Transitional cell carcinoma of the urinary bladder: a clinicopathological study

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ABSTRACT

Introduction: The aim of the paper was to highlight the clinicopathological features of urinary bladder cancer in Jordan as a model for the Middle East. Only scattered reports from this region are currently available.

Methods: A total of 115 patients with bladder cancer were managed at our hospital, between the years 1994 and 2000. Transitional cell carcinoma (TCC) comprised 110 patients. The medical records of these patients were reviewed and included in the present study.

Results: There were 99 male and 11 female patients. The mean age of the patients was 60.6 (range 19–91) years. 66 of the cases had low-grade and 44 had high-grade tumours. Pathological staging showed that 60 (54.5 percent) of the cases were stage PTa, 19 (17.3 percent) PT1, 22 (20 percent) PT2, eight (7.3 percent) PT3 and one (0.9 percent) PT4. Transurethral resection, segmental resection, radical cystectomy, and partial cystectomy with intestinocystoplasty, was performed in 81, 12, eight, and four patients, respectively. Palliative urinary diversion and radiotherapy were done in two patients. Three patients were unsuitable for surgery. Recurrence was found in 22 patients (31.4 percent). Of the 105 patients who received definitive surgical treatment, 97 patients were followed-up for a mean period of 23.1 months. By the end of the study, five patients died from cancer.

Conclusion: The age of presentation of TCC in Jordan is similar to that in the west, but a higher male-to-female ratio was observed. The stage at presentation is also very close to that in the west but inadequate follow-up may be the cause of a lower rate of recurrence observed in this study.

Keywords: bladder cancer, transitional cell carcinoma, urinary bladder

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INTRODUCTION

During 2007, approximately 67,160 new cases of bladder cancer (BC) will be diagnosed in the USA, making this disease the fourth and 12th most commonly-diagnosed malignancy in men and women, respectively.[1] The overall age-standardised annual incidence rates of BC are 25.7 and 6.2 per 100,000 population in males and females, respectively.[2] Its incidence has increased by 36% between 1984 and 1993.[3]

Primary transitional cell carcinoma (TCC) of the bladder is a relatively common tumour, comprising about 90% of all BC in the Western countries.[3] It is the second most common malignancy seen by the urologist.[3] Population at risk includes cigarette smokers, chemical industry and machine trade workers, painters, those with processing occupations, and patients on prolonged courses of cyclophosphamide or who received radiotherapy for uterine cancer.[2-6] Most TCC at initial diagnosis are papillary and superficial, and as many as 70% are characterised by a prolonged clinical course over which the patient experiences multiple recurrence after local resection without tumour progression.[7] In contrast, a smaller but significant percentage of patients have advanced and muscle-infiltrative tumour at the time of diagnosis.[8] There is no available data from Jordan on TCC. This study aimed to report the epidemiological, clinical, and pathological features of TCC in Jordan, with comparison to other countries whenever possible. This could assist in the better understanding of the important risk factors which contribute to the development of BC, and may help in drawing recommendations for screening and prevention.

METHODS

This is a retrospective study in which all cases of TCC diagnosed between the years 1994 and 2000 were included. During the study period, a total of 115 patients with primary BC were managed at our hospital (Table I). TCC comprised 110 (95.7%) patients. The medical records of these patients were reviewed and included in the present study. All patients were initially evaluated by

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Table I. Frequency of various histological cell types in 115 patients with primary bladder carcinoma.

Histological cell type	No. of cases
Transitional cell carcinoma	110
Squamous cell carcinoma	2
Undifferentiated carcinoma	0
Adenocarcinoma	3

Table II. Clinicopathological features in 110 patients with primary transitional cell carcinoma of the urinary bladder.

Features	No. (%) of patients
Gender	
Male	99
Female	11
Male-to-female ratio	9:1
Mean ± SD (range) age at diagnosis (years)	60.6 ± 13.7 (19–91)
Histological grade (WHO)	
Low	66 (60)
High	44 (40)
Clinical stage	
PTa	60 (54.5)
PT1	19 (17.3)
PT2	22 (20)
PT3	8 (7.3)
PT4	1 (0.9)

Table III. Grade distribution of cases by stage.

Grade	Stage				
	PTa	PT1	PT2	PT3	PT4
Low	51	11	3	1	-
High	9	8	19	7	1
Total	60	19	22	8	1

Table IV. Age group distribution by stage.

Age group (years)	Stage					Total
	PTa	PT1	PT2	PT3	PT4	
15–29	2	–	1	–	–	3
30–49	11	1	1	–	–	13
50–69	37	7	11	6	1	62
70–90	10	11	9	2	–	32
Total	60	19	22	8	1	110

history-taking, clinical examination, standard laboratory investigations, chest radiographs, excretory urography and/or abdominal ultrasonography. The tumours were assessed by bimanual examination under anaesthesia, cystoscopy and biopsy. Abdominal and pelvic computed tomography and radioisotope bone scan were performed for patients with evidence of advanced disease.

