Nonurothelial Cancer of the Bladder

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In this article, we review available evidence on the treatment of patients with nonurothelial cancer of the bladder. More than 150 published works were reviewed in preparation for this summary. Squamous cell carcinoma and adenocarcinoma are ideally treated with radical cystectomy. High-risk groups for these diseases are defined. Small cell carcinoma should be treated with multimodality therapy, including chemotherapy. Other rarer tumors of the bladder are also discussed. UROLOGY 69 (Suppl 1A): 93–104, 2007. © 2007 Elsevier Inc.

Worldwide, urothelial carcinoma (formerly known as "transitional cell carcinoma") is the most prevalent histologic type of bladder tumor. Superficial and invasive diseases have been extensively studied. At the other end of the bladder tumor spectrum, lie squamous cell carcinoma (SCC), adenocarcinoma, and other uncommon tumors. This latter group consists of small cell carcinoma, sarcoma, carcinosarcoma and sarcomatoid tumors, paraganglioma, lymphoma, melanoma, and pseudotumors. Other epithelial abnormalities can mimic tumors, and biopsy is frequently indicated for proper diagnosis.

SQUAMOUS CELL CARCINOMA

SCC occurs in bladders infected with and those free of bilharziasis. The incidence, epidemiology, and natural history of the 2 subpopulations are different.

SCC Not Associated with Bilharziasis

Epidemiology. Although bilharziasis is the leading cause of SCC worldwide, schistosomal infections are rare in Western countries. Primary SCC in the nonbilharzial bladder is uncommon. SCC represents the second most common bladder malignancy in Western countries, accounting for 2% to 5% of cases in most contemporary cystectomy series.[1–5] The tumors are most often diagnosed during the seventh decade of life.

Using data obtained from the Surveillance, Epidemiology, and End Results (SEER) program conducted between 1973 and 1997, Porter *et al.*[6] determined that black Americans were twice as likely as white Americans to develop SCC of the bladder, with an overall annual incidence of 1.2 per 100,000 person-years (95% confidence interval [CI], 0.4 to 1.37) in blacks versus 0.6 per 100,000 person-years (95% CI, 0.57 to 0.64) in whites.[6] This variability by race was observed in men and women of all age groups beyond 45 years, and, despite a slight decline in annual incidence over the 3 decades studied, remained relatively constant.

In the United States, although the incidence of urothelial carcinoma in men is ≥3 times that in women, less of a male predominance is noted in SCC. After compiling data from 915 patients in 10 series of SCC,[1–3] Johansson and Cohen[7] reported that the ratio of males to females was 1.4:1, which is consistent with ratios documented in other reports. As with urothelial carcinoma, women are more likely than men to present with advanced disease.[8] After analyzing data from the Netherlands Cancer Registry, Mungan *et al.*[9] confirmed that a higher incidence of T3 and T4 nonurothelial bladder cancer occurs in women (21.7% vs 14.5% in T3, and 14.5% vs 8.4% in T4).

Spinal Cord Injury

In the United States, patients with spinal cord injury represent the largest group of patients affected by SCC. This condition is thought to be owing to inflammation from chronic urinary tract irritation; SCC also is likely to occur in patients with chronic inflammatory disorders of the bladder, persistent calculi, chronic cystitis, and bladder diverticuli.[10]

It has been estimated that 10% of cases of SCC of the bladder occur in patients who have had an indwelling catheter for ≥10 years.[11] Other studies have documented a 16- to 28-fold increased risk for SCC of the bladder in paraplegic individuals. Patients who perform clean intermittent self-catheterization are less likely to develop the disease.[12,13]

The incidence of bladder cancer in patients with spinal cord injury was initially thought to be 2.3% to 10%, with most cases representing SCC.[11,14,15] A recent US Department of Veterans Affairs review[16] of admission data from 33,560 patients with spinal cord injury identified only 130 patients with bladder cancer, for an overall incidence of 0.39%. Some 42 patient records were available for review, including 23 (55%) with urothelial carcinoma, 14 (33%) with SCC, and 4 (10%) with adenocarcinoma. It is noteworthy that in 26 patients with indwelling

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catheters, the incidences of SCC and urothelial carcinoma were equal, implicating chronic inflammation caused by an indwelling foreign body in the pathogenesis of SCC. The higher prevalence of urothelial carcinoma in this population may also reflect the higher prevalence of cigarette smoking in the US veteran population.

In another study of patients from 3 Louisiana medical centers, Bickel *et al.*,[17] reported that bladder cancer was diagnosed in 8 of 2900 patients with spinal cord injuries, for an overall incidence of 0.32%. Only 2 of the 8 (25%) individuals were found to have SCC, neither of whom had an indwelling catheter.

Finally, in the largest study to date, Pannek *et al.*[18] reported results in 43,561 patients from Eastern Europe with spinal cord injury who completed a questionnaire that had been sent to all urologic departments involved in the management of spinal cord injury. In all, 48 patients with bladder cancer were identified, for an overall incidence of 0.11%. It is interesting to note that 7% of patients in this series had indwelling catheters, and only 19% had SCC. The authors concluded that the declining percentage of SCC and the declining incidence of bladder cancer may be a consequence of the reduced use of indwelling catheters.

Guidelines cannot be provided on the surveillance of patients with spinal cord injury for SCC. Initial reports, in which a high percentage of patients with spinal cord injury developed SCC, reveal a number of flaws, primarily related to the retrospective manner in which data were obtained. Although the true incidence of SCC in the spinal cord–injured population appears to be <1%, it is recommended that these patients should be monitored, particularly if they have indwelling catheters. Any history of hematuria should be evaluated. The appropriate frequency of surveillance and extent of diagnostic evaluation cannot be determined on the basis of the literature to date.

