

# Bladder Cancer in 2010

## How Far Have We Come?

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### Abstract

Bladder cancer is the fourth most common cancer and ranks eighth as a cause of death from cancer among men in the United States. Although guidelines assist in treatment, the art of managing bladder cancer, such as the decision to use neoadjuvant chemotherapy and the timing of cystectomy, is still variable. Bladder cancer has a propensity to recur, and with recurrence, a significant number of cases progress, which makes the early detection of high-risk patients imperative. Advances in detection, surveillance, and treatment of bladder cancer are reviewed in this article. *CA Cancer J Clin* 2010;60:244-272. ©2010 American Cancer Society, Inc.



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### Introduction

It is estimated that bladder cancer will account for 70,530 new cases of cancer and 14,680 cancer-related deaths in the United States during 2010.<sup>1</sup> Among men, it is the fourth most common cancer and is the ninth leading cause of death from cancer.<sup>1</sup> The ratio of men to women that develop bladder cancer is approximately 3:1.<sup>1</sup>

Of newly diagnosed bladder cancer cases, approximately 70%-80% will present with nonmuscle-invasive disease, and despite endoscopic and intravesical treatments, 50%-70% will recur and 10%-30% will progress to muscle-invasive disease.<sup>2,3</sup> Most recurrences occur within 5 years.<sup>4</sup> Higher grade lesions are at a greater risk for tumor progression.<sup>5</sup> The current TNM staging system, which will be further discussed in a later section, is shown in Figure 1, and an illustration of the extent of tumor invasion is shown in Figure 2.

Because of the lifetime need for surveillance, the treatment of recurrent tumors, and the cost of complications associated with treatment, bladder cancer poses a significant economic burden. Avritscher et al demonstrated that, among a cohort of 208 patients with bladder cancer, the average cost was \$65,158 (US dollars) and that the predicted lifetime costs for patients averaged \$99,270 under the best-case scenario and \$120,684 under the worst-case scenario.<sup>6</sup> Another study that analyzed the cost of care among Medicare cancer patients estimated the 5-year net cost of bladder cancer in the United States at approximately one billion dollars (seventh highest among all cancers).<sup>7</sup> In large part because of the low prevalence of bladder cancer in the general population, widespread bladder cancer screening is not currently recommended. Screening of high-risk populations, however, may be beneficial in detecting early stage tumors before they become invasive. Messing et al found that detecting microscopic hematuria by using repetitive home hematuria reagent-strip testing was an effective means of identifying bladder cancer at noninvasive stages and found a decreased mortality rate due to bladder cancer in the screened cohort at 14-year follow-up.<sup>8</sup> On

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| Primary Tumor (T) |                                                                                                                     | Regional Lymph Nodes (N)                                                                                                                                   |                                                                                                                                         |
|-------------------|---------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|
| TX                | Primary tumor cannot be assessed                                                                                    | Regional lymph nodes include both primary and secondary drainage regions. All other nodes above the aortic bifurcation are considered distant lymph nodes. |                                                                                                                                         |
| T0                | No evidence of primary tumor                                                                                        | NX                                                                                                                                                         | Lymph nodes cannot be assessed                                                                                                          |
| Ta                | Noninvasive papillary carcinoma                                                                                     | N0                                                                                                                                                         | No lymph node metastasis                                                                                                                |
| Tis               | Carcinoma in situ: "flat tumor"                                                                                     | N1                                                                                                                                                         | Single regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node)              |
| T1                | Tumor invades subepithelial connective tissue                                                                       | N2                                                                                                                                                         | Multiple regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node metastasis) |
| T2                | Tumor invades muscularis propria                                                                                    | N3                                                                                                                                                         | Lymph node metastasis to the common iliac lymph nodes                                                                                   |
| 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                                                                           |                                                                                                                                                            |                                                                                                                                         |
|                   |                                                                                                                     | 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 |

**FIGURE 1.** Definitions of Tumor, Node, Metastasis (TNM) Staging System. Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science and Business Media LLC, www.springer.com.

the basis of findings such as these, a randomized, prospective, screening trial is warranted to further explore the role of screening in the detection of bladder cancer.

Bladder cancer has many known risk factors, although many cases arise with no apparent exposure to carcinogens.<sup>9</sup> Age is a risk factor for developing bladder cancer, which occurs more commonly in the elderly. The median ages of men and women presenting with bladder cancer are 72 and 74 years, respectively.<sup>10</sup> Cigarette smoking is the strongest risk factor for developing bladder cancer, with smoking having a population attributable risk (PAR) of 46%.<sup>11</sup> In addition, the relative risk (RR) of death from bladder cancer among smokers is 3.3 for current smokers and 2.1 for former smokers among men; the RR for women is 2.2 for current smokers and 1.9 for former smokers.<sup>11</sup> Although the specific carcinogens in cigarette smoke responsible for the increased risk of bladder cancer are unknown, aromatic amines are thought to be the inciting factor.<sup>12</sup> After 4 years, smoking cessation can reduce the risk of bladder cancer by up to

40%, highlighting the important role physicians can have in counseling patients on smoking cessation.<sup>13</sup>

Many chemicals are thought to be carcinogens for bladder cancer, including aniline dyes, which are often found in color fabrics, and cyclophosphamide.<sup>12,14,15</sup> Occupations with increased exposure to aromatic amines, which include betanaphthylamine, 4-aminobiphenyl, and benzidine, and other potential bladder carcinogens, include those in the painting and leather industries, and other groups such as autoworkers, truck drivers, metalworkers, paper and rubber manufacturers, foundry workers, dry cleaners, dental technicians, hairdressers, and marine engineers.<sup>14,16</sup> Bladder cancer from occupational exposures often does not occur until 30 to 50 years after exposure.<sup>9</sup>

Other exposures have also been associated with an elevated risk of bladder cancer. A significantly higher rate of bladder cancer was detected in northeastern Taiwan, where high arsenic levels in water was endemic.<sup>17</sup> An increased risk of bladder cancer was also found in people who had ingested a Chinese herbal weight-reduction supplement in which—because of a manufacturing error—the herb *Stephania tetrandra* was accidentally replaced by *Aristolochia fangchi*, which is carcinogenic.<sup>18</sup> Increased fluid intake may be associated with a lower risk of bladder cancer in men and has been proposed as a dietary modification for patients with bladder cancer by increasing urine output, decreasing the contact time of carcinogens with the urothelium, and diluting their relative concentration.<sup>16,19</sup> The Health Professionals Follow-up Study followed 48,000 men for a period of 10 years and demonstrated that fluid intake was inversely associated with the risk of bladder cancer; men with the highest fluid consumption (more than 2531 mL/day) demonstrated approximately half the risk of developing bladder cancer as those with the lowest fluid consumption (1290 mL/day).<sup>19</sup>

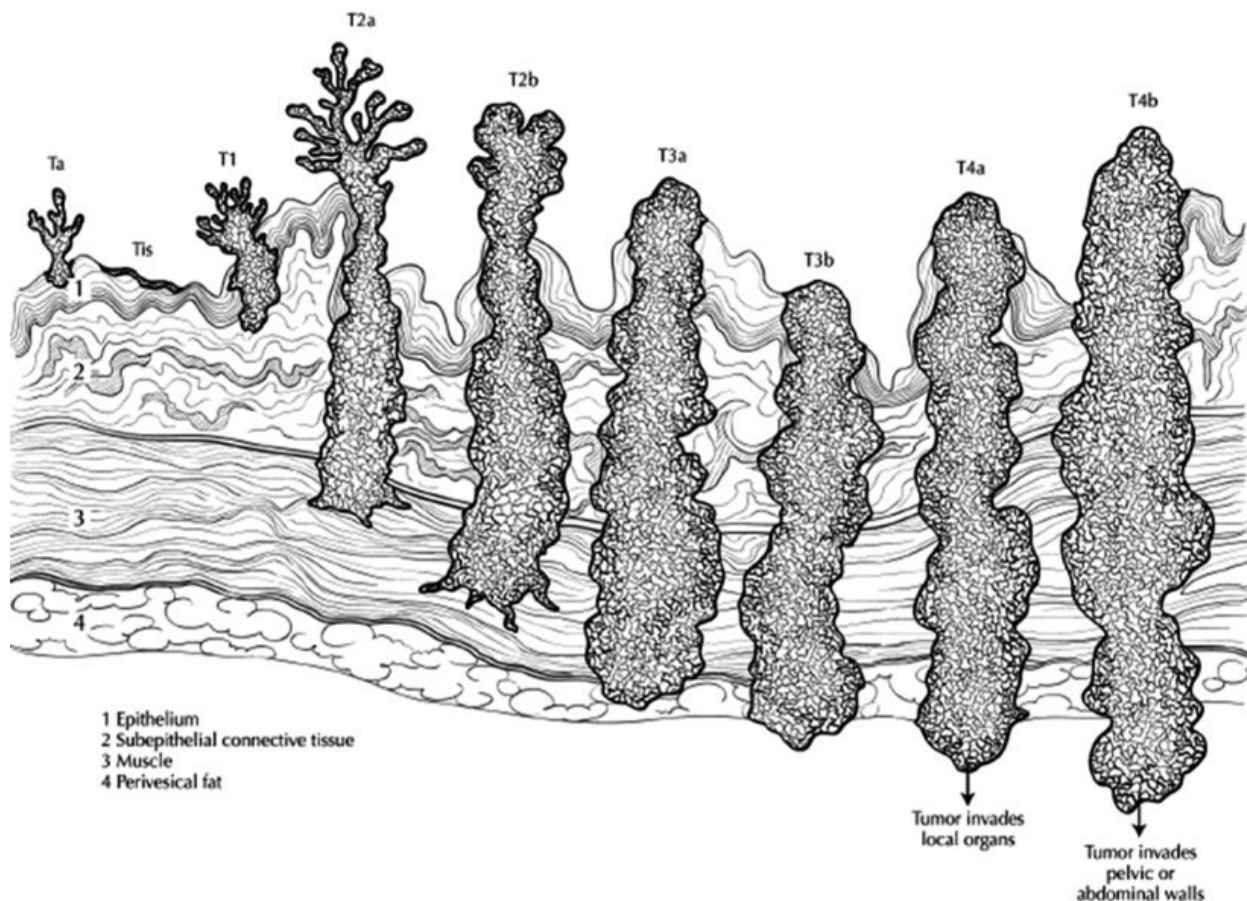


**FIGURE 2.** Extent of primary bladder cancer. Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science and Business Media LLC, www.springer.com.

Other studies, however, have failed to demonstrate any correlation between fluid intake and bladder cancer risk.<sup>20</sup> Inconsistencies also exist in the association of coffee and bladder cancer, and if coffee is a bladder carcinogen, it is a weak one.<sup>21</sup> More data are needed before definite recommendations for increasing overall or specific fluid intake as a potential preventative strategy can be made. In addition, artificial sweeteners and alcohol are not obvious risk factors for bladder cancer, and the consumption of fruits and vegetables, if they have any effect on bladder carcinogenesis, may have a protective effect.<sup>21</sup>

Urinary tract infection, chronic irritation from irritants such as catheters or bladder stones, and a non-functioning bladder are associated with an increased risk of squamous cell carcinoma (SCC) of the bladder.<sup>22,23</sup> Bladder infection by *Schistosoma haematobium* carries an increased risk of bladder cancer, especially SCC, and is endemic in Egypt; inflammation is

thought to play an important role in carcinogenesis associated with this parasite.<sup>9</sup> Exposure to pelvic radiation, for example in men with prostate cancer, appears to increase the subsequent risk of bladder cancer.<sup>24</sup> Strong epidemiologic evidence does not exist for a hereditary cause of most bladder cancers.<sup>9</sup>

## Diagnosing Bladder Cancer

### Signs and Symptoms

Bladder cancer may be detected incidentally or because of symptoms. Hematuria is the most common finding among patients presenting with bladder cancer, occurring in up to 85% of patients.<sup>25</sup> Hematuria, however, can also be present in many benign conditions such as urinary tract infections, other inflammatory conditions, nephrolithiasis, and benign prostatic hyperplasia. The American Urological Association's (AUA) Best Practice Policy Panel on Asymptomatic Microscopic Hematuria

defines microscopic hematuria as  $\geq 3$  red blood cells (RBCs) per high-power microscopic field in urinary sediment from 2 of 3 properly collected urinalysis specimens.<sup>26</sup> Irritative voiding symptoms such as frequency or dysuria can also be the presenting symptoms of bladder cancer. Because urinary tract infections are much more common in women, misinterpretation of hematuria and irritative voiding symptoms may result in delayed diagnosis in women, possibly resulting in a more advanced stage at the time of diagnosis.<sup>27,28</sup> Patients may also present with flank pain or other symptoms related to hydronephrosis, which is likely related to the location of tumor at the ureterovesical junction.

