BLADDER CANCER: A REVIEW OF DIAGNOSIS AND MANAGEMENT

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Bladder cancer is the fourth most commonly diagnosed malignancy in men and the eighth most common in women. It represents a spectrum of disease, ranging from superficial, well-differentiated disease, which does not significantly impact survival, to highly malignant tumors for which long term survival may be dismal. Transitional-cell carcinoma, which constitutes the vast majority of bladder cancers in the United States, may develop as carcinoma in situ or as invasive carcinoma. This article focuses on transitional-cell carcinoma with a review of the major aspects of the disease, including the epidemiology, diagnosis and staging, and management (including organ preservation). Therapeutic options are explored, including surgery, radiotherapy, chemotherapy, and combined modality therapy. (*J Natl Med Assoc.* 2000;92:285–294.)

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Primary malignancies of the urinary bladder represent a spectrum of disease from superficial, well-differentiated disease, which does not significantly impact patient survival, to highly malignant tumors for which long-term survival may be dismal. The vast majority of primary bladder tumors found in the United States are of transitional cell origin (90%–95%). Squamous-cell carcinoma (3%–5%) and adenocarcinoma (1%) are found in certain subsets of patients. This is in distinct contrast to primary bladder malignancies in countries such as Egypt, where the majority of bladder cancers are of squamous-cell type. Chronic inflammation of the bladder, due to infection by *Schistosoma haematobium*, is largely responsible for this finding. Malignancies such as sarcoma, pheochromocytoma, carcinoid, and small cell tumor are found infrequently. Leiomyosarcoma is the most common bladder sarcoma of the adult population, whereas rhabdomyosarcoma is the most frequently seen sarcoma in children.

We will review the evaluation and current therapy for primary bladder cancer. As transitional-cell carcinoma is the most prevalent form of bladder cancer in this country, the focus of this review will concentrate on this particular disease process. Discussion of risk factors and pathology of squamous cell carcinoma and primary adenocarcinoma will be included to contrast these cell types from transitional cell carcinoma. Evaluation and therapy for other types of primary bladder cancer are beyond the scope of this review.

EPIDEMIOLOGY

Bladder cancer is the fourth most commonly diagnosed malignancy in men and the eighth most commonly diagnosed malignancy in women. In 2000, approximately 50,000 new cases will be diagnosed, and over 10,000 deaths will be attributed to the disease. Recent trends indicate a small increase in the incidence of bladder cancer with an overall decline in mortality.[1]

The median age at diagnosis is 65 years. Although rarely diagnosed before the age of 40, primary bladder cancer, including transitional-cell car-

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cinoma, has been reported in adolescents. Tumors in young adults tend to be well differentiated and indolent in nature.[2] Males are affected at a rate of two to three times that of females. The rate of occurrence in whites is approximately twice that of African Americans, however death rates are lower in whites.[3] Evidence exists that bladder tumors may behave more aggressively in African Americans. Urban populations have a higher incidence than rural populations.[4]

Risk factors associated with bladder cancer have been extensively studied. Transitional-cell carcinoma has been associated with cigarette smoking, exposure to polycyclic aromatic hydrocarbons, benzene products, certain chemotherapeutic agents, and phenacetin. Several studies have documented an approximately fourfold increase in the incidence of transitional-cell carcinoma in smokers.[5,6] Cessation of smoking leads to a decrease in risk, but the risk remains elevated for 10 years after quitting.[6] Exposure to polycyclic aromatic hydrocarbons and benzene products, such as in the dye and petroleum industry, has been shown to lead to an increased rate of transitional call carcinoma. Cyclophosphamide (Cytoxan®, Bristol-Myers Squibb) and other similar chemotherapeutic agents have been linked to secondary transitional-cell carcinoma, which may be particularly aggressive.[4] Phenacetin, a nonsteroidal anti-inflammatory agent, is more commonly linked to upper tract transitional-cell carcinoma, but may lead to an increased incidence of bladder cancer. Caffeine and artificial sweeteners have been implicated, but the association is not clear.[4]

Squamous cell carcinoma of the bladder within the United States is most commonly associated with chronic bladder irritation. Indwelling bladder catheters and bladder calculi, which are commonly seen in patients with spinal cord injury or neuromuscular disease, are major risk factors for development of this form of bladder cancer.[4] Fortunately, the management of bladder dysfunction in this patient population has undergone significant advancements within the last 20 years, and it is believed that these modifications will decrease the incidence of squamous cell carcinoma. Squamous cell carcinoma is found in bladder diverticuli, and one must exclude this form of primary bladder cancer in any patient who presents with hematuria and a bladder diverticulum.