Smoking

The relation between SCC and cigarette smoking is not clear; however, Johansson and Cohen[7] found a higher incidence of SCC in smokers. SEER data support a direct correlation between quantity of cigarettes smoked and relative risk of developing SCC.[19] Indirect evidence from the Swedish Cancer Registry, however, does not support an association between SCC and smoking. A review of this database,[20] which plotted incidence trends in bladder cancer in Sweden between 1960 and 1993, revealed that, despite a rising incidence of urothelial carcinoma in Swedish women, which correlated with an increased prevalence of smoking during those years, the incidence of SCC remained relatively constant.

Causes

Because urinary tract infection is more common in women, a relation among squamous metaplasia, leukoplakia, and the development of SCC was proposed by Connery[21] and by Holly and Mellinger.[22] In a series of 20 patients with long-standing leukoplakia, O'Flynn and Mullaney[23] observed the development of 5 cases of SCC. Although SCC is not considered a premalignant lesion, it is often associated with squamous metaplasia.[10] Studies have confirmed the high prevalence of squamous metaplasia in the general population.[24]

A few case reports have documented the association among cyclophosphamide, bacille Calmette-Guérin (BCG), human papillomavirus, and SCC of the urinary bladder.[25,26] Recent studies have revealed possible genetic and chromosomal changes related to SCC. Abnormalities of chromosomes 3, 8, 10, 13, and 17 have been detected in SCC.[27] Studies on uroplakin II gene expression found a significant difference in expression between urothelial carcinoma and SCC, with expression being greater in SCC. Uroplakins are the major differentiation products of the urothelium that control the various pathways of urothelial differentiation.[5]

Clinical and Pathologic Features

Hematuria is the main clinical presentation in 63% to 100% of patients. Irritative bladder symptoms are seen in two thirds of patients; weight loss, back or pelvic pain, and frank obstructive symptoms are less common and are suggestive of advanced disease.[2–4,28] A urinary tract infection is present in 30% to 93% of patients at the time of diagnosis.[2–4,29,30] Symptoms are often present for a protracted time before the diagnosis is reached.[2,3,5,29] Most patients present with no previous history of urologic tumor. Superficial SCC of the bladder is rare, and most tumors are muscle invasive at presentation.

Pure SCC of the bladder must be distinguished from urothelial carcinoma with squamous differentiation. Relative to the number of series addressing treatment in patients with urothelial carcinoma, few series conducted in Western countries have addressed pure SCC. Most of these are >10 years old and did not use current staging and grading systems.

Superficial tumors are almost never seen; patients are usually given the diagnosis of SCC at an advanced stage. Most patients have a large, solitary tumor that extensively involves the bladder wall. These tumors appear as sessile lesions, often with ulceration and areas of squamous metaplasia adjacent to the primary tumor. A predilection for the trigone has been noted, but SCC can arise anywhere within the bladder. It may extend locally into the ureters and urethra. It may occupy a bladder diverticulum and has been described in association with bladder calculi.[31]

Debbagh *et al.*[32] reported that 10 of 14 patients had a palpable tumor on rectal examination, and 11 had upper urinary tract obstruction. Pretreatment imaging studies demonstrate hydronephrosis in 33% to 59% of cases.[2,3,5] Of 114 patients with SCC of the bladder, 92% had T2 to T4 disease at the time of diagnosis, and most tumors were of high grade.[3] As with urothelial carcinoma, clinical understaging is seen in as many as 73% of patients.[3,33]

Treatment

Pure SCC of the bladder has a poor prognosis, with most patients dying within 1 to 3 years of diagnosis. Despite a variety of treatment regimens, including radiation, chemotherapy, and surgery, in a series of 120 patients from the Royal Marsden Hospital, the overall 5-year survival rate was 16%, with only 8% of patients developing metastatic disease.[29] Therefore, failure to provide locoregional control appears to be the problem in managing these tumors.

Radiation. Reported results after treatment by definitive external irradiation are uniformly poor.[3,28] Radiation therapy in patients with SCC has been used as primary treatment or as an adjunct to surgery in the neoadjuvant setting. In a report by Quilty and Duncan,[30] 51 patients were treated with radical radiotherapy, delivered with a 3-field beam-directed technique, covering the entire bladder, to a prescribed dose of 55 Gy, given in 20 fractions over 4 weeks. Patients were treated prone, immediately after they had emptied their bladder. Only 4 patients had T2 cancer, and the overall survival rate was 26.9% at 3 years, with a median survival time of 14.3 months. Of 48 patients treated with radiation therapy by Rundle *et al.*,[3] 5-year survival rates for patients with T2 and T3 disease were 16.7% and 4.8%, respectively, and no patient with T4 disease survived beyond 11 months. Similarly, in a series of 17 patients with T2 and T3 tumors who were treated with radiation therapy alone, Johnson *et al.*[2] reported a 20% 5-year survival rate, which was not statistically lower than the 34.6% 5-year survival rate seen in 7 patients in which preoperative radiation was followed by radical cystectomy.

Radical Cystectomy. Surgical treatment appears to provide a better therapeutic yield. Richie *et al.*[33] reported a 5-year survival rate of 48% in 25 patients treated with radical cystectomy. Investigators believed that this compared favorably with results in patients with urothelial carcinoma; however, they did not include in the analysis 3 patients (9%) who died during the perioperative period or an additional 5 patients in whom insufficient pathologic study or follow-up data were obtained. After adjustments are made for these cases, the 5-year survival rate is significantly lower than was reported. Tumor stage was identified as the most important predictor of outcome.