### Cystoscopy

Conventional or white-light cystoscopy is the “gold standard” for the detection of bladder cancer. Flexible cystoscopy performed in the office either with or without fulguration of small bladder tumors after the administration of intraurethral lidocaine gel is associated with minimal discomfort and is well tolerated.<sup>29</sup> A disadvantage of conventional cystoscopy is the difficulty in detecting flat lesions such as carcinoma in situ (CIS), which can lead to incomplete resection and higher recurrence rates. Fluorescent agents allow visualization of tissue with elevated metabolism and have been shown to improve the effectiveness of the initial resection in superficial and early invasive bladder cancer.<sup>30</sup> 5-aminolevulinic acid (5-ALA) is a precursor in the heme biosynthesis pathway and induces an accumulation of fluorescent endogenous porphyrins, mainly protoporphyrin IX (PPIX) in tissues of epithelial origin.<sup>31</sup> The exact mechanisms by which fluorescent PPIX selectively accumulates in cancerous tissue are unknown, although several theories exist, including differences in cellular metabolism, structural characteristics of diseased urothelium, inflammation, and hyperproliferation of the urothelium.<sup>31</sup> Several single-center studies comparing 5-ALA–fluorescent cystoscopy with conventional cystoscopy have shown an increase in recurrence-free survival, a lower residual tumor rate, and an overall improvement in the diagnosis of bladder cancer.<sup>30,32</sup> The first prospective, randomized study performed at multiple centers compared white-light with 5-ALA–fluorescent cystoscopy and did not show a difference between groups in their

recurrence-free and progression-free survival rates.<sup>33</sup> This study of 300 patients looked at outcomes at 12 months, but only 21% of patients had high-grade tumors for which CIS and/or dysplasia are common.<sup>33</sup> Currently, fluorescent cystoscopy is not incorporated into the National Comprehensive Cancer Network (NCCN) guidelines nor the updated AUA guidelines on management of noninvasive bladder cancer, so more randomized studies at multiple centers are needed to better define fluorescent cystoscopy's role.<sup>34,35</sup>

### Imaging

Careful staging is imperative in the pretreatment planning for patients with bladder cancer. Radiographic imaging is a significant part of this staging. Imaging with computed tomography (CT) has essentially replaced intravenous pyelograms (IVP) in many centers. Magnetic resonance imaging (MRI) had been a reliable modality for patients with renal failure, and although recent reports of nephrogenic systemic fibrosis (NSF) from administration of gadolinium-containing contrast agents has limited the role of MRI in those with severely impaired renal function, MRIs with gadolinium can still safely be performed in the majority of patients with chronic kidney disease.<sup>36,37</sup>

To address the substantial understaging that occurs in patients with invasive bladder cancer, newer imaging techniques have been explored to improve the accuracy of pretreatment staging. Magnetic resonance imaging has good soft-tissue resolution and multiplanar capabilities, and this, accompanied with recent advances in MR imaging, has resulted in more accurate staging.<sup>38</sup> According to Tekes et al, gadolinium-enhanced MRI has an accuracy of 85% in differentiating noninvasive versus invasive disease and was 82% accurate in differentiating organ-confined from nonorgan-confined disease.<sup>39</sup> Overstaging can be a problem with MRI, however, because of acute edema and hyperemia after recent biopsy or resection, as both may give the appearance of tumor spread.<sup>38</sup> Continued advances in MRI may help to further improve staging in the future.

Virtual cystoscopy is another imaging technique that may be useful in bladder cancer staging. It involves 3-D surface-model generation and depiction of the urinary bladder on the basis of volumetric MR

or CT imaging data; this technique allows visualization of precise spatial relations between regions of pathology and adjacent normal tissue.<sup>38</sup> The advantages of virtual cystoscopy include its minimal invasiveness, the evaluation of the urethral orifice from a cranial view, the visualization of the mucosa within diverticulae, and its use in patients with urethral stricture disease.<sup>40,41</sup> The disadvantages include cost, inability to obtain tissue, low sensitivity to depict flat lesions such as carcinoma in situ (CIS), and increased radiation exposure, specifically with CT cystoscopy.<sup>38,42</sup> CT cystoscopy is performed by insufflating air or carbon dioxide into the bladder; alternatively, bladder distention can be achieved by instilling dilute contrast through a 6-French feeding tube.<sup>43,44</sup> Virtual cystoscopy is unlikely to replace conventional cystoscopy but may be used conjointly to help reduce the number of surveillance cystoscopies or to aid in diagnosis when conventional cystoscopy is inconclusive.

Conventional CT and MRI lack the ability to detect early metastatic disease, particularly in normal-sized lymph nodes.<sup>38</sup> Furthermore, reactive nodes may mimic metastatic nodal disease, and therefore, more accurate lymph node imaging is needed.<sup>38</sup> Positron emission tomography (PET) with the glucose analog 2-deoxy-2-<sup>[18F]</sup>fluoro-D-glucose (18-FDG) is a noninvasive imaging modality that is used in a variety of malignancies including lymphoma and lung cancer.<sup>38</sup> In urology, PET has been a slower area to develop than in other specialties, largely because of the urinary excretion of many PET tracers and the variable uptake in some urological tumors.<sup>45</sup> The 18-FDG detects increased glycolytic activity in neoplastic cells with a high metabolic rate and has increased uptake on PET imaging.<sup>38</sup> Using a PET/CT device allows the localization of functional findings detected on PET in anatomic structures shown on CT during one imaging procedure.<sup>45</sup> Drieskens et al evaluated the use of 18-FDG PET/CT scans preoperatively in 55 patients with bladder cancer to help diagnose metastatic disease and found the sensitivity, specificity, positive-predictive value, and negative-predictive value of 18-FDG PET/CT to be 60%, 88%, 75%, and 79%, respectively.<sup>46</sup> Kibel et al performed a prospective study of 43 patients with muscle-invasive bladder cancer with no metastatic disease detected by conventional imaging who had undergone preoperative 18-FDG PET/CT and found the sensitivity, specificity,

positive-predictive value, and negative-predictive value to be 70%, 94%, 78%, and 91%, respectively.<sup>47</sup> In addition, recurrence-free, disease-specific, and overall survival were all lower in patients with positive 18-FDG PET/CT scans.<sup>47</sup> Newer agents such as <sup>11</sup>C Methionine and choline are not excreted in urine and may be used more frequently in PET imaging of bladder cancer in the future.<sup>38</sup>

## Staging

### Clinical Staging

Clinical staging is an important yet imperfect evaluation of patients with bladder cancer with about 30% to 50% of patients clinically understaged at the time of cystectomy.<sup>48-50</sup> During an initial endoscopic evaluation, the bladder, urethra, and, when there is concern, the upper urinary tracts must be evaluated for potential disease. Tissue from any suspicious area in the bladder is removed by either bladder biopsy or transurethral resection of bladder tumor (TURBT) and sent to pathology for evaluation. When an abnormality in the upper tract is suspected on the basis of abnormal imaging or a positive selective ureteral cytology, then flexible or rigid ureteroscopy should be performed to further evaluate the area of concern. Cold-cup biopsy of any lesion suspicious for CIS should be performed; the prostatic urethra should be biopsied when the patient has a positive cytology without visible tumors or has multifocal CIS.<sup>51</sup> The prostate biopsy should have tissue from the urethra, ducts, and glands and, thus, should be performed with a resection loop.<sup>51</sup> Patients with low-risk-appearing tumors and a negative cytology should not undergo random biopsies.<sup>51</sup>

At the time of evaluation in the operating room, a bimanual exam is performed under anesthesia. When a 3-dimensional mass is palpated, the patient is considered to have T3b disease by clinical staging.<sup>52</sup> Imaging is an essential part of clinical staging and is largely performed by CT of the upper and lower urinary tracts. As mentioned earlier, MRI and ultrasound are often used in cases of renal insufficiency, and several alternative modalities are being investigated to try to improve the accuracy of clinical staging. A second TURBT should be considered in all patients with high-grade Ta or any T1 urothelial

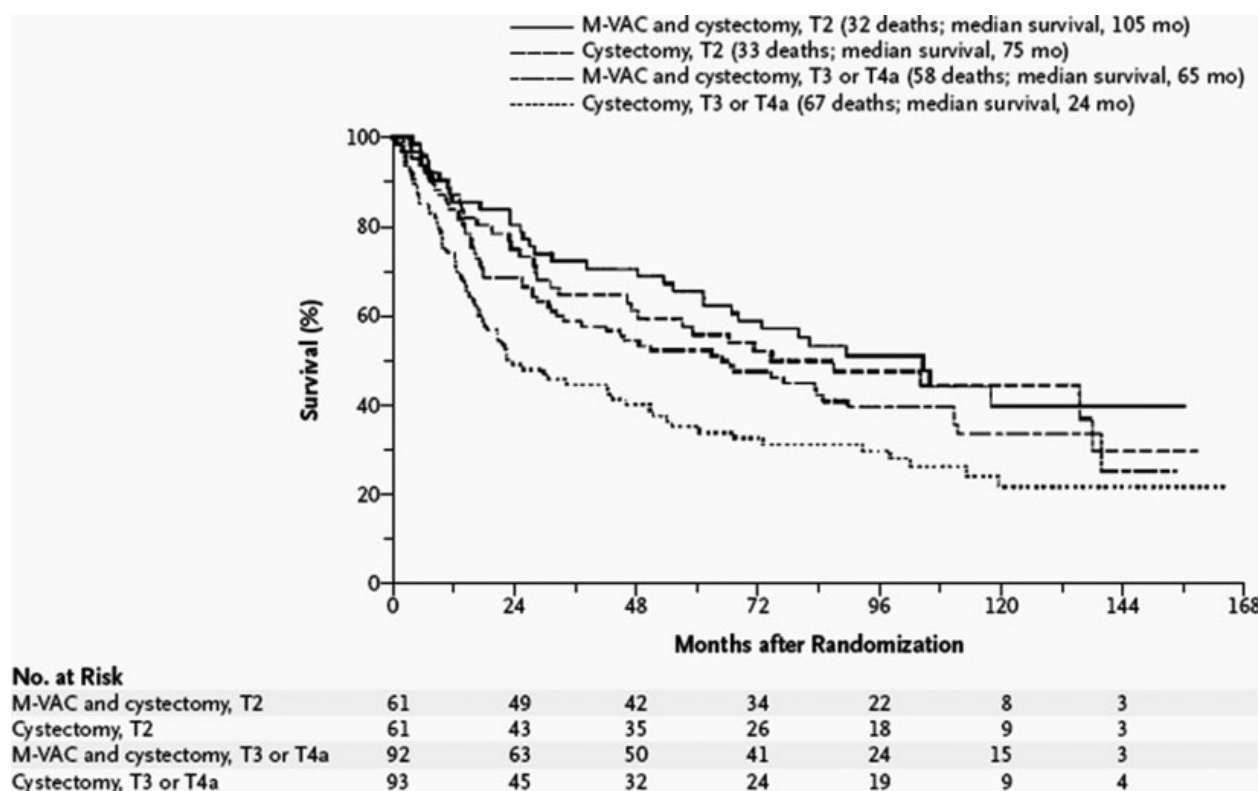


**FIGURE 3.** Survival according to treatment group and whether patients had superficial muscle involvement (Stage T2 disease) or more advanced disease (Stage T3 or T4a). M-VAC denotes methotrexate, vinblastine, doxorubicin, and cisplatin. Reprinted with permission from Grossman HB, Natale RB, Tangen CM, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. *N Engl J Med*. 2003;349:859-866. Copyright © 2003 Massachusetts Medical Society. All rights reserved.

carcinoma in an attempt to prevent understaging and possible progression to metastatic disease.<sup>51</sup>

### Pathologic Staging

The TNM staging system is shown in Figure 1, and an illustration of the extent of tumor invasion is shown in Figure 2. The term *superficial* is misleading because superficial disease implies a more benign process and is now being more appropriately called *nonmuscle-invasive*. Nonmuscle-invasive tumors do not invade the muscularis propria; they include lesions that are confined to the mucosa (Ta and CIS) and those that invade below the basement membrane into the lamina propria (T1). Carcinoma in situ (CIS or Tis) is a flat, high-grade, noninvasive bladder cancer with a very high rate of recurrence and progression within 5 years if not treated.<sup>53</sup> All lesions that invade the lamina propria are identified as T1 lesions.

