because of the tumor size and location, no muscle is shown in the specimen, lymphovascular invasion has occurred, or inadequate staging is suspected, repeat TURBT is strongly advised.²⁴ This is supported by a trial that prospectively randomized 142 patients with pT1 tumors to either a second TURBT within 2 to 6 weeks of the initial TURBT or no repeat TURBT.²⁵ All patients received adjuvant intravesical therapy. Although overall survival was similar, the 3-year recurrence-free survival rate 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. Data suggest that early cystectomy may be preferred if residual disease is found, because of the high risk for progression to a more advanced stage.²⁶ Therefore, for high-risk tumors, cystectomy rather than repeat TURBT is recommended.

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 is recommended. Follow-up is similar to that for high-grade Ta disease.

Tis

Primary CIS or Tis is a high-grade lesion that is believed to be a precursor of invasive bladder cancer. Standard therapy for this lesion is 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 reevaluation at week 12 (ie, 3 months) after the start of therapy. If the patient is unable to tolerate BCG, intravesi-

cal 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 who were under observation after initial TURBT, who show a documented recurrence based on 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 up at 3-month intervals.

Recurrence After 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 2 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.²⁷ For patients with recurrence of high-grade cT1 disease after TURBT and induction BCG, cystectomy is the main option.²⁸ However, nonsurgical candidates might consider concurrent chemoradiation within the context of 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.^{19,20,29–32} Malmstrom et al³³ 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. The optimal maintenance schedule has not been established, but patients commonly receive it for at least a year (some patients cannot tolerate the therapy beyond 2 years). Although a few NCCN Member Institutions do not routinely administer maintenance BCG, panelists agree that it should be an option.

Bladder Cancer

Based on Cytology Results: In patients without a documented recurrence but with positive cytology results and negative cystoscopy and imaging results, TUR must be performed with directed or selected mapping biopsies, including TUR biopsies of the prostate. In addition, cytology of the upper tract must be evaluated and ureteroscopy may be considered for detecting tumors of the upper tract.

If the results of the selected mapping biopsy of the bladder are positive, then the recommendation is to administer intravesical BCG treatment followed by maintenance BCG (optional) if a complete response is seen. For tumors that fail to respond to 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 to establish the efficacy of alternative agents in secondline treatments.

If results of TUR biopsy of the prostate are positive, the treatment is described in “Urothelial (Transitional Cell) Carcinomas of the Prostate” on page MS-19, or online, in these guidelines at NCCN.org. If results of cytology of the upper tract and/or ureteroscopy results are positive, then the treatment is described in “Upper Genitourinary Tract Tumors” on page MS-17, or online, in these guidelines at NCCN.org.

If results of TUR biopsies of the bladder and prostate are negative, then follow-up at 3-month intervals is recommended, and maintenance therapy with BCG is optional. If results of cytology of the upper tract and ureteroscopy are 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 the clinical staging. Laboratory studies, such as 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 and other distant organs.³⁴ 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 TUR 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 after initial TURBT is required for muscle-invasive tumors. Different treatment modalities are discussed later, including 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 understaging encountered frequently. A pelvic lymph node dissection (PLND) is considered an integral part of the surgical management of bladder cancer. A more extensive PLND, which may include the common iliac or even lower para-aortic or paracaval nodes, yields more nodes to be examined, increases yield of positive nodes, and is associated with better survival and a lower pelvic recurrence rate.^{35–39} 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 blad-

der 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.^{40–42} 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).^{40,41} Grossman et al⁴⁰ 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 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. In a meta-analysis of 11 trials involving 3005 patients, platinum-based neoadjuvant chemotherapy was associated with improved 5-year overall and disease-free survival rates (5% and 9% absolute improvement, respectively).⁴³

An international, multicenter, randomized trial (BA06 30894) investigated the effectiveness of neoadjuvant cisplatin, methotrexate, and vinblastine (CMV) in 976 patients.⁴⁴ At a median follow-up of 8 years, patients receiving CMV before surgery had a 16% reduction in mortality risk (hazard ratio, 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 of this therapy.⁴⁵ 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.⁴⁶ Studies showed a survival advantage from therapy with cyclophosphamide, doxorubicin, and cisplatin (CAP) and with MVAC or methotrexate, vinblastine, epirubicin, and cisplatin (MVEC).^{47–49} However, methodologic issues have raised questions as to the applicability of these studies to all patients with urothelial tumors. In the MVEC trial, patients who experienced relapse in the control arm did not undergo chemotherapy, which is not typical of more contemporary series. 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.⁵⁰

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.⁵¹ A minimum of 3 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 nonurothelial carcinomas, regardless of stage.