Serretta *et al.*[5] reported on 19 patients with pure SCC of the bladder. All patients had a solitary locally advanced tumor and were treated with radical cystectomy. Of patients who were treated, 63% died of locally recurrent bladder cancer during a mean follow-up period of 52 months. Distant metastases were observed in only 1 patient.

Johnson *et al.*[2] used integrated preoperative radiation therapy followed by cystectomy and reported a 5-year survival rate of 34%. Swanson *et al.*[34] reported their results with the same approach. Patients with T2 disease showed the highest survival figures. Furthermore, results were better in patients whose tumors were downstaged by preoperative irradiation than in those who showed no downstaging. However, no conclusions can be drawn about the efficacy of preoperative irradiation plus cystectomy for nonbilharzial SCC because too few patients treated in this way have been reported.[35] Because the tumor is uncommon, only a few cases are available for study. It would be extremely difficult to conduct well-controlled prospective studies that would achieve objective conclusions.

In another more contemporary series with a mean follow-up of 42 months, 9 of 14 patients (37%) with SCC who underwent radical cystectomy were still alive. Only 1 of the patients who underwent cystectomy received preoperative radiation therapy; 4 received neoadjuvant chemotherapy with M-VAC (methotrexate, vinblastine, doxorubicin [Adriamycin; Bedford Laboratories, Bedford, OH], and cisplatin), and no objective response was noted. In this series of 19 patients, 12 died of locoregional disease, and only 1 patient died of documented metastases. All 3 patients with ileal neobladder developed recurrence at the anastomosis between the neobladder and the urethra. It was not specified whether frozen section biopsies of the bladder neck or urethra were performed intraoperatively. This contrasts with no anastomotic recurrences in 5 female patients with SCC who underwent orthotopic urinary diversion in a series by Stenzl *et al.*[36] In this series, negative intraoperative frozen section biopsy specimens of the bladder neck were obtained before orthotopic reconstruction was performed.

Several large contemporary cystectomy series in the literature have compared results in patients with urothelial carcinoma with those in patients with nonurothelial bladder cancer. In a large series from Japan,[37] no significant difference was observed in 5-year postcystectomy survival for patients with urothelial carcinoma (68.0%; n = 1042) and with nonurothelial carcinoma (60.8%; n = 89). Multivariate analysis determined that nonurothelial carcinoma was not an independent prognostic factor in survival.

Chemotherapy. The role of neoadjuvant or adjuvant chemotherapy in the treatment of patients with pure SCC of the bladder is uncertain. Chemotherapy usually is not recommended because of the low chemosensitivity of SCC of the bladder. SCC is considerably less responsive to standard chemotherapy regimens used for urothelial carcinoma[38,39]; neoadjuvant M-VAC has been tried with no objective response.[40] An effective chemotherapy protocol against this disease has not yet been found, although newer combination regimens consisting of agents such as gemcitabine, paclitaxel, and docetaxel, when combined with a platinum compound, may yield sustained disease remission in up to 50% of cases; these treatments hold promise for the future.[41]

It is interesting to note that SCC has a low incidence of distant metastasis, ranging from 8% to 10%.[42] Still, the prognosis of SCC of the bladder is dismal.

Table 1. Summary of International Consultation on Urological Diseases (ICUD) modified Oxford Center for Evidence-Based Medicine grading system for guideline recommendations

• Levels of evidence	
—Level 1	Meta-analysis of RCTs or a good-quality RCT
—Level 2	Low-quality RCT or meta-analysis of good-quality prospective cohort studies
—Level 3	Good-quality retrospective case-control studies or case series
—Level 4	Expert opinion based on "first principles" or bench research, not on evidence
• Grades of recommendation	
—Grade A	Usually consistent level 1 evidence
—Grade B	Consistent level 2 or 3 evidence or "majority evidence" from RCTs
—Grade C	Level 4 evidence, "majority evidence" from level 2 or 3 studies, expert opinion
—Grade D	No recommendation possible because of inadequate or conflicting evidence

RCT = randomized controlled trial.
Adapted with permission from *Incontinence*.[48]

Most patients die of locoregional failure within 3 years. Distant metastasis is more often the cause of death in patients with urothelial carcinoma than in those with SCC. Therefore, pelvic control for SCC is more important and adds incentive to attempt methods of treatment targeted at reducing the incidence of pelvic recurrence.[43]

Prevention and Early Detection. Several screening protocols have been advocated in an attempt to diagnose these tumors earlier, thereby improving outcomes. Broecker *et al.*[44] recommended annual cystoscopy and urine cytology in patients with long-term paraplegia. Others have suggested routine random bladder biopsies every 1 to 2 years. Navon *et al.*[45] did not routinely use urine cytology or random biopsies, except in patients with spinal cord injuries lasting >10 years and in those with recurrent or chronic urinary tract infection. Celis *et al.*[46] showed that psoriasin (a calcium-binding protein expressed by squamous epithelia) is a potential marker of SCC. Other biomarkers, such as SCC antigen and bcl-2 and p53 oncoproteins, may have a possible role in early diagnosis.[47] However, the exact role of these new markers in the early detection and follow-up of bladder SCC requires further study for validation.

