

SQUAMOUS CELL CARCINOMA OF THE URINARY BLADDER

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Primary squamous cell carcinoma of the bladder is a relatively rare tumor, comprising 1% to 7% of all bladder cancers in the Western world.^{1,2} It is the most common malignant tumor in men in Egypt, where schistosomiasis is endemic.³ Nonbilharzial cases are usually associated with chronic infection, vesical stones, chronic indwelling catheters or bladder diverticula.^{4,5}

Almost all squamous cell cancers are already advanced and muscle-infiltrative at the time of diagnosis.^{6,7}

Transurethral resection, partial cystectomy, radiation therapy and chemotherapy are not effective.^{6,7} Radical cystectomy and urinary diversion appear to be the treatment of choice in selected cases. In general, the prognosis is poor.

This study is a clinicopathologic report on patients with primary squamous cell carcinoma of the urinary bladder treated in Riyadh Armed Forces Hospital between 1979 and 1995.

Patients and Methods

Between 1979 and 1995, a total of 235 patients with primary bladder cancers were treated in Riyadh Armed Forces Hospital (Table 1). Squamous cell carcinoma comprised 47 (20%) patients. The charts of these patients were reviewed and included in the present study.

All patients were initially evaluated by history-taking, clinical examination, standard laboratory investigations, chest radiographs, excretory urography and/or abdominal ultrasonography. The tumors were assessed by bimanual examination under anesthesia, cystoscopy and biopsy. A computed tomography scan of the abdomen and pelvis and radioisotope bone scan were obtained.

Clinical staging was done in all cases and the tumors

TABLE 1. Frequency of various histologic cell types in 235 patients with primary bladder carcinoma.

Histologic cell type	No. of cases	%
Transitional cell carcinoma	174	74
Squamous cell carcinoma	47	20
Undifferentiated carcinoma	11	4.7
Adenocarcinoma	3	1.3

TABLE 2. Clinicopathologic features and treatment modalities in 47 patients with primary squamous cell carcinoma of the urinary bladder.

No. of men/women	38/9
Male to female ratio	4.2:1
Mean age at diagnosis (range)	53.7 years (33-85)
Histological grade (WHO)	
G1	6
G2	22
G3	19
Clinical stage	
T2	3
T3	18
T4	26
Treatment	
Radical cystectomy + diversion	16
Radical cystoprostatectomy + diversion	1
Partial cystectomy + cystoplasty	3
Laparotomy only	3
Palliative urine diversion	2
Palliative radiotherapy	16
No active treatment	6
Follow-up (20 patients received definitive surgery)	
Mean follow-up period in months	36
Patients well and cancer-free	6
Patients died from cancer	7
Patients lost to follow-up	7
Crude five-year survival	46%

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were categorized according to the TNM system,⁸ and graded histologically according to the WHO classification.⁹

Evidence of schistosomiasis was also noted (history of treatment, significantly high schistosoma antibody titer, cystoscopic features or microscopic findings).

TABLE 3. A comparison between the important clinical features of patients with transitional and squamous cell bladder carcinomas.

Features	Transitional cell carcinoma	Squamous cell carcinoma
Number of patients	174	47
Mean age in years \pm SD	64.2 \pm 16.2	53.7 \pm 14.4
Male to female ratio	8:1	4.2:1
Nationality		
Saudis	123 (71%)	32 (68%)
Non-Saudis	51 (29%)	15 (32%)
Upper urinary tract dilatation	54/348 (15.5%)	37/94 (39%)
Tumor stage		
Superficial	70 (40%)	None
Muscle-infiltrating	104 (60%)	All cases
Associated schistosomiasis	19/174 (11%)	39/47 (83%)

Results

Forty-seven patients with histologically proven squamous cell carcinoma of the urinary bladder were studied. Patients ranged in age from 33 to 85 years (mean 53.7 \pm 14.4) and there were 39 males and nine females. Gross hematuria was the main symptom in 32 patients (68%). The duration of symptoms varied between one and 12 months. The size, location and mobility of the tumor were assessed bimanually. Bimanual examination under anesthesia showed a palpable bladder mass in 41 cases, of which 22 were fixed. The remaining six tumors were difficult to palpate.