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

Bladder Cancer

experimental procedure and is not part of routine management.

Adjuvant Radiation

Data on radiation or chemoradiation after 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 showed improvement in 5-year disease-free survival and local control compared with surgery alone.⁵² A retrospective series from Milan similarly showed improved cancer-specific survival with adjuvant radiotherapy for patients with pT2–T4a disease.⁵³ Because local recurrence rates are high for some patients after cystectomy (32% for patients with pT3–T4 disease and 68% for patients with positive surgical margins),³⁷ adjuvant radiation therapy is reasonable to consider in these patients. Radiotherapy to 40 to 45 Gy, with or without concurrent cisplatin, could be used. The safety of higher doses, especially in the setting of a neobladder, must be further studied. Because patients with pT3a to pT4a disease 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.⁵⁴ Options include aggressive endoscopic TUR alone, TUR followed by chemotherapy alone, radiotherapy alone, or a combination of chemotherapy and radiotherapy. Partial cystectomy, also a form of bladder preservation, was discussed earlier. 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.⁵⁵ There is an apparent underuse of aggressive bladder-preserving therapies for noncystectomy candidates, especially the elderly and racial minorities.⁵⁶ 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.^{57,58} Patients for whom a bladder-sparing approach is considered should undergo as complete a TUR of the tumor as possible, EUA, and metastatic workup before therapy is initiated.

With any of the alternatives to cystectomy, a concern exists over the ability to determine with certainty which bladders that appear to be endoscopically free of tumor (T0), based on a clinical assessment that includes a repeat TURBT, are in fact pathologically free of tumor (pT0). Up to one-third of bladders believed to be free of disease preoperatively after chemotherapy can have residual disease at cystectomy.⁵⁹ On the other hand, one series reported that all patients who experienced a complete response after radiotherapy with concurrent cisplatin and 5-FU also had no pathologic residual disease on immediate cystectomy.⁶⁰ 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 TUR, 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 all potential treatment options. However, only chemotherapy combined with radiotherapy has been formally evaluated in prospective randomized comparisons^{61,62}; the others are still considered investigational.

All bladder-sparing approaches are based on the principle that not all cases require an immediate cystectomy and that the decision to remove the bladder can be deferred until the response to therapy is assessed. When chemotherapy combined with radiotherapy is used, 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 TUR 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.

TUR Alone: TUR alone may be curative in selected cases in which the lesion is solitary, is smaller than 2 cm, and has minimally invaded the muscle. These cases should also have no associated in situ component, palpable mass, or associated hydronephrosis.⁶³

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

Chemotherapy After TUR: The use of chemotherapy alone is not considered to be adequate without additional treatment to the bladder, and it remains investigational. This view is based on studies showing that the proportions of complete pathologic response in the bladder using neoadjuvant chemotherapy alone were only up to 38%.⁴⁰ 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: Fewer than 5% of invasive tumors present initially in a location and pattern that is amenable to curative resection with partial cystectomy.⁶⁴ Nonrandomized studies reported 5- to 10-year overall survival rates of 69% to 73%; however, the rate of invasive recurrence was 23% to 33%.^{59,65} 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 After TUR: Radiotherapy alone is inferior to radiotherapy combined with chemotherapy for patients with an invasive bladder tumor, and it is not considered standard for patients who can tolerate combined therapy.^{61,62} In a randomized trial of 360 patients, radiotherapy with concurrent mitomycin C and 5-FU improved the 2-year locoregional

disease-free survival rate from 54% (radiotherapy alone) to 67% ($P=.01$), and the 5-year overall survival rate from 35% to 48% ($P=.16$), without increasing grade 3/4 acute or late toxicity.⁶² Hence, radiotherapy alone is only indicated for patients who cannot tolerate a cystectomy or chemotherapy because of medical comorbidities.