All cases of TCC were reviewed, and the tumours were reclassified and categorised by reviewing all the histology slides by two pathologists. The tumours were graded histologically, and staged pathologically according to World Health Organisation (WHO)/International Society of Urological Pathology consensus classification of urothelial (transitional cell) neoplasms of the urinary bladder,[9] into low- and high-grade tumours. Pathological staging was also done according to the TNM system,[10] with the following stages: pTa: limited to mucosa; pT1: invasion of the lamina propria; pT2: invasion of the superficial muscle; pT3a: invasion of the deep muscle; pT3b: invasion of the perivesical fat; and pT4: invasion of organs in the vicinity.

RESULTS

110 patients with histologically-confirmed TCC of the urinary bladder were seen during the study period. There were 99 males and 11 females, with a male-to-female ratio of 10:1. The mean age of the patients was 60.6 ± 13.7 (range 19–91) years. Gross haematuria was the main symptom in 76 patients (69%), while irritative voiding symptoms were the presenting features in the remaining 34 patients (31%). The duration of symptoms varied between three weeks and 11 months. The size, location and mobility of the tumour were assessed bimanually. Bimanual examination under anaesthesia showed a palpable bladder mass in four cases, of which one was fixed. The remaining 104 tumours were difficult to palpate. A summary of the clinicopathological features for the 110 patients is presented in Table II. 66 of the cases (60%) were low-grade and 44 (40%) were high-grade tumours. Pathological staging showed that 60 (54.5%) of the cases were stage PTa, 19 (17.3%) PT1, 22 (20%) PT2, eight (7.3%) PT3 and one (0.9%) PT4. Table III shows grade distribution of cases according to the pathological stage. Most of the low-grade tumours (77.3%) were PTa, while most of the high-grade tumours (61.4%) were ≥ PT2. Table IV shows the age distribution by stage. Evidence of distant metastases was noted in only two cases (lungs in one case and liver in the other case).

Transurethral resection was performed in 81 patients, and segmental resection was performed in 12 patients. Partial cystectomy and intestinocystoplasty were done in four cases (ileocystoplasty in three and colocystoplasty in one patient). Seven patients underwent one-stage radical cystectomy with pelvic node dissection and urinary diversion, and one patient required additional urethrectomy. The urinary diversion in these patients included ileal loop conduit in four patients, urethral Kock pouch in three and ureterosigmoidostomy in one patient. Palliative urinary diversion (ureterocutaneostomy) and radiotherapy were done in two patients. The remaining three patients were considered unsuitable candidates for surgery in view of poor general health, unresectable locally advanced or metastasising tumours. No intravesical chemo- or immunotherapy or systemic chemotherapy was given before or after the operation. Recurrence was found in 22 male patients (31.4%); ten cases from the low grade group (26%) (eight cases PTa and two cases PT1), and 12

cases from the high grade group (37.5%) (two PT1, six PT3 and two PT4).

Of these 105 patients who received definitive surgical treatment, 97 patients were followed-up for a mean period of 23.1 months. The remaining eight patients were lost to follow-up after a mean of 8.3 months. By the end of the study, five patients died from cancer.

DISCUSSION

Urinary BC represents 5% of all malignancies diagnosed in Jordan during 1998.[11] It ranked third in cancer types for males. However, there are no clinicopathological studies regarding TCC from Jordan. The crude relative frequency of BC among other male cancers in the neighbouring Saudi Arabia has been reported to vary from 3% to 10.7% depending on the region.[12] This study presents several characteristics of this tumour as seen at a major University Hospital in northern Jordan. In the present study, TCC was the most common bladder tumour (95.7%), while squamous cell carcinoma constitutes 1.8% of BC seen over a seven-year period. These figures are similar to the published results from Western countries,[3] but rather different from the neighbouring Saudi Arabia.[12] This is mainly due to the fact that schistosomiasis is not endemic in Jordan. In countries where schistosomiasis is endemic, the incidence of squamous cell carcinoma is much higher, ranging from 39% to 75%.[13-15]

In this study, the mean age of TCC was 60.6 years, which is similar to that of all cases diagnosed in Jordan in 1998 and very close to that described in the US.[16] However, the male-to-female ratio in our study was nine to one, which is much higher than that described in the USA, where it ranges from 3:1 to 4:1.[3] Since cigarette smoking is one of the main aetiological factors related to the development of TCC,[16] this high male:female ratio may be related to a lower number of Jordanian women who smoke and to the very low percentage of women who work in Jordan. Haematuria was the presenting symptom in 69% of cases. Because of the non-specific nature of the most common symptoms of BC, which are the painless intermittent haematuria and irritative voiding, late presentation seen in our patients may be due to misdiagnosis.[17,18]