Endoscopic evaluation revealed nodular fungating masses in 44 patients, ulcerative lesions in two and fibrillary in one. Tumors were bulky and solitary in 41 cases and multifocal in six. Solitary lesions were located in lateral walls in 19 cases, dome in seven, posterior wall in five and anterior wall in three. Involvement of the trigone, bladder neck and prostatic urethra was noted in six patients. One patient had a tumor in a bladder diverticulum (Figure 1).

A summary of the clinicopathologic features and therapeutic modalities for 47 patients with primary squamous cell carcinoma is presented in Table 2. The frequency of grades 1, 2 and 3 lesions were six (13%), 22 (47%) and 19 (40%), respectively. A comparison is made between patients with transitional cell carcinoma and those with squamous cell carcinoma in table 3. In this series, the mean age of patients with squamous cell carcinoma (53.7 years) was significantly less than those with transitional cell carcinoma (64.2 years). Evidence of schistosomiasis was found in 39 (83%) patients with squamous cell carcinoma. A significantly lower incidence of 11% of associated schistosomiasis was noted in 174 cases of

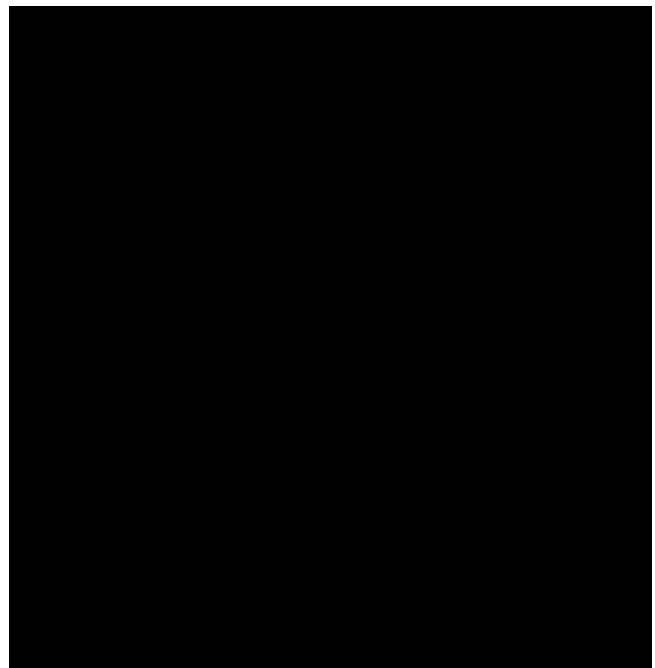


FIGURE 1A. Intravenous urography film shows overlapping of the contrast medium-filled urinary bladder by the opacified vesical diverticulum, and a large filling defect is noted occupying its upper part.

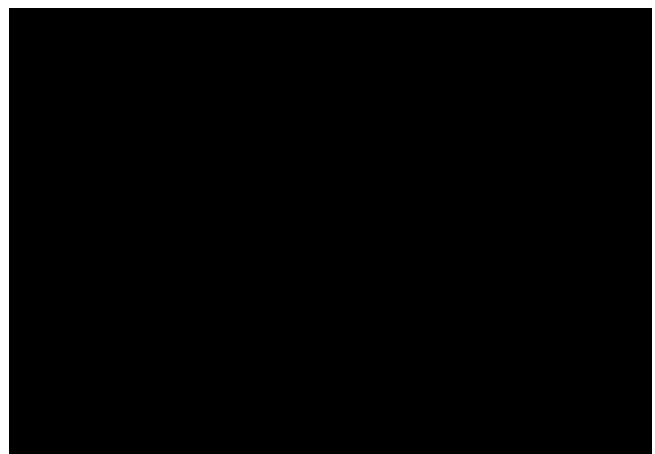


FIGURE 1B. Magnetic resonance axial gadolinium DTPA-enhanced T₁-weighted image clearly shows the bulk of the tumor as a low signal intensity surrounded by a rim of bright contrast medium in the vesical diverticulum with no intravesical extension of the tumor mass.