Organ-confined disease (T2a and T2b) has a better prognosis than disease that has extended through the bladder wall to the perivesical fat (T3).<sup>54</sup>

Urothelial carcinomas that invade the prostate (T4a) represent a challenging clinical problem generally requiring multimodality therapy. Studies have shown that overall survival is worse with higher-staged disease.<sup>55,56</sup> The Kaplan-Meier plot from Grossman et al demonstrates this in Figure 3.<sup>56</sup> Increasing incidence of lymph node involvement is found with increasing pathological stage of the primary bladder tumor, and overall 5-year survival (34%) is significantly worse with node-positive disease.<sup>55</sup>

Under the current American Joint Committee on Cancer (AJCC 7<sup>th</sup> edition) TNM guidelines, the common iliac nodes are considered to be a secondary drainage region and are not considered metastatic disease.<sup>57</sup> The nodal staging system is now the following: N1 indicates a single positive node in a primary drainage region; N2 indicates multiple positive nodes in primary drainage regions; and N3 indicates common iliac node involvement.<sup>57</sup> The prior TNM staging system considered metastasis in a single node  $\leq 2$  cm to be N1, metastasis in a single node between 2 cm and

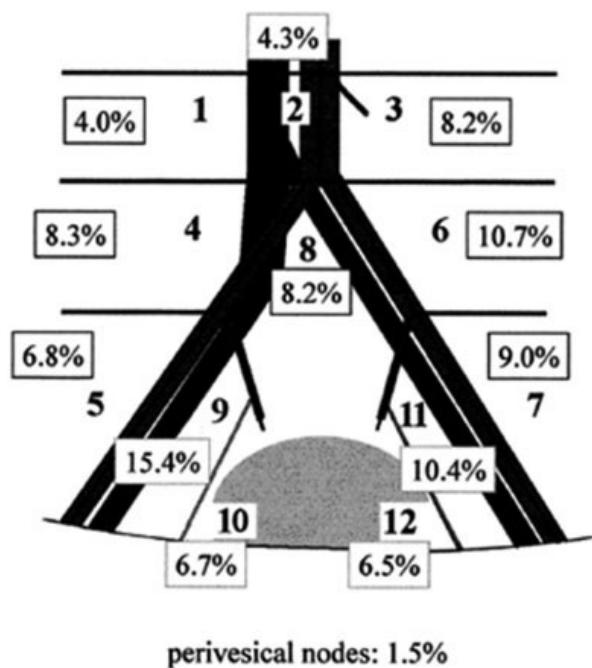


**FIGURE 4.** Regional distribution of 599 lymph node metastases. Percentage is based on a total of 599 nodal metastases observed in all patients. Reprinted from *Journal of Urology*. Leissner J, Ghoneim MA, Abol-Enein H, et al. Extended radical lymphadenectomy in patients with urothelial bladder cancer: results of a prospective multicenter study, 171 (1), 139-144 (2004), with permission from Elsevier.

5 cm or multiple nodes <5 cm to be N2, and metastasis in a node >5 cm to be N3.<sup>58</sup> Under the older staging system, lymph nodes outside the true pelvis were considered distant metastases.<sup>58</sup>

The primary lymph nodes include the external iliac, hypogastric, obturator, and presacral nodes, whereas the secondary drainage region comprises the common iliac nodes, where primary nodal regions drain.<sup>57</sup> Skip metastases to secondary drainage sites are uncommon.<sup>57</sup> A study by Leissner et al mapped the lymphatic spread of bladder cancer and found that lymph node metastases were most commonly found in the obturator spaces and adjacent to the iliac vessels; additionally, 16% of lymph node metastases included nodes above the aortic bifurcation, and 8% of nodal metastases were in the presacral region (Fig. 4).<sup>59</sup> Distant spread most commonly involves the retroperitoneal lymph nodes, lung, bone, and the liver.<sup>57</sup>

The TNM staging system provides useful estimates for recurrence risk and survival outcomes, but heterogeneity of tumor biology and patient characteristics within each TNM group leads to significant variation.<sup>53</sup> TNM staging does not take into consideration other factors that can influence outcome such

as age, sex, comorbidities, and prior treatments.<sup>53</sup> Several factors have been identified as reliable predictors of disease recurrence and progression for nonmuscle-invasive disease including stage, grade, multifocality, recurrence at 3 months, presence of CIS, and size of the initial tumor (>3 cm).<sup>60,61</sup> Clinical staging inaccuracies are highlighted by the finding that up to one-third of patients with T1 disease are upstaged at the time of radical cystectomy as well as a 50%-60% of muscle-invasive tumors that were thought to be organ confined.<sup>48,50</sup> Other pathological features including lymphovascular invasion and divergent histologic features (for example, micropapillary or small cell carcinoma) can also negatively affect overall survival.<sup>62-64</sup> Clinicians, therefore, must use their judgement to account for these factors not included in the staging system. Given the inaccuracy of personal judgement, statistical methods and predictive models should be incorporated into clinical decisions.<sup>53</sup> Nomograms have emerged as excellent tools that provide improved predictive accuracy compared with standard categorical models and have proven to be easily adapted for clinical use.<sup>53</sup>

In summary, the TNM staging system provides valuable information that helps predict outcomes and direct clinical management. Progressive stages are associated with worsening 5-year survival rates.<sup>38</sup> Given all the variables not accounted for in the TNM staging system, there is a need to better identify patients who have a low risk of recurrence (so that they are not overtreated) and to identify those who are likely to progress (for the purpose of treating them more aggressively).<sup>65</sup> The addition of tools such as nomograms and biomarkers may help achieve these goals.

## Histopathology

### Tumor Grade

The most widely used classification system for grading urothelial neoplasms has been the 1973 World Health Organization (WHO) classification, which has designations for papilloma and grades 1, 2, and 3 carcinomas. In 2004, members of the WHO and International Society of Urologic Pathologists recommended a revised consensus classification for papillary neoplasms.<sup>66</sup> A new category of papillary urothelial neoplasm of low

malignant potential (PUNLMP) was created to describe lesions with an increased number of urothelial layers in comparison with papilloma but without cytologic features of malignancy.<sup>66</sup> Grade 1 papillary urothelial carcinomas are now subdivided into PUNLMP or low-grade papillary urothelial carcinomas; grade 2 papillary urothelial carcinomas under the 1973 WHO classification are classified as either low grade or high grade, depending on the interpretation of the pathologist, and grade 3 carcinomas are now high-grade.<sup>66</sup> The current (AJCC 7<sup>th</sup> edition) TNM staging system has also converted to low-grade and high-grade designations to match the WHO grading system.<sup>57</sup>

### Tumor Histology

In recent years, several variant morphologies have been described, and most have been recognized in the 2004 WHO Classification.<sup>67</sup> Although transitional cell carcinoma (TCC) accounts for about 90% of bladder cancer, many of the remaining types of bladder cancer should be recognized because most have aggressive features and/or require alternative treatments. Pure non-TCCs are associated with more aggressive behavior, resulting in higher tumor stage at presentation and worse survival outcomes.<sup>68,69</sup> Less is known about the significance of TCCs with mixed histological features.<sup>68</sup>

Approximately 10% of TCCs contain foci of glandular morphology, and up to 60% of tumors exhibit focal squamous differentiation.<sup>70</sup> Glandular differentiation is usually in the form of small tubular or gland-like spaces in conventional bladder cancer, whereas squamous differentiation involves evidence of squamous production, including intracellular keratin, intercellular bridges, or keratin pearls; the degree of squamous differentiation reflects the grade of cancer.<sup>67</sup> The prognostic significance of squamous or glandular differentiation is unclear, although some studies have suggested an adverse outcome.<sup>71</sup> Wasco et al evaluated 448 consecutive TURBTs and identified mixed histologic features in 25% of the specimens, which were associated with muscle invasion at TURBT and with extravesical disease at cystectomy; these histologic features, however, were not shown to be significant predictors of disease-specific survival.<sup>68</sup> The spectrum of mixed histologic components included squamous (40%), glandular (18%), sarcomatoid

(11%), micropapillary (10%), small cell (9%), and plasmacytoid (1%); 11% had multiple types of mixed histologic components.<sup>68</sup> Given the more invasive nature of these mixed variants, patients may benefit from a more aggressive treatment strategy, such as early cystectomy for T1 tumors or neoadjuvant chemotherapy for T2 tumors.<sup>68</sup>

Squamous cell carcinoma (SCC) of the bladder accounts for less than 5% of all bladder cancers in the United States.<sup>72</sup> Risk factors for SCC include long-term catheterization, a nonfunctioning bladder, urinary tract calculi, and chronic infection with *Schistosoma hematobium*.<sup>22,23</sup> Squamous cell carcinoma of the bladder tends to be aggressive with many patients having pT3 or greater disease; tumors frequently have an associated desmoplastic response, a prominent lymphocytic infiltrate, and keratinization.<sup>69,72</sup> Despite these characteristics, recent series have reported 5-year, disease-specific, survival rates as high as 57% with radical cystectomy, which is similar to those with invasive urothelial carcinoma.<sup>69</sup>

Squamous cell carcinoma can occur in both nonbilharzial and bilharzial bladders. The nonbilharzial type occurs in Western countries, occurs most often in the seventh decade of life, is usually attributed to prolonged indwelling catheterization, is present at an advanced stage with tumors mostly of moderate and high grades, and has a poor prognosis.<sup>23</sup> Bilharzial SCC occurs commonly in Africa and the Middle East, where *Schistosoma hematobium* is endemic; it occurs often in the fifth decade of life and presents at an advanced stage, although mostly with tumors that are of low and moderate grades.<sup>23,73</sup> The bladder carcinogenesis is likely related to the bacterial and viral infections commonly associated with bilharzial infestation rather than the parasite itself.<sup>23</sup> Radical cystectomy is the preferred treatment for SCC in bilharzial bladders with 5-year survival rates of about 50%.<sup>23</sup>

Urachal carcinoma is rare, accounting for less than 1% of bladder neoplasms.<sup>74</sup> The urachus is a vestigial structure that connects the bladder to the allantois during early embryonic development and, after birth, becomes the median umbilical ligament.<sup>75</sup> It has intramucosal, intramuscular, and supravescical segments, and urachal neoplasms can arise from any of these areas and can be epithelial or mesenchymal.<sup>75</sup> Most urachal neoplasms are adenocarcinomas originating from the epithelium of the urachal remnant,

but other histological subtypes have been described.<sup>74,76</sup> Treatment for urachal carcinoma is primarily surgical, with extended partial cystectomy, en bloc resection of urachal mass, urachal tract, and umbilicus, and pelvic lymph node dissection; radical cystectomy can be reserved for larger tumors.<sup>74</sup> Radiation and chemotherapy are ineffective.<sup>74</sup> Herr et al reported an 88% 5-year survival rate in patients with tumor confined to the urachus, bladder, and periurachal fat compared with a 0% 5-year survival time in patients with tumors that invaded the peritoneal cavity.<sup>74</sup>

Small cell carcinoma of the urothelial tract is uncommon, representing 0.5%–0.7% of all urothelial tumors.<sup>77,78</sup> Like its neuroendocrine counterparts in the lung, small cell tumors of the bladder have a rapid growth rate but are chemosensitive.<sup>79</sup> Tumors are positive for chromogranin A and synaptophysin in greater than 60% of cases.<sup>67</sup> Clinical understaging is common, and prognosis is poor, with an overall 5-year survival rate of 8%.<sup>80</sup> Preoperative chemotherapy, even in clinically localized disease, followed by localized therapy may achieve the optimal outcome, although because the disease is rare, this is difficult to confirm.<sup>79,81</sup>

Micropapillary bladder carcinoma is a rare variant of urothelial carcinoma that closely resembles papillary serous carcinoma of the ovary, in which the predominant pattern consists of delicate filiform processes of tight infiltrating clusters of micropapillary aggregates without central vascular cores.<sup>63</sup> Micropapillary bladder carcinoma is an aggressive variant in which clinical understaging is common.<sup>63</sup> The optimal treatment for micropapillary urothelial carcinoma is unknown. Kamat et al looked at their series of 44 patients with nonmuscle-invasive micropapillary disease and found that intravesical Bacillus Calmette-Guerin (BCG) was ineffective, with 67% of patients experiencing progression and 22% developing metastatic disease.<sup>63</sup> On the basis of these findings, they advocated radical cystectomy as the initial treatment of choice for nonmuscle-invasive micropapillary urothelial carcinoma, and the incidence of disease progression appeared to be lower than the incidence in those who underwent a delayed cystectomy.<sup>63</sup> Although the data are provocative, the management of patients with micropapillary urothelial carcinoma will be optimally defined after additional study.

Nested variant of urothelial carcinoma is characterized by confluent small nests and abortive tubules of mildly atypical neoplastic cells in the lamina propria and/or muscularis propria; these characteristics overlap with various benign entities such as nested papilloma, Brunn nests, cystitis cystica, and nephrogenic metaplasia, but its distinction is important because of its aggressive behavior.<sup>82,83</sup> Nested variant should be approached clinically as high-risk disease, with early cystectomy as an option for pT1 and pT2 tumors.<sup>83</sup> The mean age of patients with nested variant is 60 years and older, and the majority of patients are men, similar to the distribution seen in conventional bladder cancer.<sup>82</sup> Immunohistochemically, similar to poor-prognosis urothelial bladder cancer, nested variant has a loss of p27 expression in the deeper component of the tumor and a high proliferation index; to the contrary of poor-prognosis bladder cancer, however, biomarkers such as p53, bcl-2, and epidermal growth factor receptor (EGF-R) are not frequently altered in nested variant.<sup>83</sup>

Sarcomatoid carcinoma and carcinosarcoma are rare diphasic tumors of the bladder that have an epithelial component adjacent to a mesenchymal component; the 2 histological subtypes are often considered to represent different points on a continuum between epithelial and mesenchymal differentiation.<sup>84</sup> These tumors are widely considered to have a poor prognosis, but the body of literature on them is limited.<sup>69,85</sup> Although the term *carcinosarcoma* is embraced by some, the 2004 WHO classification endorses the term *sarcomatoid carcinoma*.<sup>67,86</sup> Future clinical trials at multiple centers are needed to develop more effective treatment protocols for treating these aggressive variants.