Conclusion

In summary, nonbilharzial SCC is an uncommon form of bladder cancer. It has a poor prognosis, and death most often is related to locoregional failure—not to metastasis. The current literature, although limited, supports cystectomy as the treatment of choice (grade B) (Table 1).[48]

SQUAMOUS CELL CARCINOMA IN THE BILHARZIAL BLADDER

Epidemiology

This type of cancer is prevalent where urinary bilharziasis is endemic. The highest incidence of SCC of the bilharzial bladder occurs in Egypt. In a recent report by Ghoneim *et al.*,[49] SCC accounted for 59% of 1026 cystectomy specimens. A high incidence of SCC is also found in Iraq, the Jizan region in southern Saudi Arabia, Yemen, and Sudan. In Africa, the disease has been reported in the Gold Coast region and in South Africa. However, the incidence in these countries is lower because bilharziasis is less endemic and less severe.[50] The mean age of patients is 10 to 20 years younger than that seen with nonbilharzial cancer[43]; the median age is 46 years. Some 80% of cancer specimens have showed histologic evidence of bilharzial infestation.[48] A lag period of approximately 30 years has been reported between bilharzial infection and subsequent development of the disease. The male-to-female ratio is 5:1.[51] This male predominance is thought to be related to increased exposure to bilharzial infestation, in that men work more often in the fields and stay in contact longer with water that is contaminated with the infective parasite.

Causes

Good evidence from animal models suggests that the biogenesis of bladder cancer is a multistage process. It involves initiation by carcinogens, followed by promotion of tumor growth.[52] Bilharzial bladder cancer may be initiated by exposure to an environmentally or locally produced chemical carcinogen that is excreted in urine. This carcinogen reacts with the mucosal surface of the bladder to produce irreversible and potentially carcinogenic changes in the DNA of some urothelial cells. Chronic bacterial infection, which commonly complicates urinary bilharziasis, has been implicated in the production of nitrosamines, which are well-known potent carcinogens derived from precursors in the urine, and in the secretion of the β-glucuronidase enzyme, which may split conjugated carcinogens to yield free carcinogenic products.[53,54] The possibility that carcinogenic products may be of parasitic origin is not supported by recent investigation.[50] However, local mechanical irritation by schistosoma eggs appears to be an important promoting factor.[54] Vitamin A deficiency may explain the high frequency of squamous metaplasia of the bladder epithelium and the predominance of SCC in patients with bilharziasis.

Clinical and Pathologic Features

Patients usually present with symptoms of cystitis, including painful micturition, frequency, and hematuria. An

extensive irregular filling defect is usually detected on cystogram. Computed tomography (CT) scanning or magnetic resonance imaging (MRI) is helpful for diagnosis and staging. The diagnosis depends on cystoscopy, biopsy, and careful bimanual examination under anesthesia.[35] Urine cytology is also a valuable diagnostic tool for SCC in bilharzial patients.[55] Cytokeratin shedding in urine has been used as a biologic marker for the early detection of SCC.[56]

Most patients present for treatment at an advanced stage, and 25% of cases are inoperable when first seen.[43] This is so because of the overlap of symptoms of simple bilharzial cystitis with early malignant cystitis. When clinical staging was compared with pathologic findings, a clinical error of 37% was found, with a tendency toward understaging.[57] In a study of 608 patients with SCC of bilharzial bladder, pT1 disease was found in 2.6%, pT2 in 10.5%, pT3 in 80.0%, and pT4 in 6.9%.[49] Grading of the tumor in the same study showed grade A in 49.7%, grade B in 33.2%, and grade C in 17.1%. Lymph nodes were involved in only 18.7% of cystectomy specimens. The prevalence of low-grade disease and the intensive mural fibrosis associated with bilharziasis may explain the low incidence of lymph node positivity.[35]

Grossly, tumors are generally of the nodular, fungating type and are located in the dome or posterior or lateral walls of the bladder. Five gross types have been identified: nodular (60%), ulcerative (23%), verrucous (7%), papillary (7%), and diffuse (3%).[50] A variety of atypical changes in the bladder mucosa, including metaplasia, dysplasia, and, rarely, carcinoma in situ, may be associated with the disease.[58]

Treatment

Endoscopic Resection. In view of the tumor bulk and its advanced stage, transurethral resection appears to be unfeasible for definitive treatment, and no reports have described results when the procedure is used in bilharzial bladder malignancy. Endoscopic resection should be used only for obtaining a biopsy specimen for histopathologic diagnosis.

Segmental Resection (Partial Cystectomy). Segmental resection is an attractive alternative to circumvent the physiologic and social inconvenience of urinary diversion and the possible loss of sexual potency, but local resection is feasible only in select conditions. Solitary tumors must not involve the trigone, and their size must allow resection with an adequate safety margin; the rest of the bladder mucosa must be free of any associated precancerous lesions. These strict criteria are met in only a minority of cases. El-Hammady *et al.*[59] found resectable bladder cancer in only 19 of 190 (10%) patients. Augmentation cystoplasty was required in 5 patients to increase residual bladder capacity. The 5-year survival rate was 26.5%. Patients with low-grade tumor had roughly twice the survival rate of those with high-grade disease. On the other hand, less favorable results were reported by Omar[60] in a series of 22 cases. All patients except 1 developed tumor recurrence within 2 years. This different outcome may be related to the wide variability of selection criteria.

Radical Cystectomy. In view of the clinical and pathologic characteristics and the natural history of the disease, radical cystectomy with urinary diversion provides a logical treatment approach for patients with resectable tumor.[61,62] In men, the operation entails removal of the bladder, perivesical fat, peritoneal covering, prostate, seminal vesicles, and endopelvic lymph nodes. In women, the bladder, urethra (if is not used for orthotopic bladder substitution), uterus, upper vagina with pelvic fatty tissue, and aforementioned lymph nodes are removed.