transitional cell carcinoma. All squamous cell carcinomas were muscle infiltrating at the time of diagnosis, while 40% of transitional cell carcinomas were superficial. The squamous cell tumor clinical stages were T₂ in three patients, T₃ in 18 and T₄ in 26. Evidence of local extension of the tumor into the colon was noted in three cases and distant metastases in four (lungs in two, bones in one and liver in one). Radiologic evaluation showed

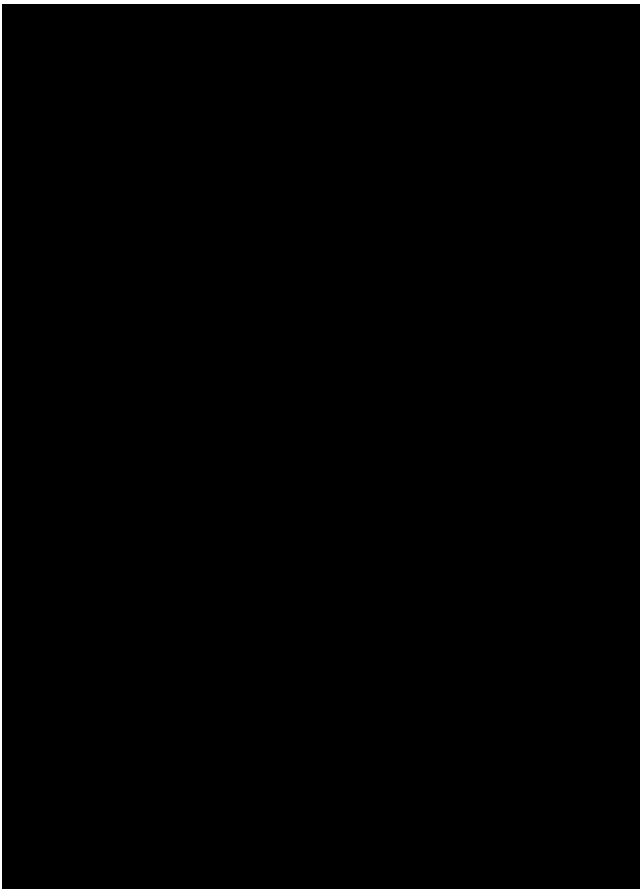


FIGURE 2A. Intravenous urography film shows a tumor occupying the left side of the bladder. There is left hydronephrosis related to the tumor.

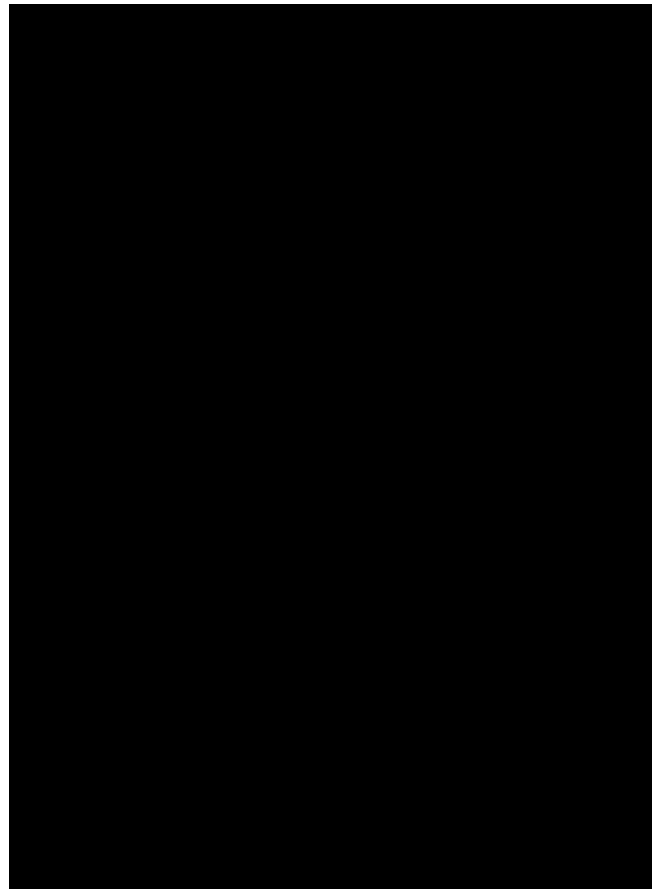


FIGURE 2B. Follow-up intravenous urography film 24 months after radical cystectomy and orthotopic bladder replacement (urethral Kock's pouch) shows adequate neobladder and improvement of the left renal configuration.

bilateral dilatation of the upper urinary tract in 15 patients and unilateral in seven (39% of renal units). This dilatation was caused by the tumor in 16 patients (Figure 2).