Tumour staging and grading currently are the two major factors for recurrence and progression, and for determination of treatment options for patients with BC.[19] Many investigators found statistically-significant survival differences between patients with noninvasive tumours (PTa), invasive tumours confined to the lamina propria (PT1) and tumours with muscle invasion.[20,21] Analysis of stage of presentation in our study revealed that early stage (PTa, PT1) tumours comprised 71.8% of the cases, which is slightly lower than the rate of 75% reported elsewhere,[22] where approximately 75% of patients had superficial (Ta, T1), 20% had invasive (> T1), and 5% had metastasised tumour at the time of diagnosis.[22] This may indicate that TCC in Jordan may present at a later stage. However, this may be statistically insignificant due to the small number of cases included in this study. We found that there was a strong statistical association between the stage and grade of TCC, which is similar to what was reported elsewhere.[23]

In addition to the haemoglobin dipstick test, conventional cytology and flow cytometry, several noninvasive markers, including bladder tumour specific antigen (BTA-Stat/TRAK), hyaluronic acid-hyaluronidase (HA-HAase), nuclear matrix protein (NMP)-22 assay, BLCA-4, ImmunoCyt, telomerase activity (using the telomeric repeat amplification protocol assay, TRAP), Quanticyt nuclear karyometry, cytokeratin 20, fibrin degradation products, urinary BC antigen, and survivin, have shown potential for managing BC patients in addition to their ability to replace voided urine cytology for detecting BC.[24-34] Despite that urine cytology is a specific (specificity > 90% for TCC), noninvasive technique, which can be useful in the screening of high-risk groups for BC, the methodology is limited by low sensitivity for the low-grade lesions (20%–40%), subjective interpretation, and expenses.[35] It produces false-positive and false-negative results in 1%–12% and 20% of the cases, respectively.[35] Regular follow-up was possible in 97 patients after definitive surgical treatment; 92 patients were well and cancer-free, five cases died from cancer, and eight were lost to follow-up. Failures are presumed due to occult local spread.

Partial cystectomy has been tried at many centres in an attempt to reduce the functional complications, but local recurrence is high. Radical cystectomy with urinary diversion is the treatment of choice for advanced TCC and recurrent refractory cases of superficial high-grade TCC.[36] Radical cystectomy is highly morbid, as it results in many changes in the quality of life, including sexual and social functions. Vallancien et al used a modified technique of radical cystectomy with prostate and seminal vesicle sparing in selected patients with BC. This modified technique offers good functional results with regard to continence and potency with cancer control comparable to the standard procedure.[37] The development of more effective modalities to reduce deaths from localised disease, such as preoperative radiotherapy and adjuvant chemotherapy, may improve the results in TCC, but not in squamous tumours.[38-40] When considering the

progress with orthotopic bladder replacement, like the urethral Kock pouch adopted in three patients in this series, 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 characterisation of newer therapeutic approaches that improve the patient survival and enhance the quality of life.

Multiple sequential recurrences are one of the characteristics of BC.[41] An important feature of TCC is its propensity for multiple recurrences.[8,42] The recurrence rate in our study was related to the stage, as the rates of recurrence were 43.5% and 62.5% in stages PTa and PT1 tumours, respectively. The corresponding rates are 52% and 77% in the USA.[43] Recurrence was also related to the grade. The recurrence rates for low- and high-grade tumours in this study were 26.3% and 37.5%, respectively. These were also lower than the corresponding rates in the literature (65% and 71%, respectively).[44] The lower rates of recurrence observed in our study are most probably related to the short study period and the retrospective nature of data collection. Other possible causes for this are referral of patients to other hospitals and the lack of adequate follow-up. Between 30% and 80% of BC patients will develop recurrence within three years following treatment of the initial tumour.

The higher progression rate of PTa tumours showed in this study may be due to initial understaging since lamina propria invasion could be missed on pathological examination, and thus leading to under-diagnosis of PT1 tumours as PTa tumours. The recurrence rate of superficial tumour is more than 60%, and tumour progression develops in 42% of patients by ten years. The stage, grade, multiplicity and size of the tumour at initial evaluation were significant factors affecting survival.[45] Progression according to stages Ta and T1, and grades I, II and III, was 4%, 30%, 2%, 11% and 45%, respectively.[46,47] In conclusion, the age of presentation of TCC in Jordan was similar to the USA, but a higher male-to-female ratio was observed. The stage at presentation was very close to that of the USA, but inadequate follow-up may be the cause of a lower rate of recurrence observed in this study. Prospective studies of TCC are needed for a better understanding of the clinicopathological features of TCC in Jordan.

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