Primary adenocarcinoma of the bladder is extremely rare, comprising only 1% of all bladder cancers. This form of bladder cancer is most often found in patients with a history of bladder extrophy or as a direct extension of urachal adenocarcinoma.

Most authorities feel that there is no difference in disease-specific survival for localized disease, regardless of the tumor type. Adenocarcinoma tends to occur in younger patients and be less symptomatic so the diagnosis is often delayed. Squamous-cell carcinoma may present at a more advanced stage leading to the appearance of decreased overall survival.

DIAGNOSIS

Hematuria is the presenting symptom in 90% of patients with bladder cancer. Hematuria may be gross or microscopic, and thus all patients with unexplained microscopic hematuria should undergo full urologic evaluation. Other symptoms at presentation may include urinary frequency, urgency dysuria, and ureteral obstruction. Systemic manifestations indicate metastatic disease and portend a poor prognosis.

The evaluation of a patient with hematuria includes a complete history and physical examination, including a pelvic and rectal exam. Directed studies should include a urine specimen for culture and cytology, intravenous pyelography, and cystoscopy. Bladder biopsies and transurethral resection of the tumor (TURBT) are indicated when tumor is found or cytologies are suggestive of malignancy. Upon the diagnosis of bladder cancer, additional studies, including complete blood count, liver function tests, and chest x-ray, are indicated. Computerized tomography scans are useful to evaluate the presence of bladder wall thickening, perivesical fat invasion, and lymph node involvement. Magnetic resonance imaging is no more specific than computerized tomography scanning for the diagnosis of extravesical involvement, and this is not routinely indicated. Unfortunately, understaging remains a common problem, with 33% of patients found to have more extensive disease than is clinically assessed.[7]

PATHOLOGY

Grading

Histologic grading for transitional-cell carcinoma involves evaluation of both cytologic and histologic characteristics. A three-tiered system is most often used. Grade 1 tumors are well-differentiated, grade

2 are moderately differentiated, and grade 3 are poorly differentiated. Grade is of particular importance in superficial tumors as a prognostic sign for recurrence and progression. Most invasive bladder tumors are high grade; rarely does a grade 1 tumor invade the musculature of the bladder wall.

Carcinoma in situ (CIS) deserves special mention in discussion of grading for transitional cell carcinoma. CIS is defined as high grade, noninvasive, transitional cell carcinoma, often involving large portions of the bladder urothelium. CIS although superficial by definition, tends to be aggressive, and may lead to metastatic disease. Of patients undergoing cystectomy for CIS, approximately 20% will harbor microinvasive disease on final pathologic review.[8]

Formal grading systems for squamous cell carcinoma and adenocarcinoma of the bladder are less well defined. Grading typically involves groupings of well-differentiated, moderately differentiated, and poorly differentiated tumors, using specific criteria for these tumor types.

Staging

The two most commonly used staging systems of bladder cancer include the Jewett and Strong system and the tumor-node-metastasis (TMN) staging system (Table 1). The TMN system delineates exophytic and superficial growth patterns and also allows for separate classifications of patterns of spread outside the bladder. Hence, it is more frequently used today. Recent modifications to this system incorporate changes in classification pertaining to depth of muscle invasion. In the past, T2 tumors involved the superficial layer of muscle, and T3a tumors had invasion of deeper muscle layers. Analysis of treatment outcomes indicated that the most important determination is whether the tumor is organ-confined. To reflect the clinical importance of this, the classification was changed. Now, all invasive tumors confined to the bladder are classified as T2 tumors, with T2a denoting superficial muscle invasion and T2b denoting deep muscle invasion. Pathologic T3 tumors are now defined as those that extend beyond the bladder to involve the perivesical fat, either microscopically (T3a), or macroscopically (T3b). It is believed that these changes will reflect survival differences found in patients with extravesical involvement by bladder tumors.