The clinical indications for surgery included resectable tumors localized to the urinary bladder (T_2 and T_3 lesions) in a generally fit patient. Radical cystectomy was performed in 17 patients. One patient required additional urethrectomy. The urinary diversion in these patients included ileal loop conduit in nine patients, urethral Kock pouch in five and ureterosigmoidostomy in three. Partial cystectomy and intestincystoplasty were done in three cases (ileocystoplasty in two and colcystoplasty in one). A case of squamous cell carcinoma treated by radical cystectomy and bladder replacement with urethral Kock pouch is presented in Figure 2. Of these 20 patients who received definitive surgical treatment, 13 patients were followed for a mean period of 36 months. Seven patients died from cancer within the first year after surgery and six patients were alive and free from cancer. The crude five-year survival of this group of patients was 46% (Table 2).

Palliative urinary diversion was done in two patients (ureterocutaneostomy). Laparotomy was performed in only three cases, where the tumors were inoperable. The remaining patients were considered unsuitable candidates for surgery in view of poor general health, unresectable locally advanced or metastasizing tumors. Palliation of the tumor with radiotherapy was done in 16 cases. Six patients had no active treatment.

Discussion

The crude relative frequency of bladder cancer in Saudi Arabia is 3% to 3.7% among other male cancers in eastern and central areas,^{10,11} while it is 9.4% to 10.7% in the southwestern region, where schistosomiasis is prevalent.^{12,13} In the present study, transitional cell carcinoma is the most common bladder tumor (74%), while squamous cell carcinoma constitutes 20% of 235 bladder tumors seen over a 17-year period. These figures are similar to the published results from other hospitals in Saudi Arabia.^{14,15} A lower incidence of 1% to 7% was

reported in the Western world.^{1,2} In countries where schistosomiasis is endemic, the incidence of squamous cell carcinoma is much higher: 75% in Egypt,³ 65% in Iraq,¹⁶ 39% in Nigeria¹⁷ and 71% in Zambia.¹⁸

The mean age in this series was 53.7±14.4 years and the male-to-female ratio was 4.2:1. The relatively younger age incidence and male predominance are in agreement with other reports.^{3,6,14,15} The relatively higher male incidence than in Western reports is because males are more prone to schistosomal infestation than females.

Hematuria was the presenting symptom in 68% of cases. The symptoms of simple bilharzial cystitis and early bladder carcinoma are overlapping. Therefore, late presentation may be due to misdiagnosis¹⁹ or to patients who do not appreciate the development of new symptoms and attribute them to bilharziasis.²⁰

Endoscopic assessment of squamous cell carcinoma revealed that the tumors were bulky, nodular, fungating masses in 44 patients and ulcerative in two. Only one fibrillary tumor was seen in this group. Lesions were located usually at the vesical vault, while involvement of the bladder base (trigone, bladder neck and/or prostatic urethra) was rare. Multifocal lesions were rare (13%). We reported a case of squamous cell carcinoma in a bladder diverticulum. Our results are similar to the published data in the literature.^{3,20}

Many of the squamous cell carcinomas were at an advanced stage at the time of diagnosis, which may be explained by their location in the bladder vault or the late development of symptoms. In our study, all the tumors were muscle-invasive at the time of diagnosis. This finding is in agreement with other reports.^{3,6,7,21} Tumor grading had shown a moderate (47%) to poor (40%) degree of cellular differentiation. Others had reported that squamous tumors are well to moderately differentiated.^{3,6} This discrepancy may be attributed to the interindividual variations in interpretation of tumor grades.²²

