Original Article

Clinicopathological spectrum and the outcome of treatment of upper tract transitional cell carcinoma

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ABSTRACT

Introduction: Disease spectrum of upper tract transitional cell carcinoma (TCC) in Indian patients is not known. Herein, we present data on clinical presentation, pathological characteristics, and the outcome of treatment of upper tract TCC.
Materials and Methods: Clinicopathological data of patients who were diagnosed for upper tract TCC between January 2000 and January 2010 were collected from the hospital information system and case records. Preoperative diagnosis was based on contrast-enhanced computerized tomography of the whole abdomen and urine cytology. Cross tab and logistic regression analysis was done on the effect of various clinicopathological characteristics on the outcome and cancer-specific and recurrence survival were derived.
Results: There were total 40 patients, 35 (87.5%) of them were male. The mean age was 62.7 ± 7.9 years. The most common symptom was gross hematuria present in 30 (75%). Mean tumor size was 2.8 ± 1.2 cm. Median duration of follow up was 36 (12 to 100) months. Laparoscopic nephroureterectomy was done in 27 patients along with bladder cuff excision and seven patients underwent open surgery. Thirty two (88.8%) patients had invasive T stage and high-grade lesions were seen in 24 (66.6%). Lymphovascular invasion was found only in one case and necrosis in 30 (83.3%). Necrosis was found to be the poor prognostic factor. Five-year recurrence-free and cancer-specific survivals were 36.33% and 26%, respectively.
Conclusion: Patients with upper tract TCC present very late with a high-stage disease and a very low 5-year cancer-specific and recurrence-free survivals.

Key words: Clinicopathological spectrum, upper tract transitional cell carcinoma

INTRODUCTION

Upper tract transitional cell carcinoma (TCC), i.e., TCC of the renal pelvis and ureter accounts for only 5% of all urothelial tumors[1,2] and 10% of all renal tumor cases.[3,4] Stage of the tumor is the single most important prognosticator for the outcome of this disease. In west, spectrum of the diseases skewed to lower stage, so that the most of the cases are detected at an early stage which is often amenable to endoscopic treatment. There is paucity of data on Indian patients regarding the clinical presentation and various pathological characteristics. Herein, we present our data and the outcome of treatment of upper tract TCC.

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MATERIALS AND METHODS

Data of 40 consecutive patients who were diagnosed for upper tract TCC between January 2000 and January 2010 were collected from medical case records, pathology data base, and hospital information system.

The age, sex, symptoms, pTNM staging, tumor size, location of the tumor with respect to the pelvis and ureter, necrosis, lymphovascular invasion, duration of follow up, details of the bladder, local and systemic recurrences were analyzed. Preoperative diagnosis was based on contrast-enhanced computerized tomography (CECT) of the whole abdomen and urine cytology (3 samples). Retrograde pyelogram was done in three patients but none of the patients had ureteroscopy with biopsy.

Of 40 patients, 34 had nephroureterectomy with bladder cuff excision and two patients imperatively had lower ureteric excision along with bladder cuff as they were having diabetic nephropathy. Four patients had systemic metastasis at the time of presentation, who were managed with either neoadjuvant chemo (2) or symptomatic treatment due to presence of widespread metastasis and poor performance status of the patients (2). Those patients who received four cycles of neoadjuvant chemotherapy showed progression of the disease and were eventually treated symptomatically.

Cystoscopy was done on every patient as part of protocol to see for concomitant bladder tumor. Then, laparoscopic nephroureterectomy along with bladder cuff excision was done in 27 cases through four ports in diamond configuration [Figure 1]. After mobilizing the colon and clipping and cutting hilar vessels, kidney was dissected outside the Gerota's fascia to the lower ureter. Then, modified Gibson incision was given and the specimen removed along with 2 cm bladder cuff [Figure 2]. Open surgery was done through two separate, i.e., sub-costal and Gibson incision.

Lymph node dissection was started since August 2007 and before that, no routine lymphadenectomy was being done. The limit of lymph node dissection was up to the common iliac group for upper ureteric and pelvic TCC and up to the external iliac group for lower ureteric TCC. Most of our patients did not have adjuvant chemotherapy.