In a series of 138 cases, Ghoneim *et al.*[62] reported a high postoperative mortality rate of 13.7%. This was due to peritonitis, adhesive intestinal obstruction, and hepatic failure. Cardiopulmonary complications were uncommon among this relatively young group of patients. In this old series, overall the 5-year survival rate was 32.6%; it was 43% in pT1 and pT2, and 30% in pT3 and pT4. Low-grade tumors showed 46% survival; high-grade disease survival was rated at 21%. Lymph node involvement reduced the 5-year survival rate to 20%.[61] In a recent report of results in 1026 patients from an endemic area of schistosomiasis who underwent cystectomy, 59% of tumors were SCC. Bilharzial ova were identifiable in 88% of specimens. Extravesical extension was not significantly different among patients with SCC or urothelial carcinoma (13.5% and 14.9%, respectively). Overall the 5-year survival rate with SCC was 50.3%. Only tumor stage, grade, and lymph node involvement had independent significant effects on survival. The latter halved the survival rate.[49]

These clinical trials provide evidence that cystectomy alone, despite the fact that it is a radical treatment, is inadequate to deal with the extent of local disease. An adjuvant treatment directed to the pelvis might improve survival. Preoperative radiation therapy has been proposed as adjuvant therapy.

Radiation

The growth characteristics of carcinoma of the bilharzial bladder have been studied with the goal of evaluating its potential radioresponsiveness.[63] Two growth features were noted: (1) high cell mitotic rate with a potential doubling time of 6 days, and (2) an extensive cell loss factor. Tumors with such growth characteristics were expected to exhibit a radiation response.[64] Nevertheless, early experiences with external beam radiation therapy for definitive control of these tumors were disappointing.[65] Factors that interfered with the efficiency of radiation treatment in these cases included coexisting bilharzial urologic lesions, which interfere with local tissue tolerance, and considerable tumor bulk, which reduces

local tumor control. Furthermore, the presence of radioresistant hypoxic tumor cells is suspected in light of the capillary vascular pattern of this cancer.[66]

Neoadjuvant Radiation. The aim of preoperative radiation is to eradicate smaller cell burdens in deeply infiltrating portions of the tumor and in microextensions into the perivesical tissues and lymphatics. These small tumor foci are expected to have a better radiation response because they are oxygenated and are composed of a relatively small number of cells with high mitotic indices. These biologic factors and the pattern of treatment failure due to local pelvic recurrence have justified the use of preoperative radiotherapy.

Awaad *et al.*[67] compared the results of cystectomy after preoperative administration of 40 Gy with outcomes in a control group treated with cystectomy only. Reported 2-year survival rates were significantly improved in the irradiated group. Ghoneim *et al.*[68] compared the results of cystectomy after preoperative irradiation using 20 Gy with those of cystectomy alone. Investigators treated 92 patients, divided into 2 groups, and followed them for 60 months. Although patients who received preoperative radiation had better survival rates, this improvement did not approach statistical significance. In low-stage tumors, regardless of grade, survival was not influenced by preoperative irradiation, as it was in high-stage tumors.

The presence of a large proportion of hypoxic cells within bulky tumors could explain the modest improvement that was observed after this regimen. To enhance the therapeutic value of irradiation, misonidazole, a hypoxic cell sensitizer, was given before the radiation regimen was delivered. The trial group was divided into 3 arms: cystectomy only, 20 Gy of preoperative radiation followed by cystectomy, and preoperative radiation followed by cystectomy with misonidazole added as a radiosensitizer. The addition of misonidazole did not provide any additional survival benefit to patients who were given preoperative radiotherapy (level 1) (Table 1).[68,69]

Chemotherapy. In the management of unresectable SCC of the bilharzial bladder, several chemotherapeutic agents have been tried by Gad-el-Mawla *et al.*[70] at the National Cancer Institute of Cairo University. All trials were phase 2 studies in which a single agent was used. The most promising results were obtained with epirubicin. Neoadjuvant and adjuvant epirubicin chemotherapy were used in a prospective, randomized study involving 71 patients with invasive cancer in bilharzial bladders. Two thirds of treated patients had SCC. Disease-free survival rates were 73.5% and 37.9%, favoring the chemotherapy group.[71] Additional long-term follow-up results have not been published.

In a recent multicenter study that consisted of 120 patients treated with neoadjuvant cisplatin and gemcitabine,[72] patients with SCC showed no survival benefit over those who underwent cystectomy alone.

Prevention and Early Detection. Bilharzial bladder cancer is a preventable malignant disease. Primary prevention entails control of bilharziasis through snail control (the intermediate host of the parasite) and mass treatment of the rural population with oral antibilharzial drugs such as praziquantel.[50] Secondary prevention includes early detection with urine cytology and selective screening of the population at risk. The yield of a single screening study done in a rural area in Egypt was 2 per 1000 individuals.[55] Such a detection rate would not justify regular screening.

Conclusion

In summary, bilharzial SCC is the most common form of bladder cancer in endemic areas. It most often presents at an advanced stage but with low-grade cells. Cystectomy is the standard treatment, but long-term survival remains disappointing (grade B) (Table 1). Limited evidence supports a potential role of neoadjuvant chemotherapy and radiation therapy but is not sufficient to facilitate a recommendation.

ADENOCARCINOMA

Overview

Adenocarcinoma of the bladder is the third most common histologic type of bladder carcinoma. It accounts for 0.5% to 2.0% of all bladder tumors.[73,74] Adenocarcinoma has the unique distinction of being the most common tumor arising in the bladder of patients with exstrophy. These patients carry a 4% lifetime risk of developing adenocarcinoma.[75] Adenocarcinoma of the bladder may also occur in association with schistosomiasis, endometriosis, bladder augmentation, and other irritative conditions of the urinary bladder.[76,77]

A study from the United States[19] used SEER data to identify only 32 patients (0.7%) with adenocarcinoma from 4045 patients with newly diagnosed bladder cancer over a 1-year period from 1977 to 1978. Similarly to urothelial carcinoma, adenocarcinoma shows a male predominance. In a total of 11 series comprising 247 patients,[7] the sex ratio of males to females was 2.7:1.