Table 1. Current TMN Staging* for Primary Bladder Cancer, including Modifications Made in 1997[9]

Primary tumor (T)
Tx, primary tumor cannot be assessed
T0, no evidence of primary tumor
Ta, noninvasive papillary carcinoma
Tis, carcinoma in situ
T1, tumor invades subepithelial connective tissue
T2, tumor invades muscle
T2a, tumor invades (inner half) superficial muscle
T2b, tumor invades deep muscle
T3, tumor invades perivesical tissue
T3a, microscopically
T3b, macroscopically (extravesical mass)
T4, tumor invades adjacent structures
T4a, tumor invades prostate, uterus, vagina
T4b, tumor invades pelvic wall, abdominal wall
Regional lymph nodes (N)
Nx, regional nodes cannot be assessed
N0, no regional lymph node metastasis
N1, metastasis in a single lymph node, 2 cm or less in greatest dimension
N2, metastasis in a single lymph node, more than 2 cm, not more than 5 cm in greatest dimension; or multiple lymph nodes, none more than 5 cm in greatest dimension
N3, metastasis in a lymph node more than 5 cm in greatest dimension
Distant metastasis (M)
Mx, distant metastasis cannot be assessed
M0, no distant metastasis
M1, distant metastasis present

*Stages: stage I, T1N0M0; stage II, T2aN0M0, T2bN0M0; stage III, T3a-bN0M0, T4aN0M0; stage IV, T4bN0M0, any T N1-N3M0, any T, any N M1.

NATURAL HISTORY

At diagnosis, 70%–80% of patients will have disease confined to the urothelium or lamina propria. Metastatic disease is found in 5%–20% of patients at diagnosis and is usually associated with invasive local disease. Patients with transitional cell carcinoma have an increased risk of developing upper tract urothelial tumors. Approximately 5% will have upper tract tumors at diagnosis, and the incidence may be as high as 20% within 5 years.[10] The natural history of superficial bladder cancer is often characterized by frequent recurrences, with progression to invasive disease occurring only in a minority of patients. Fifty to seventy percent of patients with disease initially confined to the mucosa will recur in 5 years, and approximately 10% will progress to

invasive tumors within 5 years.[11,12] The natural history of invasive disease treated with local therapy alone results in distant metastases within 2 to 3 years in the majority of patients. Metastatic disease is unfortunately often a fast-growing and lethal disease with 5-year survival rates of less than 5%.

The primary lymphatic drainage of the bladder is to the external and internal iliac chains, presacral lymph nodes, and the para-aortic and para-caval nodal chains. The incidence of positive lymph nodes is linked to many prognostic variables, of which stage and grade are the most important. The incidence according to T stage is as follows, pT1 5%, pT2 and pT3a 30%, pT3b 64%, and pT4 50%.[13]

Prognostic factors other than histopathology, grade, and nodal status include large tumor size, blood vessel invasion, multiple tumors, and the presence of concomitant CIS. Biochemical markers, such as blood group antigens and oncogene expression, are being investigated. Of these biochemical markers, it appears that p53 antigen expression may be the most clinically useful. Nuclear accumulation of p53 protein has been shown to predict a significantly increased risk of recurrence and death, independent of tumor grade, stage, and lymph node status.[14] Although it is premature to make treatment decisions based on p53 status, it may be useful in the future to identify a subpopulation of patients with particularly aggressive tumors who may benefit from adjuvant therapy.

MANAGEMENT

Treatment of Superficial Disease

The standard treatment of Ta bladder cancer is complete endoscopic resection with or without intravesical therapy. Recurrence rates are related to the grade of the tumor. The risk of recurrence for grade 1 and 2 tumors is 50%–60%, but is nearly 80% at 3 years for grade 3 tumors.[15] For Ta tumors, the risk of progression is low. Intravesical therapy is indicated when there is diffuse bladder surface involvement, frequent recurrences, or short intervals between recurrences.

CIS of the bladder may be diffuse or focal and may or may not be associated with invasive disease. Treatment involves transurethral biopsy to verify the diagnosis followed by intravesical immunotherapy or chemotherapy. Bacille Calmette-Guérin (BCG) therapy is most commonly utilized with tumor-free rates of 54% after one or two cycles of therapy.[16] Treatment of T1 disease is often challenging. Although it represents early stage disease, aggressive treatment is warranted to prevent recurrences and avoid progression. As with Ta disease, grade is an important prognostic factor. Those that are Grade 1 or 2 are usually treated with TURBT and intravesical therapy. Patients treated with TURBT alone have a higher risk of progression and decreased survival than those treated with TURBT plus intravesical BCG. Unfortunately, not all patients respond to treatment, and a radical cystectomy is required in those that fail. For T1, grade 3 lesions, consideration must be given to early surgical extirpation, because approximately 40% will progress to invasive disease.[17]

Intravesical Therapy

Commonly used agents for intravesical therapy include chemotherapeutic agents such as thiotepa, mitomycin-C (MMC), and adriamycin. Thiotepa was used frequently in the past; however, due to a high incidence of myelosuppression, it and has been largely replaced by MMC and adriamycin. These two agents have higher molecular weights and therefore less systemic absorption and fewer side effects.