SPSS17.0 software was used for statistical analysis. Cross tab and logistic regression analysis was done on the effect of various clinicopathological characteristics on the outcome which was defined as patients developing recurrence or dying due to upper tract TCC. Kaplan Meir survival analysis was done to derive cancer-specific survival and recurrence-free survival. *P* value of less than 0.05 was considered significant. Outcome analysis was done in 32 patients in whom complete follow up was present.

RESULTS

The mean age ± SD at presentation was 62.7 ± 7.9 years. Of 40 patients, 35 (87.5%) were male. Majority of them (27, 67.5%) presented on left side. The most common symptom was gross hematuria in 30 (75%). Yield of urine cytology was very low, 4/40 patients (10%).Mean tumor size was 2.8 ± 1.2 cm. Mean duration (range) of follow up was 36.6 (12 to 100) months. Eight patients were lost to follow up. Table 1 lists the demographic characteristics of the whole group of patients.

None of the patients had tumor in the bladder or contralateral kidney at the time of presentation.

Pathological characteristics of 36 patients who had undergone surgery are described in Table 2. Recurrence occurred in 16 patients (44.4%) [Table 3]. The most common site for recurrence was in the bladder. Of eight bladder recurrences, six were found on routine check cystoscopy without any symptoms. Majority of them had Ta low-grade tumors and two had high-grade lamina invasive TCC. One of the two patients died as he had associated metastasis and the other one had orthotopic neobladder and is doing well. Two patients developed local recurrence after a mean duration of 75 months. One patient was treated with cisplatinum and gemcitabine chemotherapy (six cycles) with complete response [Figure 3] and the other patient died.

Of 16 patients who had recurrences, 11 died due to TCC and five are surviving following the bladder recurrence. The 5-year cancer-specific survival was 26 ± 5.1% (20.5-39.3%) [Figure 4] and recurrence-free survival was 36.33% [Figure 5].

On logistic regression analysis of the demographic and pathological characteristics on outcome, only necrosis (*P* value 0.032 and odds ratio 6.600) had statistically significant impact on outcome. T stage, grade of the lesion and lymph node dissection did not have significant impact on outcome as most of our patient presented very late with higher stages and grades.

DISCUSSION

In the recent literature, due to improved imaging and rigorous search for the cause for microscopic hematuria, majority of upper tract TCC have been described to present as low T stage.[5,7,9] The incidence of Ta to T1 tumors vary from 44 to 60% in these studies. There are no data available on Indian patients on upper tract TCC. As microscopic hematurias is neither looked for and nor evaluated extensively, it is not surprising that our patients present very late in the course of the disease.

As the stage is considered the most important prognostic factor, early detection would improve the survival in this disease.[8,9] Most of our patients were detected with symptoms and only four patients (11.1%) presented in Ta to T1 stage. Similarly, though the grade of the disease has bearing on the survival, there are studies for[8,9] and against[6,7] grade as poor prognostic marker for recurrence. Majority of our patients had high-grade tumor at presentation.

Upper tract TCC is a malignancy of the seventh decade with male to female ratio of 3 : 1.[5-7] In our study, the mean age at the time of presentation was 62.7 years and majority of our patients were males with the male to female ratio of 7 : 1. Male preponderance was also seen in bladder cancer in our previously published data.[10] Whether this could be explained by the smoking habit in males or environmental factors requires a collaborative study from multiple centers in India.

Table 1: Demographic characteristics

Total no of patients	40
Male: Female	7: 1
Side: Left: right	27: 13
Mean age (year) + SD	62.7+ 7.9
Mean follow up in months (range)	36.6 (12 to 100)
Mean tumor size +SD	2.8+ 1.2
Symptoms	
Hematuria	30
Flank pain	8
Loss of weight	3
Incidental	1
Tumor location	
Pelvis	29
Pelvis and upper ureter	7
Lower ureter	4

Table 2: Pathological characteristics

T stage	Number of the patients
Metastatic	04
Non metastatic	36
Ta	01
T1	03
T2	09
T3	18
T4	05
Concomitant CIS	02
LN dissection	Done in 14: not done in 22
LN positivity	5 out of 14
Yield of LN dissection	01
Grade	
Low	12
High	24