Radiotherapy With Concurrent Chemotherapy After TUR: 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.^{66,67}

RTOG protocol 8903 compared concurrent cisplatin and radiotherapy with versus without 2 cycles of induction MCV (methotrexate, cisplatin, and vinblastine) chemotherapy.⁵⁸ 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 radiotherapy.^{67,68}

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.^{54,57,58,60–62,66,67} After a complete TURBT, 40 Gy of external beam radiotherapy is administered, typically with a 4-field technique. Two doses of concurrent cisplatin are given on weeks 1 and 4. After this induction phase, an endoscopic reevaluation is performed. If residual disease is noted, a cystectomy is advised. If no disease is visible and the cytology and biopsy are negative (T0), an additional 25 Gy of 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 shown the effectiveness of this approach. In RTOG 89-03, in which 123 patients with clinical stage T2–T4a were treated with radiotherapy with concurrent cisplatin, with or without induction MCV chemotherapy, the 5-year overall survival rate was approximately 49% in both arms.⁵⁸ In RTOG 95-06, in which 34 patients were treated with twice-daily irradiation and concurrent cisplatin and

Bladder Cancer

5-FU, the 3-year overall survival rate was 83%.⁶⁹ In RTOG 97-06, in which 47 patients were treated with twice-daily irradiation and concurrent cisplatin and patients also received adjuvant chemotherapy with methotrexate, vinblastine, and cisplatin,⁷⁰ the 3-year overall survival rate was 61%. In RTOG 99-06, in which 80 patients were treated using twice-daily irradiation plus cisplatin and paclitaxel followed by adjuvant cisplatin and gemcitabine, the 5-year overall survival was 56%.⁷¹ In these trials, the complete response rate ranged from 59% to 81%. Whether twice-daily radiotherapy results in better outcomes than daily treatment or whether adding taxol or 5-FU improves radiosensitization over cisplatin alone, is unclear.

Up to approximately 80% of long-term survivors maintain an intact bladder, whereas other patients ultimately require radical cystectomy.^{57,58,66–71} 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).⁷² 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.

Currently, 3 drug types are active in the management of advanced bladder cancer: cisplatin, the taxanes, and gemcitabine. Combinations of 2 or 3 of these agents have shown clinical benefit (Table 2, "Combination Chemotherapy Regimens," available online, in these guidelines, at NCCN.org [MS-22]). Commonly used combinations include GC^{73,74} and dose-dense MVAC.^{75,76} A large, international, phase III study randomized 405 patients

with locally advanced or metastatic disease to either GC or standard MVAC.⁷⁷ At a median follow-up of 19 months, overall survival and time to progression were similar in the arms. However, less-toxic deaths were recorded among patients receiving GC compared with 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).⁷⁴ Another large, randomized, phase III trial compared dose-dense MVAC versus standard MVAC.^{75,76} At a median follow-up of 7.3 years, 24.6% of patients were alive in the dose-dense MVAC cohort compared with 13.2% in the standard MVAC cohort; one toxic death occurred in each arm, but less overall toxicity was seen in the dose-dense group. Based on these data, standard MVAC is inferior to high-dose-intensity MVAC in terms of toxicity and efficacy, and is inferior to GC in terms of toxicity (and therefore no longer used). Both GC and dose-dense MVAC are category 1 recommendations for metastatic disease.

The performance status of the patient is a major determinant of which regimen is used, and regimens with lower toxicity profiles are recommended in patients with compromised liver or renal status or serious comorbid conditions. In patients with a glomerular filtration rate (GFR) of less than 60 mL/min, carboplatin may be substituted for cisplatin in the regimen mentioned earlier. A phase II/III study assessed 2 carboplatin-containing regimens in medically unfit patients (performance status 2).⁷⁸ 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).