Plasmacytoid variant of urothelial carcinoma has a histologic appearance similar to plasma cells and is a rare aggressive subtype associated with poor prognosis.<sup>87</sup> This variant may pose diagnostic difficulties where it may be mistaken for an inflammatory process; immunohistochemical staining can help distinguish plasmacytoid urothelial carcinoma from plasmacytoma and metastatic carcinoma.<sup>87</sup> In the largest series to date (17 cases), no patients with more than 1 year of follow-up survived the disease, emphasizing the aggressive nature of this variant.<sup>87</sup>

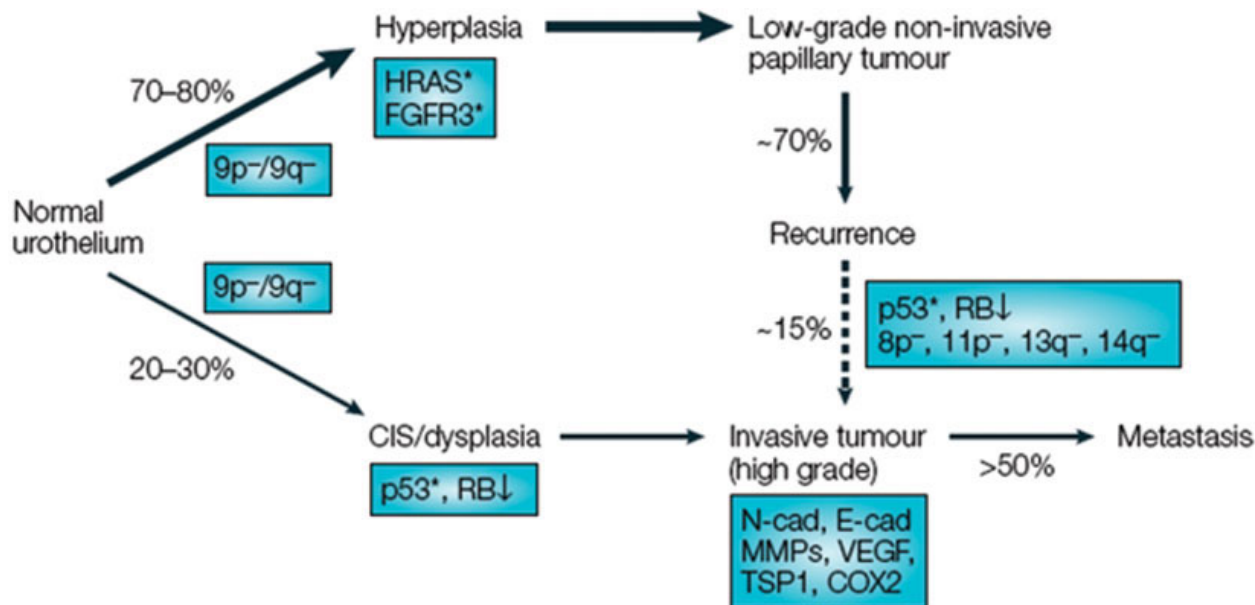


**FIGURE 5.** Important genetic and epigenetic defects that characterize the divergent pathways of urothelial tumorigenesis. Clinical data and experimental evidence indicate that urothelial tumors arise and progress along 2 distinct pathways. The first of these (top pathway), which accounts for 70% to 80% of urothelial tumors, is often preceded by simple and papillary hyperplasia and exhibits a tumor morphology that is low-grade, superficial, and papillary. About 70% of these tumors will recur, but only approximately 15% will proceed to infiltrate the musculature (dashed line). These tumors harbor frequent mutations in the *HRAS* gene (30% to 40%) and fibroblast growth factor receptor 3 (*FGFR3*) gene (approximately 70%), indicating that RTK-Ras activation has an early and crucial role in this tumorigenesis pathway. Deletions in the short arms of chromosomes 8 and 11 (8p- and 11p-) and long arms of chromosomes 13 and 14 (13q- and 14q-) are often associated with tumor progression to the invasive stages. The second tumor pathway (bottom pathway) (accounting for 20% to 30% of the urothelial tumors) is characterized by high-grade muscle-invasive tumors, which either originate from flat carcinoma in situ/severe dysplasia or arise de novo. Over half of these tumors contain structural and functional defects in the tumor suppressors *p53* and/or the retinoblastoma protein (*RB*), and over 50% of these tumors progress to local and distant metastases despite radical cystectomy and chemotherapy. Invasion and metastases are promoted by several factors that alter the tumor microenvironment, including the aberrant expression of N- and E-cadherins (*N-cad* and *E-cad*), matrix metalloproteinases (*MMPs*), angiogenic factors such as vascular endothelial growth factor (*VEGF*), and antiangiogenic factors such as thrombospondin 1 (*TSP1*) and cyclooxygenase 2 (*COX2*). Deletion of both arms of chromosome 9 (9p-/9q-) occurs early during urothelial tumorigenesis, but they do not seem to be markers that differentiate the 2 tumor pathways. Elucidating the genetic and epigenetic causes of the 2 distinct pathways of urothelial tumorigenesis should have a tremendous impact on the rational management of different urothelial carcinomas. Asterisk indicates mutated proteins. Reprinted by permission from Macmillan Publishers Ltd: Nature Reviews/Cancer. Wu, XR. Urothelial tumorigenesis: a tale of divergent pathways. *Nat Rev Cancer*. 2005;5:713–725; Copyright ©2005.

## Tumor Biology and Markers

Urothelial carcinomas are thought to arise from at least 2 separate mechanisms.<sup>88</sup> (Fig. 5) These carcinomas present as a heterogeneous group of diseases that consist of 2 main phenotypic variants, low-grade papillary variant and invasive tumor variant, which have drastically different biological behaviors and prognoses.<sup>89</sup> Low-grade noninvasive tumors are characterized by mutations in the *HRAS* and fibroblast growth factor receptor 3 (*FGFR3*) genes, whereas high-grade invasive tumors frequently have defects in the *p53* and *pRb* tumor-suppressor pathways.<sup>89</sup> Tumor invasion and progression in bladder cancer appears to be a multifactorial process, promoted by microenvironmental changes, many of which are mentioned in Figure 5.<sup>89</sup>

The tumor suppressor gene *p53* plays a key role in regulating cell-cycle progression and apoptosis under toxic conditions. Because of the frequency of *p53*

alterations in high-grade bladder cancer, investigators have looked at *p53* expression in combination with other markers. In a study conducted at multiple centers, Shariat et al looked at a combination of *p53*, *pRB*, *p21*, and *p27* to evaluate whether these markers could improve the prediction of clinical outcomes in patients with advanced bladder cancer who had undergone radical cystectomy and lymph node dissection.<sup>90</sup> The combination of molecular markers improved the predictive accuracy for disease recurrence and cancer-specific mortality after cystectomy, whereas individual markers did not.<sup>91</sup> Future studies are needed to better elucidate whether using *p53* as a bladder cancer prognostic marker either alone or in conjunction with other markers will enhance clinical management of nonmuscle-invasive and muscle-invasive disease.

Agents that restore the tumor-suppression functions of tumor-suppressor genes such as *p53* or *Rb* may potentially have a therapeutic role.<sup>92,93</sup> Pagliaro

et al treated a series of bladder cancer patients with replication-defective adenoviral particles that encode wild-type *p53* (*Ad5CMV-p53*); the intravesical instillations were well tolerated, and the vector was detected in the targeted bladder tissue.<sup>94</sup> Another way gene therapy can be used is by introducing viral replication within the tumor that will amplify the engineered virus, potentially leading to spread of the virus throughout the tumor mass.<sup>95</sup> Moreover, it is hypothesized that tumor antigens released from lysed tumor cells could promote a systemic antitumor immune response.<sup>95</sup> Continued research in this area is needed to determine the degree of antitumor response that can be achieved from these methods.

One of the greatest interests recently in bladder cancer is in looking for potential genetic markers that could help detect bladder cancer earlier and/or alleviate the need for frequent cystoscopy. Among the most common genetic changes in bladder cancer is the loss of heterozygosity (LOH) on chromosomes *9p* and *9q*, which is found regardless of tumor grade and stage; the LOH on other chromosomes is found more frequently in tumors with higher grade and stage.<sup>96</sup> DNA microsatellites are highly polymorphic repeats found throughout the genome, and microsatellite markers can detect cancer-associated alterations in genetic material, including microsatellite instability and LOH.<sup>97</sup> A recent, prospective study conducted at multiple centers showed that microsatellite analysis was a strong predictor for future recurrences but that the sensitivity was not high enough to implement its use in routine practice.<sup>98</sup> A more recent analytical tool that has been developed to detect genomic instability in urinary DNA uses small nucleotide polymorphisms (SNPs). SNP chips have a potential advantage over microsatellite analysis in that they can screen more than 300 genetic loci at once compared with 13–20 loci, which leads to a greater sensitivity of the detection of molecular changes.<sup>99</sup>

Fluorescence in situ hybridization (FISH) test is another test that is based on the detection of genetic abnormalities in cells present in urine (Table 1). One 2005 meta-analysis examining urine markers for surveillance showed that FISH had a median sensitivity of 79% and median specificity of 70%.<sup>100</sup> The main disadvantages of FISH are the lack of standardization of the criterion for a positive test, the low sensitivity of detecting low-grade tumors, its expense, and the

need for specially trained laboratory personnel to perform the test.<sup>96,101</sup> Combined testing with other assays may improve the effectiveness of this biomarker. Park et al evaluated gene amplification, mRNA expression, and protein expression of the gene Aurora kinase A (*AURKA*) which encodes a key regulator of mitosis that is frequently amplified and/or overexpressed in cancer cells.<sup>102</sup> The FISH test for *AURKA* gene amplification had a 96.6% specificity and an 87% sensitivity in detecting bladder cancer in exfoliated cells in voided urine.<sup>102</sup>

Proteomics has led to the discovery of markers that could potentially be used to detect bladder cancer. Surface-enhanced laser desorption/ionization (SELDI) is a mass spectrometry technique that can identify and quantify biomarkers in urine such as CXCL1 and matrix metalloproteinase (MMP).<sup>103</sup> CXCL1 is a CXC chemokine known to be overexpressed in invasive bladder cancer.<sup>104</sup> Kawanishi et al evaluated urine samples from normal individuals and patients with nonmuscle-invasive and muscle-invasive bladder cancer.<sup>104</sup> Expression of CXCL1 in urine samples had a sensitivity of 70% and a specificity of 81% for predicting patients with bladder cancer.<sup>104</sup> MMP-related complexes, which are thought to be elevated in various cancers, were studied by Roy et al.<sup>105</sup> Both MMP-2 and MMP-9 dimers were significantly elevated in urine samples from 41 patients with bladder cancer compared with controls.<sup>105</sup> Urinary assays have been developed to target these markers (Table 1).

Epigenetics is a field that has coevolved with genomics and proteomics and refers to reversible changes in gene function that occur without changes in genetic sequence.<sup>103,106</sup> The most common epigenetic changes studied in bladder tumor markers relate to DNA methylation.<sup>103</sup> Lin et al evaluated the promoter methylation of *E-cadherin*, *p16*, *p14*, and *RASSF1A* in 57 patients with bladder cancer and found *RASSF1A* to be the best individual marker, with a sensitivity of 65%, and found the combination of *RASSF1A*, *p14*, and *E-cadherin* to have a sensitivity of detecting bladder cancer of 83%. Hypermethylation of these genes was not detected in any of the 20 urine samples from healthy control subjects.<sup>107</sup> These markers will require validation in future studies; however, urinary assays are currently being designed.