In the present series, 28% of patients with bladder tumors in general and 83% with squamous cell carcinoma had evidence of urinary schistosomiasis. The high frequency of squamous cell carcinoma in schistosomal patients is related to squamous metaplasia and dysplasia, which are common in these patients.²³ A close relationship between schistosomiasis and bladder cancer was suggested by Fergusson in 1911²⁴ and supported by many investigators,²⁵⁻²⁷ but rejected by others.^{28,29} The occurrence of squamous cell carcinoma in a younger age group, its predominance in males, its association with evidence of schistosomiasis in 83% of cases, absence of superficial squamous tumors and the significantly lower incidence of schistosomiasis in association with transitional cell carcinoma (11%) in this study, are all suggestive of an etiologic relationship between schistosomiasis and squamous cell carcinoma.

There are four strategies to reduce deaths from squamous cell carcinoma of the bladder: prevention, early detection, the development of more effective therapies in selected cases with localized disease, and improved approaches to the management of advanced disease.

Prevention should be the ultimate way to reduce deaths from this disease. Public education, elimination of the parasite by snail control and mass therapy of infected populations will help cancer prevention in the future. This might also explain the changing age incidence and pathological types of schistosome-associated bladder carcinoma in a recent report.³⁰

Since almost all cases of squamous cell carcinoma are muscle-infiltrative at the time of diagnosis, the importance of early detection is obvious. Emphasis should be placed on the need for medical education programs aiming at early diagnosis of the disease by general practitioners and primary care medical personnel. If we are able to detect localized early stages, we might be able to improve the outcome of patients. Different methods have focused on investigating tumor cells in the urine and these have included conventional cytology, flow cytometry, ABO(H) cell surface isoantigens and quantitative fluorescent image analysis or detection of tumor products in urine, such as bladder tumor antigen test that detects the presence of basement membrane complexes in urine.^{31,32} This marker should be a subject of large clinical trials to obtain definitive results.

Urine cytology is a specific, noninvasive technique which can be useful in the screening of high-risk groups in endemic bilharzial areas.^{33,34} However, the methodology is hampered by subjective interpretation, expense and the results can be time consuming.

The usefulness of flow cytometry as a screening test or as an initial diagnostic modality is limited due to the high frequency of diploid squamous cell cancers (30%) and inadequate information obtained in voided urine samples and bladder washings.²¹ Reports in cases of squamous cell carcinoma have indicated that flow cytometry can be an additional objective method to classify the tumors according to their DNA profile and proportion of S-phase cells. This classification is useful in predicting their metastatic potential and prognosis.³⁵ The most significant prognostic indicators in cases of carcinoma of the bilharzial bladder were the DNA index and the status of the pelvic lymph nodes at operation.³⁶ Diploid tumors were associated with a low metastatic potential (7.7%) and a better five-year survival (54%), in contrast to aneuploid cases that had a higher metastatic potential (45.5%) and a low five-year survival (21%). The expression of ABO(H) cell surface antigens is heterogenous due to the absence of noninvasive squamous cell cancers and did not correlate with the pathologic parameters or the clinical course of the disease.

Radical cystectomy with urinary diversion evolved to be the treatment of choice in selected patients with squamous cell carcinoma, but the five-year survival rates are still unsatisfactory, ranging from 27% to 33%.^{7,37} Regular follow-up was possible in 13 patients after definitive surgical treatment. Six patients were well and cancer-free, seven cases died from cancer, and seven were lost to follow-up. The crude five-year survival in this group of patients treated surgically was 46%. Failures are presumed due to occult local spread since, following contemporary surgery, the pelvis is the first site of recurrence in 50% of patients with relapse.⁷ The development of more effective modalities to reduce deaths from localized disease, such as preoperative radiotherapy and adjuvant chemotherapy, may improve the results in transitional cell carcinoma but not in squamous tumors.^{6,38-41} When considering the progress with orthotopic bladder replacement, like the urethral Kock pouch adopted in five patients in this work, the acceptance of patients for surgical treatment had improved. The current treatment modalities do not alter the dismal prognosis of those unfortunate patients diagnosed with far-advanced disease. Thus, there is a need for identification and characterization of newer therapeutic approaches that improve the patient survival and enhance the quality of life.

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