Adenocarcinoma of the urinary bladder is classified according to its site of origin as primary adenocarcinoma, urachal adenocarcinoma, or secondary (metastatic) adenocarcinoma, the latter of which represents the local extension of primary colon, prostate, or ovarian cancer.[78] Primary, urachal, exstrophy-associated, and metastatic adenocarcinoma are discussed below.

Primary Adenocarcinoma

Epidemiology. El-Bolkainy *et al.*[43] reported an incidence of primary adenocarcinoma of 8.1% in a series of 229 cases of bladder cancer. Between 1970 and 1995, 1870 cystectomies were performed in the Urology and Nephrology Center of Mansoura, Egypt. Of these, 185 cases

(9.9%) proved on histopathologic examination to be primary nonurachal adenocarcinoma of the bladder.[79]

Clinical Features. In most patients, primary adenocarcinoma of the bladder presents with hematuria, which may be associated with irritative voiding symptoms and, occasionally, passage of mucus in the urine.[72,73,79–82] Cystoscopically, the tumor is usually sessile, but it may be papillary.[81] It can arise anywhere along the lateral walls, trigone, dome, and anterior wall of the bladder.[72,79,81–83] Multiple tumors are present approximately 50% of the time.[72,79] Adenocarcinoma is virtually always invasive; only 1 series documented 2 tumors of 27 that were Ta or T1.[83] It is interesting to note that both patients were alive at 51 and 61 months after treatment with transurethral resection alone.

Primary adenocarcinoma of the bladder has a poor prognosis, regardless of the modalities used for treatment. The 5-year survival rates range from 0% to 31%; the small number of patients in each series precludes individual comparisons on the basis of treatment provided. In a retrospective series of 48 patients treated for primary adenocarcinoma of the bladder, stage was the only factor that was highly predictive of outcome.

Pathologic Features. For a diagnosis of primary adenocarcinoma of the bladder to be made, it must be distinguished from urothelial carcinoma with areas of glandular metaplasia. The pathogenesis of primary nonurachal adenocarcinoma is based on the ability of the urothelium to undergo metaplastic changes.[84] Mostafi[85] proposed that the metaplastic potential of the urothelium has 2 distinct patterns. Progressive invagination of hyperplastic epithelial buds into the lamina propria (von Brunn's nests) leads to the formation of cystitis cystica. Subsequently, metaplasia of the urothelial lining of these cysts to columnar mucin-producing cells results in the production of cystitis glandularis, which is a premalignant lesion. Follow-up is necessary.[86] Alternatively, cuboidal or columnar metaplasia of the surface epithelium may occur with no downward invagination. Chronic vesical irritation and infection are the predisposing factors for these changes.[84,87] This explains, at least in part, the higher incidence of these tumors among patients with bilharzial cystitis.

Histologically, adenocarcinoma may be non–mucin producing or mucin producing. Most of these tumors are mucin secreting, but the passage of mucus during micturition is uncommon.[88] In a large series in Egypt, two thirds of tumors were mucin secreting, and, in most, the site of deposition was extracellular (interstitial). Less commonly, mucin is secreted within the lumen of the acini and, infrequently, excessive intracellular mucin displaces the nucleus to a peripheral crescent, giving the cells a signet ring appearance. It is generally believed that this variety has a poor prognosis.[89,90]

No grading system for adenocarcinoma of the bladder has been uniformly accepted. On the basis of histopathologic findings, Anderstrom *et al.*[77] classified vesical adenocarcinoma into 5 patterns: glandular with columnar, sometimes enteric-appearing, cells; colloid carcinoma; papillary adenocarcinoma; signet ring cell carcinoma; and clear cell carcinoma. Several other histologic subtypes have been described, including mucinous; enteric (colonic); adenocarcinoma not otherwise specified; clear cell; hepatoid; and mixed type.[82] Unfortunately, no clear data have been gathered on whether these different varieties have an impact on survival or indicate prognosis, although signet ring cell carcinoma appears to impart a rapid course, resulting in death in most patients within 6 months of diagnosis.[83]

Treatment. Several treatment modalities have been used in the management of primary adenocarcinoma of the bladder. The therapeutic yield after transurethral resection with or without radiotherapy has been shown to be poor; Kramer *et al.*[80] reported a 5-year survival rate of 19%.

Partial cystectomy for localized disease in mobile parts of the bladder has been used by several investigators. Analysis of the published data indicates that results attained with this procedure are dismal.[73,91–93] On the other hand, Anderstrom *et al.*[77] reported a 5-year survival rate of 54% among 15 patients treated with partial cystectomy.