Although cystoscopy is the “gold standard” for the detection of bladder cancer, it is invasive and relatively expensive.<sup>108</sup> A voided urine cytology is the

TABLE 1. Review of Current Bladder Tumor Markers

| MARKER                                    | POINT OF SERVICE | TARGET                                                                           | FDA APPROVED | COMMENTS                                                                                         |
|-------------------------------------------|------------------|----------------------------------------------------------------------------------|--------------|--------------------------------------------------------------------------------------------------|
| Urine cytology                            | No               | Urothelial cells                                                                 | Yes          | Poor sensitivity for low-grade disease; dependence on expertise of pathologist                   |
| Fluorescence in situ hybridization (FISH) | No               | Chromosomes 3,7,17, and 9p21                                                     | Yes          | Lack of standardization of criteria for positive test; expensive; specially trained personnel    |
| NMP-22                                    | Yes              | Nuclear mitotic protein involved in distribution of chromatin during replication | Yes          | Results can be influenced by benign urologic conditions                                          |
| BTA stat                                  | Yes              | Complement factor H-related protein                                              | Yes          | Specificity is low among patients with benign urologic conditions                                |
| BTA-TRAK                                  | No               | Complement factor H-related protein                                              | Yes          | Same as BTA stat                                                                                 |
| Fluorescence immunocytochemistry          | No               | Sulfated mucin glycoproteins and glycosylated carcinoembryonic antigen           | No           | Need significant experience for interpreting and time to examine slides                          |
| BLCA-4                                    | No               | Nuclear mitotic protein                                                          | No           | Found in both tumor and normal regions of bladder                                                |
| BLCA-1                                    | No               | Nuclear mitotic protein                                                          | No           | Expressed only in tumor areas of bladder                                                         |
| Aurora kinase A ( <i>AURKA</i> )          | No               | Gene that encodes a key regulator of mitosis                                     | No           | Overexpression of <i>AURKA</i> can cause aneuploidy in urothelial cells                          |
| CXCL1                                     | No               | Secreted protein that is part of CXC chemokine family                            | No           | CXCL1 may be associated with tumorigenesis; may have increased levels in invasive bladder cancer |
| Matrix metalloproteinase (MMP) complexes  | No               | Zinc-dependent endopeptidases                                                    | No           | MMP's are key regulators of tumor growth and angiogenesis                                        |
| <i>FGFR3</i>                              | No               | Glycoprotein that is part of tyrosine kinase receptor family                     | No           | <i>FGFR3</i> mutations are associated with nonmuscle invasive bladder cancers                    |
| Methylation markers                       | No               | Methylation of a gene locus                                                      | No           | Hypermethylation of promoter sequence DNA is a mechanism for silencing tumor suppressor genes    |

standard noninvasive method for diagnosing or monitoring bladder cancer (Table 1).<sup>97</sup> It requires no patient preparation and is the most reliable marker for the detection of CIS.<sup>96</sup> The strength of urinary cytology is its high specificity of >90% for bladder-cancer detection.<sup>100,109</sup> The disadvantages of urine cytology are its poor sensitivity of low-grade disease and its dependence on the level of expertise of the pathologist for interpretation.<sup>96</sup> Thus, a noninvasive, inexpensive, and highly sensitive and specific bladder-cancer marker could decrease patient morbidity and cost associated with surveillance cystoscopy.

NMP-22 is a nuclear mitotic apparatus protein that is involved in the proper distribution of chromatin to daughter cells during cellular replication.<sup>110</sup> In 2005, the performance of the NMP-22 point-of-care (POC) assay was compared with urinary cytology in more than 1000 patients at risk for bladder cancer.<sup>111</sup> The sensitivity and specificity of the NMP-22 POC test was 55.7% and 85.7%,

respectively, and no significant difference was found between the NMP-22 POC and urine cytology, both used in conjunction with cystoscopy. The NMP-22 results can be falsely positive as a result of various benign conditions including inflammation, urinary tract infection, and renal calculi.<sup>112,113</sup>

BTA stat and BTA-TRAK tests (Polymedco, Cortlandt Manor, NY) detect a complement factor H-related protein in urine.<sup>96</sup> BTA stat is an immunoassay that can be performed in 5 minutes, whereas BTA-TRAK is a standard enzyme-linked immunosorbent assay (ELISA) that quantitatively measures the amounts of complement factor H-related protein and complement factor H in urine (BTA-TRAK product insert).<sup>96,97</sup> Complement factor H is present in human serum at high concentrations, and, thus, the BTA stat test may be falsely positive in many benign conditions that cause hematuria.<sup>114,115</sup> The specificity of BTA stat and BTA-TRAK tests among healthy individuals is > 90% but is

approximately 50%–60% among patients with various benign genitourinary conditions.<sup>96,116</sup>

Fluorescence immunocytochemistry uses fluorescein-labeled monoclonal antibodies to detect bladder-cancer cells. The average sensitivity and specificity is approximately 80%, and the test appears to have similar sensitivity for both low-grade and high-grade lesions.<sup>96</sup> The drawbacks of fluorescence immunocytochemistry are the need for significant experience, regular quality control, and the time needed to examine the slides.<sup>96</sup>

BLCA-4 is a transcription factor that is found throughout the bladder in patients with bladder cancer, including both tumor and normal regions, but BLCA-4 is not found in bladders in the absence of cancer.<sup>117</sup> The assay for BLCA-4 is a sandwich ELISA with 2 monoclonal antibodies.<sup>96</sup> Contrary to BLCA-4, BLCA-1 is expressed only in tumor areas in the bladder and has increased levels with higher tumor stages.<sup>96</sup> Antibodies have been designed to detect BLCA-1 in urine by means of Western blots and ELISA.<sup>118</sup> Both BLCA-4 and BLCA-1 are potentially useful bladder cancer markers because they detect bladder cancer with both high sensitivity and specificity; large clinical trials conducted at multiple centers are needed to further evaluate these markers.<sup>96</sup>

*FGFR3* is a glycoprotein that is part of the tyrosine kinase receptor family.<sup>119,120</sup> *FGFR3* mutations occur in about 50% of bladder cancers, and these mutations occur mostly in nonmuscle-invasive tumors with a low rate of recurrence and are thought to be associated with a favorable prognosis.<sup>119–121</sup> Activated receptor tyrosine kinases are targets for small molecule-based and antibody-based approaches to therapy, and thus, there is great interest in *FGFR3* as a potential therapeutic target in bladder cancer.<sup>122</sup> A phase 2 study with TK1258 (Novartis, Basel, Switzerland), an inhibitor with fibroblast growth factor receptor (FGFR), vascular endothelial growth factor receptor (VEGFR), and platelet-derived growth factor receptor (PDGFR) pharmacology, in second-line advanced bladder cancer is planned; it has suppressed in vitro proliferation and xenograft growth in bladder cancer cell lines that overexpress *FGFR3*.<sup>123,124</sup>

In summary, several markers have shown promise as noninvasive biomarkers of bladder cancer, and some may be useful as therapeutic targets. To date, however, none have found a strong niche in clinical care because of the lack of evidence demonstrating

that outcomes are altered on a practical basis. In addition, at this time, none of these markers can supplant cystoscopy, and most add little advantage to the combination of cystoscopy and cytology.

## Treatment

### TURBT

The transurethral resection of bladder tumor (TURBT) is diagnostic, prognostic, and often therapeutic.<sup>125</sup> After an initial TURBT, many patients will still have residual disease present, which increases the risk of early recurrence and progression.<sup>49,125</sup> To optimize staging, a repeat TURBT is often performed 2 to 6 weeks after the initial resection in patients with bulky high-grade Ta tumor, incompletely resected tumor, or any T1 tumor, particularly those without muscle in the specimen.<sup>51,54,125,126</sup> On repeat TURBT, anywhere from 34% to 76% of patients will have residual disease.<sup>49,127</sup> In Divrik et al, the rate of recurrence-free survival at 3 years was approximately 30% higher in patients who had undergone a repeat TURBT followed by intravesical mitomycin C (MMC) compared with those that had undergone an initial TURBT and intravesical MMC.<sup>127</sup> Critics of a repeat resection argue that it requires a second anesthetic, increases the risk of complications, is costly, and, with a good resection and intravesical chemotherapy and/or immunotherapy, is unnecessary.<sup>125,128</sup> Because of the importance of identifying residual invasive disease, however, performing a repeat TURBT is gaining acceptance.

### Nonmuscle-Invasive Disease

The goal in treating nonmuscle-invasive bladder cancer is to prevent disease recurrence and possible progression to muscle-invasive disease for the purpose of decreasing cancer-specific mortality. In an attempt to reduce the risk of recurrence, perioperative intravesical therapy at the time of TURBT has been used. A meta-analysis of 7 randomized trials comprising 1476 patients examined whether 1 immediate instillation of intravesical chemotherapy after transurethral resection (TUR) decreased the risk of recurrence in patients with Ta and T1 bladder cancer.<sup>129</sup> At a median follow-up of 3.4 years, 37% of patients receiving 1 postoperative instillation of

either epirubicin, MMC, thiotepa, or pirarubicin had a recurrence compared with 48% of patients with TUR alone ( $P < .0001$ ); patients with both single and multiple tumors benefited; however 65% of patients with multiple tumors recurred, demonstrating that 1 instillation of postoperative chemotherapy alone was not sufficient treatment.<sup>129</sup> Postoperative chemotherapy was instilled within 24 hours, although generally this was performed either immediately after TUR or within 6 hours after surgery; there were no appreciable differences in efficacy among the different chemotherapies.<sup>129</sup> One immediate instillation of chemotherapy adds minimal morbidity to the operation itself but is contraindicated with a bladder perforation or with an extensive TURBT.<sup>129</sup> The 2007 update of the AUA guidelines for the management of nonmuscle-invasive bladder cancer supports the use of a single postoperative instillation of a chemotherapeutic agent in the immediate postoperative period to decrease the risk of recurrence in patients after an uncomplicated TURBT.<sup>35</sup>

Adjuvant intravesical therapy is another treatment strategy used to reduce the risk of recurrence. According to the National Comprehensive Cancer Network (NCCN) guidelines for bladder cancer, a TURBT followed by adjuvant intravesical chemotherapy or immunotherapy is recommended for patients with low-grade Ta recurrences and high-grade Ta and T1 lesions; intravesical therapy with *Bacillus Calmette-Guerin* (BCG) is recommended after resection of CIS.<sup>54</sup> The 2007 update of the AUA guidelines supports the induction course of either intravesical chemotherapy or BCG for the treatment of nonmuscle-invasive bladder cancer that has an increased risk of recurrence but a low risk of progression.<sup>35</sup>

Intravesical BCG delays the time to recurrence after TURBT. A meta-analysis of 25 trials including 4767 patients was performed in which intravesical BCG with maintenance treatment significantly reduced the risk of tumor recurrence in patients with nonmuscle-invasive disease.<sup>130</sup> Despite this finding, however, there has been a discrepancy as to whether BCG has an effect on time to progression to muscle-invasive disease, with some studies showing an effect and some not; small patient sample sizes and short-term follow-up contributed to these differences.<sup>4</sup> A meta-analysis of 24 trials with progression data on 4863 patients at a median follow-up of 2.5 years

assessed whether the administration of intravesical BCG reduced the risk of progression.<sup>4</sup> Intravesical BCG after TURBT reduced the risk of progression in papillary tumors by 32% and in CIS by 35% when maintenance BCG was used.<sup>4</sup> There was a suggestion that BCG may be able to reduce the risk of death due to bladder cancer, but the number of disease-specific deaths reported was too small to make a firm conclusion.<sup>4</sup> The optimal dose, instillation schedule, and BCG strain still remain unclear, but improved cancer outcomes can be achieved through the use of maintenance therapy.<sup>4,131</sup>

The administration of BCG is associated with many side effects, a few of which may be serious, such as sepsis. Consequently, intravesical agents with lesser toxicity have been used to treat nonmuscle-invasive bladder cancer. A meta-analysis of 11 trials including 2749 patients compared the therapeutic efficacy and toxicity of intravesical BCG versus MMC on the recurrence of Ta and T1 bladder lesions.<sup>132</sup> With a median follow-up time of 26 months, 38.6% of patients in the BCG group and 46.4% of patients in the MMC group had tumor recurrence ( $P = .005$ ); in the subgroup treated with BCG maintenance, all 6 studies showed a significant superiority over MMC ( $P < .001$ ).<sup>132</sup> The results from this meta-analysis suggested that BCG was superior to MMC in preventing tumor recurrence, particularly in the BCG maintenance subgroup.<sup>132</sup> Among the toxicities reported, cystitis was the most common local adverse reaction in both the BCG and MMC groups, with BCG-associated cystitis occurring more frequently; no significant difference in cystitis was observed between patients with or without BCG maintenance therapy.<sup>132</sup> In general, symptoms of local and systemic toxicity were manageable and were more frequent in the BCG group, except for allergy and skin reactions, which were more common in the MMC group.<sup>132</sup>

To further explore the roles of BCG and MMC in the treatment of nonmuscle-invasive bladder cancer, a meta-analysis including 9 trials and 2410 patients compared their therapeutic efficacies on progression of Ta and T1 bladder cancer.<sup>133</sup> At a median follow-up of 26 months, 7.7% of patients in the BCG group and 9.4% of patients in the MMC group developed tumor progression, which was not statistically significant; in the subgroup of 5 studies with BCG maintenance, however, the rate of recurrence

was lower than with MMC.<sup>133</sup> These findings were further supported in a separate meta-analysis including 6 trials and 1527 patients by Shelley et al in which tumor recurrence was significantly lower with intravesical BCG than with MMC only in patients at high risk for tumor recurrence; no difference in disease progression or survival between the 2 agents was found, although the authors mention this could be a result of limited data availability or the need for longer follow-up.<sup>134</sup> Overall, the percentage of patients experiencing local and systemic toxicities were 30% and 12% for the MMC group and 44% and 19% for the BCG group, respectively.<sup>134</sup> Recently, a meta-analysis using individual patient data from 9 randomized studies including 2820 patients with nonmuscle-invasive bladder cancer was performed, comparing the efficacy of BCG and MMC.<sup>135</sup> Overall, no difference in time to first recurrence occurred; patients who had received BCG maintenance, however, had a 32% decrease in risk of recurrence compared with MMC, but those receiving BCG without maintenance had a 28% increased risk of recurrence compared with MMC.<sup>135</sup> No significant difference was found for progression, overall survival, or cancer-specific survival between the 2 groups.<sup>135</sup>