More recently, the taxanes have been shown to be active as both frontline 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,⁷⁹ gemcitabine/paclitaxel,⁸⁰ cisplatin/gemcitabine/paclitaxel,⁸¹ carboplatin/gemcitabine/paclitaxel,⁸² and cisplatin/gemcitabine/docetaxel,⁸³ have shown modest activity in bladder cancer in phase I and 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.⁸⁴ 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) statistically significant survival advantage in favor of the 3-drug regimen ($P = .03$). No difference in progression-free survival was seen. 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 these 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 panel recommends enrollment in clinical trials of potentially less toxic therapies.

The regimens effective for urothelial carcinoma histologies have limited efficacy for patients with nonurothelial carcinomas. These individuals are often treated based on the identified histology. For example, adenocarcinomas are managed surgically with radical or segmental cystectomy, individualizing the adjuvant chemotherapy and radiotherapy for maximum benefit. Pure squamous cell tumors are treated with 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 nonurothelial carcinomas is limited.

Independent of the specific regimen used, patients with metastatic disease are reevaluated after 2 to 3 cycles of chemotherapy, and treatment is continued for 2 more cycles in patients whose disease responds or remains stable. Surgery or radiotherapy may be considered in patients who show a major partial response in an unresectable primary tumor or 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 is not considered an option are gen-

erally treated with chemotherapy for a maximum of 6 cycles, depending on their response. If no response is noted after 2 cycles or if significant morbidities are encountered, a change in therapy is advised, taking into account the patient's current performance status, extent of disease, and specific prior therapy administered. The same applies to patients who experience systemic relapse after adjuvant chemotherapy.

Second-line chemotherapy data are highly variable and unclear in this setting; therefore, no standard therapy exists. The panel highly recommends enrollment in a clinical trial. The available options for palliative chemotherapy depend on what was offered as first-line therapy. Docetaxel, paclitaxel, or gemcitabine monotherapy is preferred.^{85–88} Other options include cisplatin, carboplatin, doxorubicin, 5-FU, ifosfamide, pemetrexed, methotrexate, and vinblastine, with modest benefit limited to small phase II trials.^{89–93}

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 to 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 T2, T3, and T4a lesions with no nodal disease seen on abdominal/pelvic CT or MRI scan is a radical cystectomy and pelvic lymphadenectomy, with strong consideration of neoadjuvant chemotherapy based on 2 randomized trials (category 1).^{40,41} Stronger evidence supports neoadjuvant chemotherapy for T3 disease. If no neoadjuvant chemotherapy was given, postoperative adjuvant chemotherapy is considered based on pathologic risk, such as positive nodes and pathologic T3–T4 lesions (category 2B recommendation).

Partial cystectomy can be considered only in patients with T2 disease with a single tumor in a suitable location and no presence of Tis, along with consideration of neoadjuvant chemotherapy. Partial cystectomy is not an option for patients with T3 or T4a disease. Adjuvant radiotherapy or chemotherapy based on pathologic risk, such as positive nodes, positive margin, high-grade lesions, and pathologic T3–T4 lesions, may be considered (category 2B recommenda-

tion). As with radical cystectomy, patients who have received neoadjuvant chemotherapy should not receive adjuvant chemotherapy after partial cystectomy.

Bladder-preservation strategy with concurrent chemotherapy and radiation (category 2B recommendation) is an option in highly selected patients. Candidates for bladder-sparing approaches are patients whose tumors present without hydronephrosis and tumors that allow a visibly complete or a maximally debulking TURBT. In patients with extensive comorbid disease or poor performance status, treatment options include TURBT alone, concurrent chemoradiation, or chemotherapy alone. Based on high-level evidence, only cisplatin alone or 5-FU and mitomycin C together are the drugs proven to be radio-sensitizing with radiation and are superior to radiation alone.^{61,62}

If radiotherapy alone was offered initially, it may be continued up to 66 Gy. In addition, adjuvant chemotherapy may be considered for these patients to sustain remission (category 2B recommendation).

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 patients with T4a node-negative disease, cystectomy with or without chemotherapy is another primary treatment option. If no evidence of tumor is present after primary chemotherapy, one may consider the consolidation chemotherapy regimen with or without radiation. Alternatively, cystectomy may also be considered as the subsequent management option for these patients. However, if residual disease is noted on 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 who do and do not experience response to primary therapy.