BCG, an attenuated strain of *Mycobacterium bovis*, is the most commonly used form of intravesical immunotherapy. Although the mechanism of action has not been clearly defined, it may act as an immune system stimulant or to induce a direct inflammatory effect when given intravesically. BCG has been shown to be superior to both MMC and adriamycin in randomized studies.[18] Prior exposure to tuberculosis does not preclude the use of BCG. A positive purified protein derivative test is not uncommon in patients being treated with intravesical BCG and is neither an indication to treat the patient for tuberculosis nor an indication to cease use of BCG. BCG is currently the most frequently utilized intravesical therapy for CIS and recurrent superficial disease.

A randomized study comparing TURBT and BCG with TURBT alone was conducted at Memorial Sloan-Kettering Cancer Center. 10- and 15-year data are now available from this study. Significant differences in survival and progression were noted between the two groups. At 10 years, the disease-specific survival was 75% in those treated with BCG, compared with 55% in those treated with TURBT

alone. The 15-year survival in the BCG-treated group was 62%. Progression rates in the BCG-treated group show that 36% progressed to invasive or metastatic disease in 10 years, whereas those not treated with BCG showed a progression of 60% at 10 years.[19] Intravesical therapy is only indicated in patients with transitional cell carcinoma. There are currently no intravesical therapies that have efficacy for squamous cell carcinoma, adenocarcinoma, or other rare tumors of the bladder.

TREATMENT OF INVASIVE DISEASE

Surgical

Treatment of muscle-invasive bladder cancer remains challenging. Standard treatment in the United States is a radical cystectomy with urinary diversion. Historically, urinary diversion consisted of either intestinal conduit diversions that allow urine to drain through a segment of bowel (usually the ileum) to the skin surface or ureterosigmoidostomy. Conduit diversions require an external pouch to collect the urine, much in the way a colostomy functions.

Ureterosigmoidostomy involves redirection of the ureters directly into the sigmoid colon. Metabolic complications, consisting of severe hypokalemic, hyperchloremic metabolic acidosis and secondary colon malignancies are frequent.

Continent urinary diversions are widely utilized in patients following radical cystectomy. Ileocecal and ileal heterotopic reservoirs utilize a defunctionalized segment of bowel from which a pouch is created into which the diverted ureters may drain. Formation of a stoma to the abdominal wall allows the pouch to be catheterized at regular intervals. These diversions require significantly more bowel than ileal conduits; therefore, their use may be limited by concomitant bowel disease, previous bowel surgery, or previous external beam radiotherapy. The risk of metabolic complications and secondary malignancies is lower than with ureterosigmoidostomies, but the patient must be compliant with catheterization to prevent complications. The most frequent complications include infection, excess mucus production within the pouch, difficulty with catherization, and mild metabolic acidosis. The degree of acidosis is not as pronounced as in patients with ureterosigmoidostomy diversion. Pouch rupture may occur if the patient is noncompliant and requires immediate surgical correction with significant morbidity and mortality.