The administration of BCG and intravesical chemotherapy has also been used to treat patients with isolated CIS, an aggressive carcinoma with a high risk for progression and death due to bladder cancer.<sup>136</sup> A meta-analysis examined the short-term and long-term efficacy of BCG and chemotherapy in the treatment of patients with CIS.<sup>136</sup> Nine randomized trials including 700 patients with CIS were evaluated, comparing BCG to MMC, epirubicin, doxorubicin, or sequential MMC/doxorubicin.<sup>136</sup> Sixty-eight percent of patients had a complete response with BCG versus 52% with intravesical chemotherapy ( $P = .0002$ ), and at a median follow-up of 3.6 years, 47% of patients receiving BCG had no evidence of disease versus 26% with intravesical chemotherapy ( $P < .0001$ ). In a subgroup analysis of BCG and MMC, BCG was found to be superior when maintenance BCG was used.<sup>136</sup> Intravesical BCG was shown to significantly reduce the risk of both short-term and long-term treatment failure compared with intravesical chemotherapy and is considered the intravesical agent of choice for the treatment of CIS.<sup>136</sup>

Efforts to enhance BCG efficacy have included the use of combined immunologic intravesical therapies. In a phase 2 trial conducted at multiple centers, a combination of BCG and interferon- $\alpha$  (IFN- $\alpha$ ) was given to 1007 patients with nonmuscle-invasive bladder cancer; 59% of patients naive to BCG and 45% of patients who had a had prior BCG failure remained disease-free at a median follow-up of 24 months.<sup>137</sup> The use of BCG and IFN- $\alpha$  is a treatment option but is not currently recommended by the NCCN guidelines.<sup>34</sup> A randomized phase 3 study comparing BCG plus IFN- $\alpha$  to BCG will be needed to definitively demonstrate superiority of the combination over BCG monotherapy.<sup>137</sup>

Although BCG is an effective treatment for nonmuscle-invasive bladder cancer, approximately 20% to 40% of patients fail after BCG and have recurring tumors.<sup>138</sup> In these BCG failures, about 35% of patients will achieve durable success with a second BCG cycle.<sup>139</sup> The tumor status at the initial surveillance cystoscopy after BCG treatment is an important prognostic factor.<sup>140</sup> Data supporting the use of standard intravesical chemotherapeutic agents such as thiotepa, doxorubicin, and MMC in patients who failed initial BCG therapy are limited. Malmstrom et al looked at MMC in patients who had failed BCG and reported a 19% 3-year disease-free rate among intermediate and high-risk patients.<sup>141</sup> Valrubicin, a semisynthetic analog of doxorubicin and lipid soluble anthracycline, has demonstrated antitumor activity in nonmuscle-invasive bladder cancer and was evaluated as treatment for patients with CIS who failed BCG treatment.<sup>142</sup> Ninety patients with recurrent CIS after BCG failure were given 6 weekly instillations of 800 mg of intravesical valrubicin; 21% of patients initially had a complete response, but at a median follow up of 30 months, 88% of patients recurred, and 56% of these patients went on to have a radical cystectomy of which 15% had pT3 disease at time of surgery.<sup>143</sup> Given these results, conventional intravesical chemotherapy appears to offer little success for patients failing BCG, especially for T1 or CIS disease.<sup>139</sup>

Better delivery of standard intravesical chemotherapy agents may improve outcomes. Factors that can prevent the optimal delivery of intravesical MMC, for example, include its dilution by the drug solution and/or by the ongoing production of urine during treatment and its instability in acidic urine.<sup>144</sup>

A randomized phase 3 study by Au et al compared 119 patients who had refrained from drinking fluids for 8 hours before treatment, received 40 mg of MMC, and were given 3 doses of sodium bicarbonate before treatment with 111 patients who had received 20 mg of MMC without any pharmacokinetic manipulations or urine alkalinization.<sup>144</sup> The optimized treatment arm demonstrated a longer median time to recurrence (29.1 months vs 11.8 months;  $P < .001$ ) and a higher recurrence-free rate at 5 years (41.0% vs 24.6%;  $P = .005$ ), suggesting that adjustments can be made to increase the efficacy of MMC.<sup>144</sup>

Other techniques have been investigated to improve the treatment with intravesical chemotherapy. In a randomized trial performed at multiple centers, local microwave hyperthermia in conjunction with MMC was compared with intravesical MMC alone in 83 patients; at minimal follow-up of 24 months, the rate of recurrence was 58% in the chemotherapy-alone group and 17% in the chemothermotherapy group.<sup>145</sup> Hyperthermia has also been used as a prophylactic protocol in high-grade nonmuscle-invasive disease, demonstrating a 63% recurrence-free rate at a mean follow-up of 35 months.<sup>146</sup>

Electromotive intravesical MMC has been proposed to improve drug delivery across biological membranes with increased accumulation in bladder tissue.<sup>139</sup> In a randomized trial involving CIS patients, groups were randomized to receive instillations of electromotive MMC, passive MMC, or passive BCG.<sup>147</sup> At 6 months, there was a statistically superior response rate for electromotive MMC (58%) than for passive MMC (31%), and the response rate of electromotive MMC approached that of BCG (64%).<sup>147</sup>

Photodynamic therapy combines photosensitizers that selectively bind to tumors and a powerful intravesical light source to destroy them.<sup>138</sup> Waidelich et al used photodynamic therapy after oral administration of 5-ALA in 24 high-risk BCG-failing patients and found 3 of 5 CIS patients and 4 of 19 patients with papillary tumors to be recurrence-free at a median follow-up of 36 months; hypotension and tachycardia occurred in the majority of patients.<sup>148</sup> Photodynamic therapy may be a reasonable second-line alternative to BCG failure, although more research is needed in this area.

More recently, both gemcitabine and docetaxel have been tried intravesically to treat bladder cancer. As nonvesicants, both gemcitabine and docetaxel

have been well tolerated with minimal cystitis and little systemic absorption.<sup>139</sup> In the largest and most dose-intensive regimen, however, the 1-year complete response rate in BCG-refractory disease was 21%, suggesting that single-agent gemcitabine may not be a salvage drug.<sup>139</sup> Docetaxel, a microtubule depolymerization inhibitor, was investigated as an intravesical agent in a phase 1 trial in which docetaxel was administered with 6 weekly instillations starting at a dose of 5 mg. Eighteen (100%) patients completed the trial, and 56% of patients had no evidence of disease at their post-treatment cystoscopy and biopsy.<sup>149</sup> Docetaxel was well tolerated, and future trials will further evaluate its efficacy in a phase 2 trial.<sup>149</sup>

The 2007 update of the American Urological Association (AUA) guidelines for management of nonmuscle-invasive bladder cancer states that cystectomy or further intravesical therapy may be considered for CIS or high-grade T1 cancer that persists or recurs after initial intravesical treatment.<sup>35</sup> The European Association of Urology (EAU) guidelines echo this viewpoint by mentioning cystectomy as the treatment of choice for CIS patients failing adequate BCG and as an option in other high-risk tumors.<sup>150</sup> Recurrent aggressive disease 6 months after diagnosis or disease persisting after 2 courses of BCG therapy is a strong indication to consider radical therapy.<sup>139</sup> When patients with nonmuscle-invasive bladder cancer have a recurrence with invasive disease, a window of opportunity is missed, which emphasizes the importance of close, active surveillance and aggressive treatment of patients with high-risk nonmuscle-invasive disease.<sup>138</sup> The decision to delay cystectomy until progression to muscle-invasive cancer appears to be associated with a higher cancer-related mortality than cystectomy performed for refractory nonmuscle-invasive disease.<sup>151</sup> Huguet et al evaluated 62 patients with nonmuscle-invasive disease who were found to have high-grade recurrences after BCG treatment, and all of these patients subsequently underwent radical cystectomy.<sup>152</sup> Twenty-seven percent of these patients were found to have  $\geq$  pT2 disease on final pathology and were, thus, understaged; in those patients who progressed, the 5-year, disease-specific, survival rate was 38% versus 90% in those without invasive disease ( $P = .006$ ).<sup>152</sup> In summary, although there is no

prospective randomized trial comparing early cystectomy to second-line intravesical therapy for high-risk nonmuscle-invasive bladder cancer, radical cystectomy is the preferred treatment option for patients with BCG failure given the poor long-term response rates of salvage intravesical treatments. Nonetheless, salvage intravesical therapy continues to have a significant role in managing patients who are poor surgical candidates or who refuse radical surgery.<sup>139</sup>

## Surveillance

Surveillance cystoscopy is essential after tumor resection because of the frequency of recurrence; frequent cystoscopy should allow the detection of recurrence at an earlier stage, thus lowering the progression rate and the progression to muscle-invasive disease.<sup>96</sup> According to the 2010 NCCN guidelines for bladder cancer, surveillance cystoscopy and urine cytology for nonmuscle-invasive disease should be performed every 3 months for the first 1-2 years, repeated at increasing intervals over the next 2 years, and annually thereafter; for high-grade tumors, upper tract imaging should be considered every 1-2 years.<sup>34</sup> With recurrent disease, post-treatment surveillance starts again at 3-month intervals. The European Association of Urology (EAU) guidelines for surveillance of nonmuscle-invasive bladder cancer are more lenient for low-grade lesions, recommending that patients with tumors at low risk of recurrence undergo a cystoscopy at 3 months and, if negative, again at 9 months, and then yearly for 5 years if the patient remains free of tumors.<sup>126</sup>

## Muscle-Invasive Disease

### *Radical Cystectomy*

For organ-confined muscle-invasive disease (T2 disease), the bladder cancer NCCN guidelines recommend a radical cystectomy with the consideration of neoadjuvant chemotherapy.<sup>54</sup> Large single-center experiences report a 45%-66% 5-year overall survival after radical cystectomy.<sup>55,153, 154</sup> In recent studies, the mortality rate after radical cystectomy is less than or equal to 3%, and the complication rate varies between 25% and 57% in the first 30 days after surgery.<sup>55,155-158</sup> With surgery alone, 20%-30% of patients with pT2 disease, 40%-60% of patients with pT3 disease, and 70%-90% of patients with pT4

disease will develop distant metastases or local recurrences and die of their cancer; consequently, 5-year survival rates after radical cystectomy in contemporary series average 66% for pT2 disease, 35% for pT3 disease, and 27% for pT4 disease.<sup>159</sup>

Both patients and physicians should avoid any unnecessary delays when treating bladder cancer with cystectomy. Sanchez-Ortiz et al evaluated 290 patients and found that a delay in performing radical cystectomy greater than 12 weeks was associated with advanced pathological stage and decreased survival.<sup>160</sup> Lee et al also looked at 214 patients with clinical T2 bladder cancer and found a decrease in disease-specific and overall survival when a cystectomy was delayed by 3.1 months after diagnosis; this was likely attributed to the development of micrometastases because pathologic staging was similar between groups.<sup>161</sup> Although a consensus does not exist on how long is too long to wait for a cystectomy, there is general agreement that a cystectomy should be scheduled within 3 months of diagnosis of muscle-invasive bladder cancer.

Hospital and surgeon volume may also impact patient outcomes after cystectomy. Hospitals that perform a high volume of radical cystectomies have lower mortality and complication rates than low-volume centers.<sup>162</sup> Some have suggested that hospitals offering radical cystectomy should perform more than 10 cases annually.<sup>162</sup> Others have evaluated surgeon volume and, because of improved patient outcomes with higher volumes, have recommended that 10 radical cystectomies should be performed per surgeon annually to maintain proficiency.<sup>163</sup> Increased surgeon volume may improve outcomes because of better clinical judgement, improved technical proficiency in the operating room, and a better global understanding of the disease.<sup>164</sup>

Surgical quality may also be evident through histologic assessments of the cystectomy specimen and associated lymphadenectomy. Both surgical margin status and number of nodes removed at surgery are independent predictors of postcystectomy survival and local recurrence in multivariate analysis, suggesting that the quality of surgery can affect bladder-cancer outcomes.<sup>165</sup> Single-institution cystectomy series and analysis of the Surveillance, Epidemiology, and End Results (SEER) registry have both shown increased disease-specific survival and overall survival with an increasing number of lymph nodes removed

at time of cystectomy.<sup>166-168</sup> Moreover, meticulous lymph node dissection may cure up to 30% of patients with node-positive disease.<sup>169,170</sup> One caveat is that the node count can vary based on the pathologist and how the nodes are submitted for analysis. Herr et al found that submitting node packets separately rather than en bloc with the bladder could increase the number of nodes reported.<sup>165</sup>

There is a wide range in the average total lymph-node yield and the number of lymph nodes removed from the various anatomical sites obtained by different surgeons.<sup>59</sup> At multiple centers, Leissner et al performed a prospective analysis of lymph node metastases to obtain precise information about lymphatic spread of bladder cancer; 290 radical cystectomies were performed with an extended lymphadenectomy template, which was defined as the level of the inferior mesenteric artery cranially, the genitofemoral nerve laterally, and the pelvic floor caudally.<sup>59</sup> The mean total number of nodes removed was 43, and nodal metastases were present in 28% of patients.<sup>59</sup> Metastatic lymph nodes were found in all locations in the extended lymph node template; if lymphadenectomy had been restricted to the obturator spaces, nodal involvement would have been overlooked in 7% of patients.<sup>59</sup> Because of the complex lymphatic drainage pathway of the bladder, it was suggested that bilateral lymphadenectomies are needed even for unilateral bladder tumors; the concept of a sentinel node has not been confirmed in bladder cancer.<sup>59</sup> This study concluded that, although an extended lymphadenectomy adds about an hour to the procedure, patients undergoing radical cystectomy with curative intent should have this performed to increase the accuracy of staging and, likely, to improve postoperative survival.<sup>59</sup>

Despite the emphasis on removing more lymph nodes at the time of cystectomy, no consensus exists as to the minimal number of nodes needed to be removed to increase chance of survival. Studies have recommended removing a minimum of 9 to 20 lymph nodes to optimize outcomes.<sup>166,167</sup> Koppie et al attempted to answer this question of whether a threshold number of lymph nodes existed, above which removing additional lymph nodes was of no clinical benefit.<sup>171</sup> A total of 1121 patients who had undergone a radical cystectomy and lymph node dissection were retrospectively reviewed; an extended

lymph node dissection was found to be more beneficial than a limited dissection, and the risk of death continued to fall as the number of lymph nodes removed increased; thus, defining a minimum number of lymph nodes that would be sufficient for optimizing outcomes was not possible.<sup>171</sup> The study favored using a thorough anatomically templated dissection as a therapeutic goal as opposed to focusing on a reported number of lymph nodes.<sup>171</sup>

Lymph node density, the number of lymph nodes removed with tumor divided by the total number of lymph nodes removed, is another characteristic that has generated interest. It accounts for both lymph node burden and extent of lymph node dissection, which have each been shown to have prognostic significance.<sup>172</sup> Stein et al showed that a lymph node density less than or equal to 20% had significantly better recurrence-free and overall survival than those with a lymph node density greater than 20%.<sup>172</sup> Similarly, Osawa et al showed an increase in 5-year overall survival for patients with a lymph node density less than or equal to 25%.<sup>173</sup> Although the exact cutoff for lymph node density remains to be established, these findings should support future, prospective, clinical trials that will help define the extent of lymph node dissection.