Table 3: Recurrence after surgery

Recurrence Site and incidence	Median time to recurrence in months	Clinicopathological characteristics of the recurrence group	No. of patients
Bladder 8 (22.2%)	14.4	Mean tumor size was 2.6 cm	3
Local 2(5.5%)	75		
Liver 2 (5.5%)	13		
Lung 4 (11.1%)	12	Pelvic + upper ureteric growth	13
		Pelvic growth	
		Low t stage	5
		High t stage	11
		Low grade	4
		High grade	12

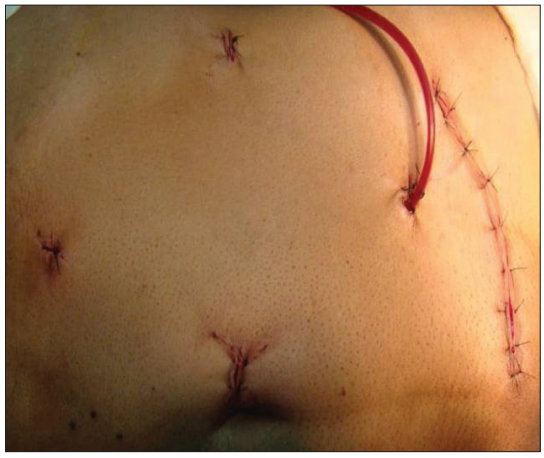

Figure 1: Port sites and Gibson incision

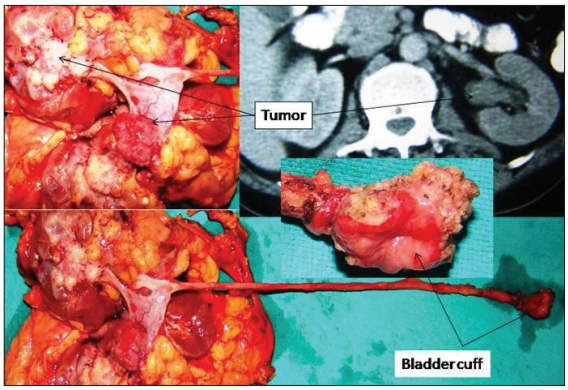

Figure 2: Hypovascular tumor in left pelvicalyceal system with nephroureterectomy specimen

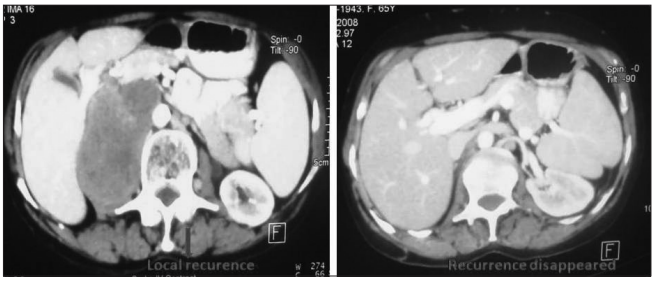

Figure 3: Local recurrence which responded to chemotherapy

The most common sites for the recurrence were bladder and lung. Bladder recurrence has been described in the range of 18 to 37%.[7,11] In one study of 60 patients of upper tract TCC, none of the clinical or pathological parameters were having statistically significant impact on intravesical recurrence.[12] In our study, all patients with bladder recurrence presented within 18 months and most of them had low stage and low grade. This is in contradiction to the concept of field change described with TCC as despite having high stage and grade of TCC in the upper tract, none had concomitant bladder tumor at the time of presentation. Secondly, most of them had recurrence of low grade and stage.

Bladder recurrence did not present with any symptoms, which underscores the importance of regular check cystoscopy. This pattern and incidence of bladder recurrence (22%) is similar to the pattern described in the western studies. Another important observation from this study was that all of the recurrences after initial surgical treatment, bladder recurrence was the least likely to cause death.