Adenocarcinoma is not a radioresponsive disease. Reported 5-year survival is <20% in patients treated with external irradiation alone. The addition of preoperative irradiation did not improve survival in 2 studies of 34 and 25 patients.[76,91]

Experience in the use of chemotherapy for the treatment of patients with bladder adenocarcinoma is limited. From results observed with gastrointestinal adenocarcinoma, combination chemotherapy based on 5-fluorouracil has been attempted by several investigators. Most published series involve small numbers, and the response is universally unsatisfactory.[94–96]

Radical cystectomy with or without adjuvant therapy has been reported by several authors. Most published reports are based on few patients and involve short-term follow-up. Reported 5-year disease-free survival rates range from 0% to 80%.[76,91–93,97,98]

In an Egyptian series, 5-year survival after cystectomy was 55%, and no difference was noted between cases of urothelial or squamous cell origin.[47,99] Cox regression analysis proved that stage, grade, and lymph node involvement were all independent prognostic factors. No histologic varieties, regardless of cell type or site of mucin deposition, were shown to be independent prognostic factors.[78]

Conclusion

In summary, the treatment of patients with adenocarcinoma varies according to subclassification. Primary adenocarcinoma is poorly responsive to radiation and chemotherapy, and patients should be treated with radical cystectomy (grade B) (Table 1). Urachal adenocarci-

noma should be treated with en bloc resection of the urachus and umbilicus with partial cystectomy (grade B). The incidence of adenocarcinoma is much higher in patients with exstrophy. Any patient with bladder exstrophy who has retained his or her bladder should be closely followed, although an exact regimen cannot be prescribed on the basis of currently available evidence (grade C). Patients with metastatic adenocarcinoma involving the bladder should undergo complete resection of the involved portion of the bladder, with partial cystectomy with verified negative margins or with the use of radical cystectomy (grade B).

SMALL CELL CARCINOMA

Epidemiology

Small cell carcinoma is a neuroendocrine tumor that most commonly arises in the lungs. Extrapulmonary small cell carcinoma may occur in multiple locations, including the urinary bladder. Primary small cell carcinoma of the urinary bladder is exceedingly rare, with only 286 cases reported in the English-language literature.[100] Evidence is limited and is provided primarily in the form of small case series and case reports.

Two prior reviews have shown that small cell carcinoma accounts for 0.48% to 0.7% of all cases of primary bladder tumor.[101–104] One review of 243 cases of small cell carcinoma of the bladder revealed that 62% were pure small cell carcinoma and 38% were combined carcinomas, most frequently with urothelial carcinoma, adenocarcinoma, or SCC.[105] It is interesting to note that the reverse (32% pure small cell carcinoma, 68% other histologic types) was seen in a recent multi-institutional review by Cheng *et al.*[106]

Clinical Features

An analysis of the characteristics of 238 patients with small cell carcinoma of the bladder has been reported by Sved *et al.*[100] Mean patient age was 67.8 years, with a range of 20 to 91 years, and 80% of patients were male. Similarly, a review of 64 patients by Cheng *et al.*[106] showed a male-to-female ratio of 3.3:1 and a mean age of 66 years (range, 36 to 85 years). Hematuria was the presenting symptom in 88% to 90% of patients in the 2 reviews. Rarely, paraneoplastic syndromes herald the diagnosis.[105,107] The initial workup is the same as for any patient with hematuria and a suspected bladder tumor. Small cell carcinoma cannot be distinguished from urothelial carcinoma on cystoscopy, but when a pathologist identifies this lesion, the patient should undergo a full metastatic workup.[103] The vast majority of patients (94% of 183 patients on whom this information is available) present with muscle-invasive disease. Metastatic disease is reported in 67% of cases, most commonly to lymph nodes, liver, bone, lung, and brain.[100]

Pathologic Features

The tumor is composed of a population of relatively uniform cells with scant cytoplasm and hyperchromatic nuclei. Frequent mitotic figures and extensive necrosis are common.[108] The origin of small cell carcinoma is uncertain. It may be derived from neuroendocrine cells or multipotent stem cells of the bladder.[103] Diagnosis is usually made with hematoxylin and eosin; however, special stains to confirm the neuroendocrine origin may be required.[109]

A retrospective analysis of 29 urine specimens from patients in whom small cell carcinoma was diagnosed showed that 56% could be diagnosed by urinary cytopathology. The other cases were interpreted as high-grade urothelial carcinoma. Five patients had both small cell carcinoma and urothelial carcinoma, and 3 of these were identified as small cell carcinoma on cytologic examination.[110]

Treatment

The most common site for small cell carcinoma is the lung. High-quality studies have been performed and treatment regimens are well defined for primary small cell lung carcinoma. Small cell carcinoma of the lung is treated as a systemic disease because, as with primary small cell carcinoma of the bladder, fewer than one third of patients present with organ-confined disease. Chemotherapy is the mainstay of management. Patients with early-stage small cell carcinoma of the lung are most commonly treated with cisplatin plus etoposide or with alternating cyclophosphamide, doxorubicin, and vincristine.[111] The median survival time for these patients is 10 to 14 months.[112] Radiation confers an additional survival advantage in early-stage disease but is not helpful in patients with advanced disease.[113] Surgical resection has not been shown to be beneficial.[111] Patients with advanced disease have a uniformly poor prognosis.

The small number of reports on patients with small cell carcinoma of the bladder suggests that it behaves similarly to small cell carcinoma of the lung. Overall, local treatment yields poor survival rates, and systemic therapy provides improvement. In the review by Sved *et al.*,[100] 7 patients who underwent cystectomy alone all died between 1 and 25 months after surgery. The dismal prognosis of patients treated with radical surgery invited the use of neoadjuvant and adjuvant chemotherapy regimens.

Adding chemotherapy to the regimen appears to enhance survival. In 5 small series reviewed by Sved *et al.*,[100,114–117] 13 of 18 patients who were treated with cystectomy plus chemotherapy were alive at a mean of 27 months. In addition, Walther[101] reported favorable response rates in 7 patients treated with systemic etoposide and cisplatin in neoadjuvant and adjuvant protocols.