### **Robotic Cystectomy**

Recently, the use of robot-assisted radical cystectomy has been reported. The potential advantages of robotic assistance include lower blood loss, reduced need for intraoperative fluids, smaller incisions, reduced exposure of bowel to the exterior, and the ability for the surgeon to perform the operation more ergonomically.<sup>174</sup> The urinary diversion can be performed intracorporeally, but because of prolonged operative times, this is usually performed extracorporeally by extending one of the incisions.<sup>175</sup>

The main concerns for robot-assisted radical cystectomy are compromised lymph node dissections and suboptimal oncologic outcomes.<sup>175</sup> A few recent studies, however, have refuted these claims, demonstrating adequate lymph node dissection and short-term oncological outcomes.<sup>176-178</sup> The future role of robotic assistance in the management of bladder cancer will depend on the long-term outcomes, specifically oncologic outcomes; randomized trials at multiple centers are needed to compare this approach with the standard, open, radical cystectomy.

### Urinary Diversion

A variety of urinary diversion options exist for patients who are undergoing a cystectomy. Recently, an international consensus panel reported contemporary experience in the performance of urinary diversion worldwide in more than 7000 cystectomy patients.<sup>179</sup> Neobladder (47%), conduit (33%), anal (10%), continent cutaneous (8%), and incontinent cutaneous (2%) diversions were performed across several countries.<sup>179</sup> When considering the type of urinary diversion to perform, patients must be counseled on the safest method for cancer control, potential complications in both the short and long term, and the effects on quality of life.<sup>179</sup> Patient anatomy and physician experience with a given diversion are also important factors. In some centers, the proportion of cystectomy patients undergoing orthotopic neobladder diversion has greatly increased to between 50% and 90%.<sup>180–183</sup> An orthotopic diversion eliminates the need for a cutaneous stoma and urostomy appliance and has been shown to decrease physician reluctance and increase patient acceptance of an early cystectomy.<sup>55,184</sup> Another exciting type of “diversion” that may have clinical applications in the near future is the tissue-engineered neobladder that uses autologous urothelial and smooth-muscle cells cultured on biocompatible synthetic or naturally derived substrates.<sup>179</sup>

Absolute contraindications to a continent diversion include renal dysfunction that results from long-standing obstruction or chronic renal failure and severe hepatic dysfunction.<sup>179</sup> In addition, patients with compromised intestinal function, such as from inflammatory bowel disease, may benefit from an incontinent diversion.<sup>179</sup> Orthotopic reconstruction in particular is contraindicated in patients who require a simultaneous urethrectomy based on tumor characteristics and is relatively contraindicated in patients with mental impairment, external sphincter dysfunction, and recurrent urethral strictures.<sup>179,185,186</sup> Patients who want to resume normal daily activities as soon as possible, are elderly and live in social isolation, or are less concerned about body image may be better served with an incontinent cutaneous diversion (conduit) rather than a neobladder.<sup>179</sup> Multiple studies have evaluated patient quality of life (QOL) after cystectomy and diversion. Currently, no diversion type has a superior QOL over the others. This is likely due to patient selection, preoperative counseling, and patient adjustment.<sup>179</sup>

### Perioperative Chemotherapy

Many patients undergoing a cystectomy likely have occult metastases that are not detected by standard staging studies.<sup>52</sup> As mentioned previously, about 30% to 50% of patients are clinically understaged at the time of cystectomy.<sup>48–50</sup> Moreover, high-risk patients with pathologic stage T3, T4, or node-positive tumors have a greater than 50% chance for systemic relapse after cystectomy.<sup>54</sup> Consequently, the use of neoadjuvant systemic chemotherapy has been investigated in patients with muscle-invasive bladder cancer to eradicate micrometastases, downstage tumor, reduce implantation of circulating tumor cells during surgery, and ultimately improve survival.<sup>187</sup> The use of neoadjuvant chemotherapy is supported by data from randomized clinical trials and rigorous meta-analyses.<sup>52,56,188–190</sup>

As reported by Grossman et al in the Intergroup 8710 trial, cystectomy alone was compared with neoadjuvant methotrexate, vinblastine, doxorubicin (Adriamycin), and cisplatin (MVAC) followed by radical cystectomy. The group receiving neoadjuvant chemotherapy had an increased likelihood of eliminating residual cancer in the cystectomy specimen (pT0) and had an associated improved survival (Fig. 6); the neoadjuvant chemotherapy did not adversely affect the patient's chance of undergoing a cystectomy and did not increase the risk of postoperative complication.<sup>56</sup> In the combined analysis of 2 Nordic studies, neoadjuvant, platinum-based, combination chemotherapy was associated with an 8% increase in survival at 5 years.<sup>188</sup> Two meta-analyses of randomized controlled trials demonstrated a survival benefit to receiving neoadjuvant chemotherapy.<sup>189,190</sup> Specifically, in one meta-analysis, platinum-based neoadjuvant chemotherapy showed a 13% relative reduction in the risk of death compared with the control group, which is a 5% absolute-survival benefit at 5 years.<sup>189</sup> Complication and mortality rates after cystectomy are not increased in patients who receive neoadjuvant chemotherapy.<sup>165,191,192</sup> The bladder-cancer NCCN guidelines now recommend cystectomy with consideration of cisplatin-based combination neoadjuvant chemotherapy for nonorgan-confined disease.<sup>54</sup>

In addition to the survival advantage, the neoadjuvant strategy offers other advantages including

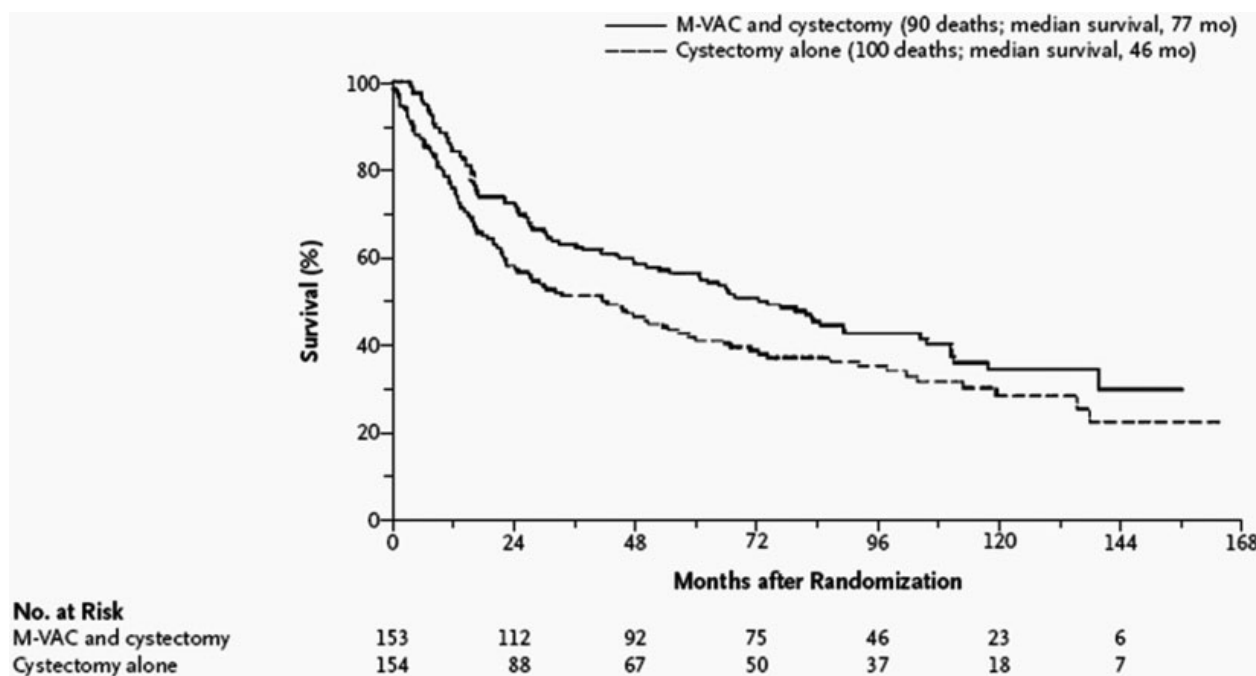


**FIGURE 6.** Survival among patients randomly assigned to receive methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) followed by cystectomy or cystectomy alone, according to an intention-to-treat analysis. Reprinted with permission from Grossman HB, Natale RB, Tangen CM, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. *N Engl J Med.* 2003;349:859-866. Copyright ©2003 Massachusetts Medical Society. All rights reserved.

primary tumor response as an objective measure of treatment efficacy, the ability to change treatment based on the response, downstaging with improved resectability and reduction of positive surgical margins, early systemic treatment of possible micrometastases, and the potential for bladder preservation based upon the response. The disadvantages of neoadjuvant chemotherapy include the overtreatment of some patients and the delay in time to cystectomy with the theoretical risk of progression.<sup>52</sup> Despite the evidence supporting the use of neoadjuvant chemotherapy, a review of more than 7000 patients treated for stage III bladder cancer in the United States between the years 1998 and 2003 showed that only 1.2% of patients received neoadjuvant treatment, and only 10.4% received adjuvant treatment.<sup>193</sup>

The evidence for adjuvant therapy is primarily based on a meta-analysis of 6 small trials, totaling about 600 patients; although this study suggested a 25% relative decrease in the risk of death with chemotherapy compared with no therapy, the number of patients was insufficient to recommend adjuvant treatment.<sup>194</sup> Unfortunately, large trials evaluating adjuvant treatment have not been performed, and the smaller studies included in the above meta-analysis

have been criticized for methodologic flaws. Nonetheless, the advantages of adjuvant chemotherapy include the careful selection of patients based on pathological staging, the lack of delay to cystectomy, the alleviation of patient anxiety, and the enhancement of chemotherapy against small-volume disease. The disadvantages include poor tolerance in the postoperative period, the delay in receiving postoperative chemotherapy due to surgical complication, and the challenges of measuring efficacy only with recurrence and/or survival.<sup>52,195</sup> Donat et al showed that about 30% of patients undergoing a radical cystectomy might have a surgical complication that could preclude or delay their ability to receive adjuvant chemotherapy, supporting the use of perioperative chemotherapy in the neoadjuvant setting.<sup>196</sup>

The disadvantage of both neoadjuvant and adjuvant chemotherapy is the toxicity associated with the different regimens. MVAC has been shown to have significant toxicities including severe granulocytopenia, nausea and vomiting, stomatitis, and diarrhea or constipation.<sup>56</sup> Historically, MVAC has been associated with a death rate of 3% to 4% from toxicity, and a long-term, disease-free, survival rate of approximately 4% at 6 years.<sup>197-199</sup>

Because of the significant side effects associated with MVAC, several alternative treatment strategies have been investigated. In a phase 3 trial of patients with locally advanced or metastatic bladder cancer, gemcitabine and cisplatin (GC) had similar efficacy as MVAC, but less toxicity, with patients experiencing less neutropenia, mucositis, and neutropenic fever.<sup>200</sup> The 5-year survival rates between GC and MVAC were also similar.<sup>201</sup> A phase 3 trial of high-dose-intensity MVAC with recombinant human granulocyte colony-stimulating factor (G-CSF) versus MVAC alone demonstrated that high-dose-intensity MVAC enabled delivery of higher doses of chemotherapy in a shorter time, but there was no difference in survival between the 2 groups.<sup>202</sup>