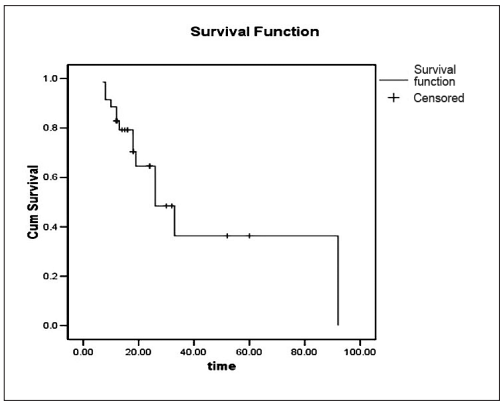

Figure 4: Cancer specific Kaplan Meir survival plot of the total patients

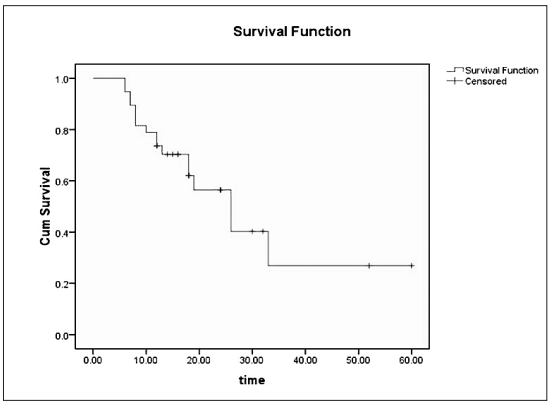

Figure 5: Recurrence free Kaplan Meir survival plot of the total patients

The need and the extent of lymph node dissection has been standardized recently.[13-15] In one of the largest experiences on 830 patients, the lymph nodes identified in the biopsy specimen was only 13.2% and the median yield was only 1.[6] Lymph node dissection was started since 2007 and it was done in 38.8% of cases. The Laparoscopic nephrectomy positivity rate of 35.7% in our study is much higher than the reported incidence of 4 to 9.9% in the literature.[7,8] This could be explained by the late presentation in the course of the disease. Due to the small sample size, impact of lymph node dissection on the survival could not be derived.

Five-year recurrence-free and cancer-specific survivals in our study were 36.33% and 26 ± 5.1% (20.5-39.3%), respectively, which is much lower than the reported survival in western literature in current series. In the study by Margulis *et al*.,[8] data on 1 363 patients treated with radical nephroureterectomy at 12 academic centers were collected and the 5-year Recurrence free survival and cancer specific survival was ~69% and 73%, respectively. In another series on 100 patients, 5-year CSS was 72%.[7] The poor result in Indian patients may be due to late presentation as most of our patients had higher stage of the disease, which is the single most important predictor for the survival.

Though the cytology and ureteroscopy form the integral part of initial investigations, all our patients were diagnosed on CECT. Surprisingly, the yield of cytology despite having a high stage and grade was very low (10%). Possible explanation could be that most of our patients presented with gross hematuria indicating necrosis and slough at the higher stage of the disease and patients had dead cells in urine instead of living cancer cells. Ureteroscopy would help in very early stage of the disease in patients who get evaluated for microscopic hematuria; therefore, it did not form the mainstay of diagnosis as most of our patients were diagnosed on CECT.

Lymphovascular invasion and necrosis are other poor prognosticators and are associated with higher T stage and grade of the disease.[16-19] Though lymphovascular invasion was reported in only one case, it possibly explains the reporting bias (under-reporting) in our series but necrosis was almost a universal finding, which was found in 30 (83.3%).

This study has limitation of sample size. Since Indian patients are presenting late and having high stage at the time of presentation, importance of proper evaluation of patients presenting with microscopic hematuria should be stressed which will help in detecting upper tract TCC at an early stage.

CONCLUSION

Indian patients with upper tract TCC present late and are having high stage at the time of diagnosis. Five-year cancer-specific and recurrence-free survival is very low in comparison with the western literature. Recurrence in the bladder than other sites portents a good prognosis. Importance of proper evaluation of patients presenting with microscopic hematuria should be stressed, which will help in detecting upper tract TCC at an early stage, and also in paving the way for preserving nephron by adopting to less-invasive approaches.

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