Orthotopic neobladders have been developed in the recent past and have become increasingly popular.[20–23] As the name suggests, this diversion allows for the reservoir to be connected directly to the urethra to allow voiding with abdominal pressure. Initially recommended only for men, orthotopic neobladders are increasingly performed in women.[24–27] This form of diversion allows for the most anatomic recreation of the urinary system. Patients are usually able to completely empty without the need for catherization. Complications are similar to those found in heterotopic continent diversions. The risk of incontinence is estimated to be between 20%–40% and typically occurs as nocturnal enuresis. Pouch rupture is rare in this form of diversion, as most will empty spontaneously as capacity is reached. Continent urinary diversions are contraindicated in a significant number of patients undergoing radical cystectomy. Mild chronic renal insufficiency may be exacerbated due to the absorption of solutes and the mild metabolic acidosis that accompanies these diversions. Previous bowel surgery or concomitant bowel disease may make the use of larger segments of bowel, which are required for these procedures, difficult. Care must be taken when utilizing chemotherapeutic agents and other medications, because bowel segments may absorb these agents from the stored urine, thus elevating serum levels. Fat and fat-soluble vitamin absorption may be affected due to alterations in bile salt absorption. Vitamin B_{12} absorption occurs in the terminal ileum, and thus levels must be followed carefully in patients who have this segment of bowel utilized in bladder reconstruction. Lastly, one must consider the overall health status and compliance of the patient. Patients who are either unwilling or unable to care for the continent diversions should undergo incontinent conduit diversion.

Survival rates with radical cystectomy for various stages serve as the comparison for other modalities. Published results suggest 5-year survival rates for T2 tumors are 50%–86%, T3a 63%–64% and T3b 29%–33%.[28–30]

MULTIMODALITY THERAPY

Radical Cystectomy and Radiotherapy

In an effort to improve survival rates in patients treated surgically, the addition of radiotherapy to a

radical cystectomy has been explored. Preoperative external beam radiation was used extensively in the past. Several randomized studies published in the 1980s showed no statistically significant survival benefit,[31–33] and a recent study by the Southwest Oncology Group also found no survival benefit to preoperative radiation therapy.[34] However, small sample sizes and large confidence intervals prevent definite conclusions from being made, and it is possible that preoperative radiation therapy may benefit a subset of patients. In general, however, it is not considered standard treatment.

Postoperative external beam irradiation has also been evaluated. Following a radical cystectomy, recurrence rates are high if the margins are positive. However, radiation has not been shown to benefit these patients, and in fact the complication rates are too high to justify this treatment in most circumstances.

Radical Cystectomy and Chemotherapy

As most patients who die of bladder cancer succumb to metastatic disease, the addition of chemotherapy to surgery seems an attractive option. Studies using single agent chemotherapy have been disappointing, with only rare complete responses. Various combinations of agents have been developed that have improved response rates. The most commonly used regimens are MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin), CMV (cisplatin, methotrexate, and vinblastine), and CISCA (cisplatin, cyclophosphamide, and doxorubicin). Response rates range from 56% to 71% with clinical complete response rates ranging from 25% to 50%.[35–37]

Neoadjuvant chemotherapy allows for treatment of early micrometastases and possible downstaging of the primary tumor. Nonrandomized studies indicate response rates that vary inversely with T stage.[38,39] Few randomized studies have been published. One study, the Nordic 1 trial, evaluated 311 patients who were randomized to receive radiation and cystectomy with or without neoadjuvant chemotherapy. Results showed a statistically significant difference in survival for patients with muscle invasive disease who were treated with neoadjuvant chemotherapy. However, the difference in survival was less than was expected and the long term survival effect was inconclusive.[40] In contrast to this study, data have been published from a study done by European Organization for the Research and Treatment of Cancer evaluating neoadjuvant MCV (methotrexate, cisplatin and vinblastine) chemotherapy versus no chemotherapy before cystectomy. This study found no difference in survival with neoadjuvant MCV.[41] Longer follow-up on this study is awaited, as are the results of other neoadjuvant chemotherapy trials.

Offering chemotherapy in the postoperative setting allows for more accurate staging and assessment of the need for further therapy based on the pathologic criteria. Several randomized studies using adjuvant chemotherapy have been published. Skinner et al.[42] reported the results of a trial using CAP (cyctophorphanide, dioxyrubicin, cisplatin) after a radical cystectomy versus no further treatment. Only 91 patients were randomized during the study and, of those who received chemotherapy, the regimens varied. This study was terminated prematurely. The authors concluded that postoperative chemotherapy is superior to observation, although the survival analysis did not reach statistical significance.[42] Another study, published by Stockle et al.[43] was performed in which patients were randomized to receive postoperative MVAC or MVEC (methotrexate, vinblastine, cisplatin, and epirubicin) versus observation. It was a small study, with only 49 patients randomized, and was also terminated early after an interim analysis showed a large number of relapses in the no treatment arm. A follow-up report of this trial demonstrated a survival benefit with chemotherapy; however, this was anticipated because patients did not receive chemotherapy at the time of relapse.[43]

These studies have been criticized for various reasons, including having small sample sizes and premature closure. As yet, there are no definitive answers of the treatment benefit of postoperative chemotherapy. However, the data do suggest a benefit and most urologists recommend chemotherapy to patients with stage T3 and T4 tumors or with node-positive disease.