Paclitaxel is a drug that stabilizes microtubules and promotes their assembly, which results in an M-phase cell-cycle arrest.<sup>203</sup> In phase 2 studies, paclitaxel has been shown to be effective both as a single agent and in combination with gemcitabine and/or cisplatin.<sup>204–206</sup> Poor renal function prohibits the use of cisplatin-based regimens, and thus, carboplatin was used with the intent of providing similar efficacy to cisplatin with less renal toxicity.<sup>207</sup> A study of the paclitaxel, carboplatin, and gemcitabine regimen was shown to have a high response rate and median survival of 14.7 months, making this regimen a potential alternative to cisplatin-based chemotherapy.<sup>207</sup>

There is no standard of care for the treatment of patients with bladder cancer who have failed cisplatin-based regimens in the first-line setting.<sup>208</sup> Single-agent therapy is typically used in the second-line setting, with several agents having response rates between 10% and 20%, but typically these trials have a small number of patients, and no long-term benefits or survival advantage over supportive care alone has been demonstrated to date.<sup>208</sup>

### Surveillance

Patients with muscle-invasive bladder cancer need to be closely followed. According to the NCCN bladder cancer guidelines, after a cystectomy, patients should obtain a urine cytology, electrolyte and creatinine levels, and a chest x-ray along with abdomen and pelvis imaging every 3 to 12 months for 2 years and then as clinically indicated; in addition, a urethral washing should be obtained every 6 to 12 months. A vitamin B<sub>12</sub> level should be checked annually when

the patient has had a continent diversion.<sup>34</sup> For bladder-sparing protocols, patients should also have a cystoscopy and urine cytology and/or bladder biopsies every 3 to 6 months for 2 years and then at increasing intervals.<sup>34</sup> Bone scans are indicated only for patients with bone pain suspicious for metastatic disease and for patients with advanced disease ( $\geq$  T3 and pN+).<sup>209</sup>

## Bladder Preservation

The primary goal of neoadjuvant chemotherapy is to improve cancer control and, thus, survival, but a secondary goal is bladder preservation.<sup>52</sup> The advantages of bladder preservation include less surgery, no need for urinary diversion, and preservation of sexual function, all of which presumably contribute to a better quality of life; the debate is whether bladder preservation can occur while obtaining the same survival rates that are achieved with radical cystectomy.<sup>210</sup>

TURBT alone can be an alternative treatment strategy for muscle-invasive bladder cancer. In Herr et al, a repeat TURBT found residual tumor in 78% of patients diagnosed with T2 tumors; the 22% of patients without residual tumor were followed conservatively, and the 4% with  $\geq$  T3 lesions were treated with chemotherapy.<sup>49</sup> On the basis of the results of the repeat TURBT, 26% of patients were spared a cystectomy.<sup>49</sup> Solsona et al reported their results on patients with T2 lesions in which random biopsies, and a repeat resection of the resection bed were performed 3 months after the initial resection; conservative treatment was used when the re-resected tissue was negative, and a cystectomy was performed when residual disease was present.<sup>211</sup> The recurrence-free survival rates in patients treated with TURBT alone were 45.8% at 5 years and 35.6% at 10 years, and cause-specific survival was comparable to those in their control group that had undergone a cystectomy.<sup>211</sup> Treatment of muscle-invasive lesions with TURBT alone is an alternative treatment option in select patients who, then, must be diligently followed.

Radiation therapy alone is not sufficient for bladder-sparing treatment of bladder cancer with 5-year survival rates in the range of only 30% to 50%.<sup>212</sup> Historically, factors that are thought to contribute to this unfavorable outcome include the inability to

accurately define the true extent of the tumor, the selection of patients generally with a poorer prognosis, and the finding that most invasive bladder cancers have occult metastases at the time of presentation.<sup>213</sup> Combined-modality treatment including chemotherapy and radiotherapy, however, is a bladder-sparing alternative to cystectomy when strict criteria are used to select patients, including small tumor size ( $\leq 4$  cm) and low stage ( $\leq T3a$ ).<sup>214</sup> The best candidates are patients with a unifocal tumor, a tumor located away from the bladder neck, no hydronephrosis, and no associated CIS.<sup>214</sup>

In the past 20 years, the Radiation Therapy Oncology Group (RTOG) has completed 6 prospective protocols of combined-modality therapy for patients with muscle-invasive cancer who were candidates for cystectomy; 5 of these were phase 1/2 studies of concurrent chemotherapy and radiation therapy, and one was a phase 3 study that tested the efficacy of adjuvant chemotherapy with methotrexate, cisplatin, and vinblastine (MCV).<sup>215</sup> A total of 415 patients were enrolled in these trials, which demonstrated a 5-year overall survival rate of approximately 50% with 75% of those 50% achieving a cure for their bladder cancer while maintaining a functioning bladder.<sup>215</sup> The trimodality approach of intravesical surgery, chemotherapy, and radiation was more effective than both the radiation monotherapy offered in the 1970s and the chemotherapy-only protocols.<sup>215</sup> The trimodality approach is a reasonable bladder-sparing alternative for carefully selected and highly motivated patients who are not willing to undergo a radical cystectomy, although these patients should realize that a delayed cystectomy is an available option should combined chemotherapy and radiation therapy treatment fail.<sup>215</sup> Patients must have close and lifelong cystoscopic surveillance of their bladders, with prompt cystectomy for those who develop invasive recurrence.<sup>216</sup>

Critics of organ conservation argue that bladder cancer causes a field change that affects the entire transitional epithelium and exposes patients to multiple tumors arising in both space and time.<sup>216</sup> Zietman et al, however, looked at 121 patients who had a complete response with trimodality therapy and found that the majority of these patients retained their bladders free from relapse; of the 25% who experienced a nonmuscle-invasive relapse, the irradiated bladders tolerated TURBT and intravesical

therapies well, with complete response rates comparable to patients with an initial occurrence of nonmuscle-invasive disease. The main disadvantages of bladder-sparing strategies are the dependence on TURBTs before and after treatment, the need for lifelong surveillance, the risk of radiation and chemotherapy toxicities, and the potential need for salvage cystectomy after unsuccessful treatment.

Partial cystectomy is a bladder-sparing surgical option for carefully selected patients with muscle-invasive bladder cancer. It is usually performed as definitive treatment with the intent to cure, but it is occasionally performed as either a therapeutic intervention for tumors unable to be completely resected by TUR or as a palliative procedure for patients who are not surgical candidates for a radical cystectomy.<sup>217</sup> The advantages of a partial cystectomy are that it permits accurate staging by lymphadenectomy and involves complete tumor excision with wide surgical margins while preserving adequate bladder and sexual function.<sup>217</sup> In addition, perioperative morbidity and postoperative complications with partial cystectomy are less than with radical cystectomy.<sup>218</sup> Ideal patients have a functional bladder and a solitary primary tumor in the dome or posterolateral bladder wall that can be resected with an adequate margin without need for reimplantation of the ureter.<sup>217</sup> Partial cystectomy can be performed after systemic chemotherapy.<sup>219</sup> The presence of CIS on an initial TURBT or in the partial cystectomy specimen and the presence of lymph node involvement significantly predict tumor recurrence, and patients with these findings should be considered poor candidates for partial cystectomy.<sup>220</sup>

## Metastatic Disease

The prognosis for patients with metastatic bladder cancer remains poor, with a median survival time of approximately 12-15 months.<sup>206</sup> Given the relatively high response rate obtained with combined chemotherapy, cisplatin-based regimens are considered the standard treatment for fit patients with metastatic bladder cancer.<sup>221</sup> With MVAC, in otherwise healthy patients with only nodal and/or soft tissue disease, there is a 10%-15% chance of prolonged progression-free survival with 6 cycles of chemotherapy; the toxic complications of MVAC can be significantly reduced with the use of granulocyte colony-stimulating

factor (G-CSF).<sup>221</sup> Factors predicting a lower response rate, increased toxicity, and poor overall survival with MVAC are the presence of visceral metastases, the presence of an abnormal alkaline phosphatase, and a low performance status score.<sup>197,222</sup> Loehrer et al evaluated 269 patients with advanced bladder cancer and reported a median survival of 18.2 months for patients with favorable prognostic features versus 4.4 months for patients with adverse prognostic features; no patients with liver or bone metastases were alive at 6 years.<sup>197</sup> Because of toxicities associated with MVAC, GC is a common alternative regimen used to treat metastatic disease. Patients receiving GC appear to have similar survival rates as those receiving MVAC, and the GC patients experience less toxicity.<sup>200</sup> For patients with poor renal function, carboplatin can be used instead of cisplatin, although it is generally felt to be less effective. In a study of 16 “unfit” patients, defined as having a performance status greater than 2 and/or creatinine clearance of less than 60 mL/min, the relative response rate was 43.5%, and median survival was 14.4 months.<sup>223</sup>

Both paclitaxel and docetaxel have been studied as chemotherapeutic agents for metastatic bladder cancer. Single-agent paclitaxel given with G-CSF produced a response rate of 42% in 26 previously untreated patients.<sup>204</sup> A phase 3 study comparing docetaxel and cisplatin (DC) with G-CSF versus MVAC with G-CSF found MVAC to be more effective than DC for metastatic cancer; MVAC demonstrated both a superior median time to progression (9.4 vs 6.1 months;  $P = .003$ ) and median survival time (14.2 vs 9.3 months;  $P = .026$ ).<sup>224</sup>

A phase 2 study of bevacizumab in combination with cisplatin and gemcitabine in metastatic or locally advanced bladder cancer involving 36 patients showed a complete response in 6 (17%), and a partial response in 18 (50%); this combination is now being studied in a phase 3 trial.<sup>123,225</sup> Another phase 2 study involving trastuzumab (Herceptin), which is an antibody to *HER-2*, has been evaluated in metastatic or locally advanced bladder cancer patients with *HER-2* expression in combination with chemotherapy; responses were seen in 70% of patients (5 complete and 26 partial responses).<sup>123,226</sup>

Postchemotherapy surgery in patients with unresectable or metastatic disease may impact survival. Herr et al evaluated 80 patients who had undergone postchemotherapy surgery after treatment with a

cisplatin-based regimen for unresectable or regionally metastatic disease and found no viable cancer in the postchemotherapy surgical specimen in 30% of cases.<sup>227</sup> Residual cancer was completely resected in 61% of cases; postchemotherapy surgery did not benefit patients who failed to have a major complete or partial response to chemotherapy.<sup>227</sup> This study showed that postchemotherapy surgical resection of residual cancer may result in disease-free survival in select patients who would otherwise die of disease.<sup>227</sup> In summary, metastatic bladder cancer is a deadly disease, and although advances have been made, more research with novel, targeted agents is needed to continue to improve outcomes in this cohort of patients.

Patients who are unable to undergo a cystectomy because of advanced stage or poor overall health may require a urinary diversion because of uncontrollable symptoms or uremia.<sup>179</sup> In this case, a percutaneous nephrostomy tube is preferable to a cutaneous ureterostomy because it is less invasive, especially when the patient has a short life expectancy. In patients who undergo a palliative cystectomy, a cutaneous ureterostomy is preferred in some parts of the world, although in the United States, an ileal conduit is well tolerated and ideal.<sup>179</sup> Palliative radiotherapy is another treatment option that can improve patients' quality of life by reducing or eliminating symptoms due to tumor growth.<sup>228</sup>

## Conclusions and Future Directions

Over the last decade, several advances have been made in the diagnosis and treatment of bladder cancer such as the expansion of available molecular markers, the understanding of the prognostic implications of urothelial carcinoma variants, the improvement in technology including the use of fluorescent cystoscopy, the re-emphasis on the importance of neoadjuvant chemotherapy and extended lymph node dissection, and the increasing use of the orthotopic neobladder. Despite this, however, there is still room for improvement. Perioperative and adjuvant intravesical therapies remain underused, with only about 31% of patients with nonmuscle-invasive bladder cancer receiving intravesical chemotherapy.<sup>229</sup> Approximately 30%–50% of patients are understaged at the time of cystectomy, and those undergoing cystectomy have a complication rate of 25%–57%.<sup>48–50,55,155,156,158,230,231</sup> Continued

improvement in imaging technique and molecular-marker sensitivity are needed to improve the accuracy of clinical staging. Neoadjuvant chemotherapy and the extended lymph node dissection are underused, citing factors such as delayed cystectomy or added time to an already lengthy surgery, respectively, but increasing evidence exists suggesting that these interventions improve disease-specific and overall survival. As many as 31% to 47% of deaths from bladder cancer are potentially avoidable, emphasizing the need for earlier detec-

tion, "early" cystectomy for aggressive disease, and improvements in systemic therapies.<sup>232</sup> Bladder cancer is one of the most costly cancers, from diagnosis until death.<sup>108</sup> In the face of today's healthcare and imminent changes in healthcare policy, the challenge will be to provide the best care for our patients, continue to make advances in surgery, technology, and basic science research to decrease the morbidity and mortality associated with bladder cancer while, at the same time, doing so in a cost-efficient manner. ■

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