Similarly, in a recent retrospective review from the M. D. Anderson Cancer Center, at the University of

Texas, Houston, median survival and 5-year disease-free survival were significantly improved in patients who received preoperative chemotherapy.[118] Of 25 patients who underwent cystectomy with or without postoperative chemotherapy, median cancer-specific survival was 23 months, and the 5-year disease-free survival rate was only 36%. Conversely, of 21 patients who were given preoperative chemotherapy, the median cancer-specific survival rate had not yet been determined at the time of the report, and the 5-year disease-free survival rate was 78%. Only 4 cancer-related deaths occurred in these 21 patients, all before 2 years. The preoperative chemotherapy regimen determined response; only 2 of 12 patients who received a regimen directed toward small cell carcinoma (etoposide and cisplatin or ifosfamide and doxorubicin) had residual small cell tumors in their cystectomy specimen. Six of 9 patients who were given a regimen directed toward urothelial carcinoma (M-VAC, or taxol, methotrexate, and cisplatin) had residual small cell carcinoma on cystectomy.[118]

Reports of probable cure do exist. One patient with small cell carcinoma metastatic to the pelvic lymph nodes who received M-VAC before undergoing radical cystoprostatectomy was alive at 9 years.[117] Another patient treated with neoadjuvant M-VAC before radical cystoprostatectomy had no evidence of disease in the specimen and remained disease free 3 years after surgery.[119]

Radiation therapy alone has not been successful for treating patients with small cell carcinoma; mean survival of <8 months has been reported in 40 cases, but long-term survival has been reported in patients treated with radiation therapy and chemotherapy. Of 5 patients who had complete remission after receiving chemotherapy and radiation, all were alive after 4 years, and only 1 required cystectomy for local recurrence.[100]

Of 12 patients who received partial cystectomy with chemotherapy or radiation therapy, 3 remained alive at the time of reporting, with a median survival of 34.9 months. Management with transurethral resection of the bladder tumor (TURBT) alone has resulted in uniformly poor results, with a mean survival time of <8 months in most small series.[100]

Conclusion

In summary, small cell carcinoma of the bladder is an aggressive disease that often presents at advanced stages. Because of the rarity of this lesion, evidence is limited. Cure is most likely with aggressive multimodal therapy and a combined local and systemic approach.

RECOMMENDATIONS

Classification grades and levels of evidence are described in Table 1.

SCC

1. A surveillance schedule for SCC in patients with spinal cord injury cannot be determined from the currently available evidence (grade D).
2. Cystectomy is the best primary therapy for SCC, whether bilharzial or nonbilharzial (grade B).

Adenocarcinoma

1. Patients with bladder exstrophy who have retained their bladders should be closely followed, but no particular regimen can be recommended on the basis of currently available evidence (grade D).
2. Patients with primary adenocarcinoma should be treated with radical cystectomy (grade B).
3. Those with urachal adenocarcinoma should be treated with en bloc excision of the urachus and umbilicus with partial cystectomy (grade B).
4. Patients with metastatic adenocarcinoma involving the bladder should undergo complete resection of the involved portion of the bladder, with partial cystectomy with verified negative margins or with the use of radical cystectomy (grade B).

Small Cell Carcinoma

1. When small cell carcinoma is identified on a TURBT specimen, the patient should undergo a full metastatic workup, including CT of the abdomen and pelvis, bone scan, chest x-ray, and a neurologic examination (grade C).
2. Patients with small cell carcinoma of the urinary bladder require aggressive combination therapy, such as combined chemotherapy and radical cystectomy or chemotherapy and radiation therapy, to achieve cure (grade B).

Bladder Sarcoma

1. Patients with bladder sarcoma should be treated with radical cystectomy with negative margin resections (grade C).
2. Those with metastatic sarcoma should be treated with a multimodality protocol (grade C).

Carcinosarcoma and Sarcomatoid Tumors

- Carcinosarcoma and sarcomatoid tumors have a poor prognosis, and surgical management is inadequate. Multimodality therapy is recommended (grade C).

Paraganglioma and Pheochromocytoma

- The standard treatment for patients with paraganglioma and pheochromocytoma is partial cystectomy with pelvic lymph node dissection, with the same precautions taken as for any other pheochromocytoma with adrenergic blockade (grade C).

Table 2. Optimal treatment of patients with nonurothelial bladder tumor

Disease	Optimal Treatment	Grade of Recommendation
Squamous cell carcinoma	Radical cystectomy	B
Primary adenocarcinoma	Radical cystectomy	B
Urachal adenocarcinoma	En bloc excision of urachus and umbilicus with partial cystectomy	B
Metastatic adenocarcinoma involving the bladder	Complete resection of involved portion of the bladder; partial cystectomy with negative margins or radical cystectomy	B
Small cell carcinoma	Local treatment and chemotherapy	B
Bladder sarcoma	Radical cystectomy	C
Carcinosarcoma, sarcomatoid tumors	Multimodality therapy	C
Paraganglioma and pheochromocytoma	Partial cystectomy with pelvic lymph node dissection; perioperative adrenergic blockade	C
Pseudotumor	Transurethral resection or partial cystectomy	C
Melanoma, primary, of bladder	Radical cystectomy	C
Lymphoma, primary	Local irradiation	C

Bladder Pseudotumor

- When the diagnosis of a bladder pseudotumor is clear, transurethral resection or partial cystectomy is the appropriate treatment. If necessary, to exclude sarcoma, radical cystectomy may be performed (grade C).

Melanoma

- Patients with primary bladder melanoma should be treated with radical surgery, but the prognosis remains poor (grade C).

Lymphoma

- Those with primary lymphoma of the bladder should be treated with local irradiation (grade C) Table 2.

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