Bladder Preservation Treatment Options

Although radical cystectomy offers a definitive treatment, quality-of-life issues encouraged the search for ways to effectively treat bladder cancer without removing the bladder. There have been many studies focusing on the issue of bladder pres-

ervation, including monotherapy and multimodality therapy.

Monotherapy options include limited surgical procedures such as TURBT alone and partial cystectomy. Both of these options are only applicable to patients having small, unifocal tumors and they are not advised as definitive treatment for most patients. Chemotherapy alone also has disadvantages. Although complete response rates in studies with chemotherapy alone were initially high, the response was not found to be durable. Chemotherapy alone as definitive treatment is not recommended for patients with bladder cancer. Using radiotherapy as a monotherapy in bladder preservation includes both interstitial brachytherapy and external beam radiation. Interstitial brachytherapy, like limited surgery, is suitable for only a small subset of patients. It has been used in combination with external beam radiotherapy with success in some patients, but it is limited to those having tumors less than 5 cm in size. Thus, it is not advocated for most patients.

External beam radiotherapy alone as definitive treatment, although not used frequently in the United States, is considered the standard in some countries, such as the United Kingdom. Typically, patients are treated to 50 to 55 Gy, using 2.5 to 2.75 Gy per fraction. Complete response rates range from 40% to 52%, and 5-year survival rates are 23%–40%. Although a direct comparison between these results and radical cystectomy results is not possible, it does appear that external beam radiotherapy is an inferior treatment. In addition to the lower survival rates, cystectomy is required in approximately 20% of the patients treated with external beam radiotherapy alone.[44–47]

There have been several randomized studies comparing external beam radiotherapy with cystectomy for salvage us. planned preoperative external beam radiotherapy followed by cystectomy. The Danish National Group demonstrated a lower rate of pelvic recurrence with preoperative radiotherapy and planned cystectomy compared to external beam radiotherapy alone with cystectomy as salvage. Survival analysis showed no statistically significant difference, but showed a trend toward favoring preoperative external beam radiotherapy and planned cystectomy.[48] This finding was similar to findings reported from a UK cooperative group.[49] One study from the M.D. Anderson Cancer Center did show a significant benefit in survival with preoperative external beam radiotherapy and planned cystectomy, although the sample sizes were small.[50] These studies do not offer final conclusions on the treatment, but seem to suggest that deferred cystectomy does not adversely affect survival in patients and serves as a basis for bladder preservation trials.

Although some patients may be successfully treated with monotherapy alone, the success rate is low. Combined modality approaches for bladder preservation have been explored and continue to be studied. Results of studies using limited surgery, such as TURBT or partial cystectomy, combined with chemotherapy indicate disappointing results, with 5-year survival rates with the bladder intact ranging from 20% to 30%.[51,52]

The addition of radiation to treatment with TURBT and chemotherapy offers higher bladder preservation rates, and these three modalities are now often linked in a complimentary fashion. In the early 1990s, four important trials were published regarding bladder preservation with combined modality approaches. These include reports from the University of Erlangen in Germany,[53] the University of Paris,[54] the Massachusetts General Hospital,[55] and the Radiation Therapy Oncology Group.[56] Those with 5-year data show survival rates of 47% and 48% and 5-year survival with bladder intact in 40% and 38% of cases. Three-year data was available for two of the studies, which show survival rates of 59% and 64%. All of these studies used a combination of TURBT, followed by radiotherapy and chemotherapy, although exact details differ between the studies.

The optimal schedule for chemotherapy and radiotherapy has not been determined at the present time, but the most commonly used chemotherapy regimen involves a cisplatin-based regimen given concurrently with radiation. An evaluation is typically performed after two cycles of chemotherapy and approximately 40 Gy of radiation. At that point, complete responders continue with more radiation and chemotherapy, whereas partial responders undergo cystectomy. A recent randomized study by the Radiation Therapy Oncology Group demonstrated no advantage to giving neoadjuvant chemotherapy before treatment with TURBT, chemotherapy, and radiotherapy.[57]

In summary, there is now much data supporting the option of bladder-sparing treatments for patients with muscle-invasive tumors. Although a direct comparison between these bladder preserva-

tion trials and radical cystectomy has not been done, the survival results appear to be similar. Treatment with transurethral surgery, radiation therapy, and chemotherapy is an appropriate option to be presented to patients.