For patients with positive nodes, documented on imaging, a biopsy is considered, if possible, to confirm nodal spread. Patients with positive nodes should receive chemotherapy with or without radiation and 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 after primary therapy, patients should follow the pathway for metastatic disease.

Follow-Up After Surgery

Follow-up after a cystectomy should include urine cytology, liver function tests, creatinine, and electrolytes every 3 to 6 months for 2 years and then as clinically indicated. Chest, abdomen, and pelvis imaging should be conducted every 3 to 12 months for 2 years based on the risk of recurrence, and then as clinically indicated. Patients should be monitored annually for vitamin B₁₂ deficiency if a continent diversion was created. Urethral wash cytology every 6 to 12 months is advised, particularly if Tis was found within the bladder or prostatic urethra.

Follow-up after a partial cystectomy is similar to that for a radical cystectomy, with the addition of monitoring for relapse in the bladder through 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, attention to the bladder as a site of recurrence is only one part of the overall management, because these individuals remain at risk for recurrence elsewhere in the urothelial tract and distantly. Imaging studies and laboratory testing should be performed as outlined under postcystectomy 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, then at increasing intervals as appropriate.

Recurrence or Persistent Disease After Surgery

Metastatic disease or local recurrence after cystectomy may be managed with palliative chemotherapy, radiation, or a combination of these.

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 following sections.

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 after BCG treatment, a cystectomy is advised. Invasive disease

Bladder Cancer

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 previously undergone radiotherapy, a course of such is an alternative. Palliative TURBT is also an option.

Metastatic Disease

Approximately half of all patients experience relapse after cystectomy, depending on the pathologic stage of the tumor and nodal status. Local recurrences account for 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 the same as those with 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 these. Details on the choice of regimens were discussed earlier.

Summary

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

For patients with more extensive disease, newer treatments typically involve combined modality ap-

proaches using recently developed surgical procedures, or 3-dimensional treatment planning for more precise delivery of radiation therapy. Although these are not appropriate in all cases, they offer the promise of an improved quality of life and prolonged survival.

Finally, within the category of metastatic disease, several new agents have been identified that seem superior to those currently considered standard therapies. Experts believe, therefore, that the treatment of urothelial tumors will evolve rapidly over the next few years, with improved outcomes for patients at all stages of disease.

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Bladder Cancer

Individual Disclosures for the NCCN Bladder Cancer Panel					
Panel Member	Clinical Research Support	Advisory Boards, Speakers Bureau, Expert Witness, or Consultant	Patent, Equity, or Royalty	Other	Date Completed
Neeraj Agarwal, MD	None	None	None	None	8/3/12
Matthew C. Biagioli, MD, MS	None	None	None	None	10/16/12
Peter E. Clark, MD	None	Archimedes Pharma Ltd.	None	None	8/28/12
Mario A. Eisenberger, MD	Bristol-Myers Squibb Company; Genentech, Inc.; Agensys, Inc.; and sanofi-aventis U.S. LLC	Ipsen	None	None	8/31/12
Richard E. Greenberg, MD	Endo Pharmaceuticals	Endo Pharmaceuticals	None	None	3/9/12
Harry W. Herr, MD	None	None	None	None	8/28/12
Brant A. Inman, MD, MSc	GlaxoSmithKline plc	None	None	None	8/28/12
Deborah A. Kuban, MD	None	None	Immtech Pharmaceuticals, Inc.	None	8/28/12
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Sumanta K. Pal, MD	None	Genentech, Inc.; GlaxoSmithKline; Novartis Pharmaceuticals Corporation; Pfizer Inc.; and sanofi-aventis U.S. LLC	None	None	3/27/12
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Donald L. Trump, MD	None	None	None	None	5/17/12
Geoffrey Wile, MD	None	None	None	None	6/13/12
Timothy G. Wilson, MD	None	Covidien	None	None	1/6/12

The NCCN guidelines staff have no conflicts to disclose.