Treatment of Metastatic Disease

Metastatic bladder cancer is usually incurable and the general approach is to help palliate symptoms. Although some patients with minimal metastatic disease may benefit from aggressive treatment, the vast majority of patients with metastatic disease should be managed with palliative intent. Individualized treatment plans are required, because each patient differs in his or her needs. Radiation can help alleviate many symptoms and chemotherapy may be offered as well. Radical surgery is not usually warranted in these cases.

CONCLUSION

Bladder cancer includes a broad spectrum of diseases. The majority of cases are superficial diseases that may have little impact on patient survival. Management of these tumors consists of endoscopic resection and continued surveillance to ensure that progression does not occur, or is detected early if it does occur. The addition of intravesical therapy is based on prognostic factors, including grade of disease, rapidity of recurrences, and the presence of CIS. For patients with concomitant CIS or high grade superficial lesions, early surgical intervention may be warranted, due to the high risk of progression and the limited efficacy of treatment modalities for advanced disease. Radical cystectomy remains the "gold standard" for those with muscle invasive disease. However, select patients may benefit from therapy designed for bladder preservation. This involves the use of aggressive TURBT combined with other treatment modalities, including radiation therapy and chemotherapy. Patients must be carefully selected and managed with input from a radiation oncologist, a medical oncologist, and a urologic oncologist. Metastatic bladder cancer is a highly lethal disease with limited two-year survival. Most therapy for this patient population should be managed with a palliative goal. All patients with good performance status should be considered for clinical trial participation.

There are many important questions to be answered in the management of bladder cancer. Ongoing investigations continue in the area of superficial disease to help better predict which patients will progress to invasive disease, thus helping to determine optimal therapy from the outset. For patients with muscle-invasive tumors, studies continue in the area of bladder-sparing treatment, including determining the optimal regimen.[58] In addition, new chemotherapeutic agents and different combinations of agents are being evaluated that may offer benefit for invasive as well as metastatic disease.

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CORRECTION

In the February issue of the Journal, Table 2 in the article by Bell et al., "Adherence to Antiviral Drug Regimens in HIV-Infected Adolescent Patients" was printed incorrectly. The corrected version is printed below.

Table 2. Means and standard deviations of study variables for all subjects by Adherence group

Variable	N	Total sample Mean ± SD	Adherers (N = 5) Mean ± SD	Non-Adherers (N = 13) Mean ± SD	Non-Medicated (N = 5) Mean ± SD
Age at enrollment	23	19.0 ± 1.4	18.8 ± 1.4	18.8 ± 1.4	19.4 ± 0.9
Prior STD's/preg.	23	2.3 ± .81	2.4 ± .89	2.4 ± .77	1.8 ± .84
Housing and instability	21	1.4 ± .51	1.0 ± 0*	1.6 ± .51*	1.5 ± .58
Months of treatment	23	15.3 ± 14.5	9.0 ± 9.0*	22.1 ± 15.2*	3.8 ± 4.4
Hx of keeping apptmts.	22	1.5 ± .60	1.6 ± .55	1.4 ± .52	1.5 ± 1.0
Viral load					
First visit	14	27.3K ± 57.3K	55.9K ± 106.1K	19.4K ± 23.3K	1.7K ± 1.4K
Last visit	13	19.6K ± 59.9K	499 ± 0	25.3K ± 68.0K	499 ± n/a
Change	10	−12.2K ± 22.2K	−3.5K ± 4.9K	−16.1K ± 26.0K	−2.3K ± n/a
CD-4 value					
First visit	20	414.4 ± 231.0	380.3 ± 145.8	327.7 ± 188.6	708.8 ± 197.5
Last visit	20	398.7 ± 225.8	402.0 ± 205.0	297.9 ± 159.8	697.8 ± 165.6
Change	19	−20.6 ± 134.2	21.8 ± 88.3	−39.5 ± 165.8	−11.0 ± 69.8
Health status change	15	2.6 ± .74	3.0 ± 0	2.4 ± .84	3.0 ± 0

*$p < 0.05$