

Original Research Article

Clinico-pathological profile of patients with upper tract TCC: a single centre experience

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Received: 02 June 2018

Accepted: 27 June 2018

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ABSTRACT

Background: Urothelial carcinomas are rare tumors and this rarity have made these tumors greatly significant. Urothelial Carcinoma of Upper Urinary Tract (UC-UUT) are still rarer and occur in elderly population. Much of the literature concerning urothelial neoplasms has focused on the urinary bladder, which is understandable given that the majority of these tumors occur in the bladder. Most common UC-UUT are the renal pelvic tumors followed by distal ureteric tumors. There is paucity of literature of UC-UUT in the Indian context hence this study assumes importance.

Methods: 16 cases of UC-UUT were included in the study. A complete preoperative evaluation was done. Radical Nephroureterectomy (RNU) with bladder cuff excision was undertaken and histopathology of resected specimen was noted. Adjuvant therapy was given wherever necessary. A systematic follow-up was done, and recurrences were noted and treated. Data was then analyzed.

Results: Male to female ratio was 3:1. Most patients presented with hematuria. Most lesions were left sided. Renal pelvis was the most affected site. 73% tumors were of high grade and 47% were in pT3 stage. There was a single case of systemic metastasis in present study. 15 out of 16 cases underwent radical nephroureterectomy with bladder cuff excision. In follow up, recurrence free survival was 66.67% and cancer free survival was 86.6% after surgery.

Conclusions: Upper urinary tract urothelial tumor is a rare disease In Indian context, majority of patients presented late and were having high stage and grade at the time of diagnosis. Invasive disease was more common. Radical nephroureterectomy is still the gold standard treatment. Conservative treatment should be considered in specific cases. Recurrences in bladder are common and should be treated early.

Keywords: Distal ureteric tumors, Renal pelvic tumors, Radical nephroureterectomy, Urothelial carcinoma of upper urinary tract

INTRODUCTION

Urothelial carcinomas are the fourth most common tumors after prostate cancer, lung cancer and colorectal cancer.¹ However urothelial carcinomas of upper urinary tract (UC-UUT) involving renal pelvis or ureter are relatively uncommon, with most urothelial tumors occurring in urinary bladder. UC-UUT are less than 1% of all genito-urinary neoplasms and 5-7% of all urothelial

tumors.² The estimated annual incidence of Urothelial Carcinoma of Upper Urinary Tract (UC-UUT) in Western countries is about one or two new cases per 100,000 inhabitants. Highest incidence appears to occur in Balkan countries where urothelial cancers represent 40% of all cases.³ UC-UUTs have a peak incidence in people in their 70s and 80s. Male to female ratio is approximately 3:1. Whites are about twice as likely as African-Americans to develop upper tract tumors. There

are familial/hereditary cases of UC-UUTs linked to hereditary nonpolyposis colorectal carcinoma (HNPCC).⁴ Pelvic tumors are about twice as common as ureteral tumors.

Distal ureteral tumors are more common than upper and mid ureteric tumors. In 8-13% of cases, concurrent bladder cancer is present. Recurrence of disease in the bladder occurs in 20-70% of UC-UUT patients, whereas recurrences in the contralateral upper tract are observed in 2-6%.^{5,6}

The natural history of UC-UUTs differs from that of bladder cancer: 60% of UC-UUTs are invasive at diagnosis compared with only 15% of bladder tumors.⁷ No definitive predilection for involvement of the right or left side has been found, and fewer than 3% are synchronous and bilateral.⁸

Much of the literature concerning urothelial neoplasms has focused on the urinary bladder, which is understandable given that the majority of these tumors occur in the bladder. Most of what is known about bladder carcinoma, including pathogenesis, classification, prognostic indicators have been applied to urothelial tumors of upper tract. However, there are distinctions between urothelial tumors of bladder and upper tract.

A review of urothelial neoplasms of the kidney and ureter has not appeared in the pathology literature for some time. In 1993, Melamed and Reuter wrote a comprehensive review on upper tract tumors, which focused primarily on tumor pathology.⁹ Similarly, thorough chapters on the topic have been written by Bonsib and Eble.¹⁰ Owing to its relative rarity, clinical decision making has historically been based on limited data. Because renal pelvic tumors are generally not reported separately, world-wide statistics vary substantially between nations and are not accurate.

There is paucity of data on Indian patients regarding urothelial carcinomas of upper tract. Herein, we present our data of urothelial carcinomas of upper tract presenting to our institute in terms of clinical presentation, various pathological characteristics and its management.

METHODS

Present study was a prospective study conducted in the Department of Urology after approval from Institutional Ethics Committee. Study period was from March 2013-March 2015.

Inclusion criteria

All new patients of primary urothelial carcinomas of upper tract (Transitional cell tumor) presenting in either early stage of disease, locally advanced or with distant metastasis.

Exclusion criteria

- Patients with squamous and adenocarcinoma of upper urinary tract.
- Patients with primary renal cell carcinoma.
- Patients with proven primary urinary bladder or urethral carcinoma.

Total 16 patients of urothelial tumors of upper tract were studied. All of them were evaluated as per study proforma and informed written consent was taken. Detailed history and examination findings were noted. Baseline blood and urine evaluation, ultrasound abdomen and pelvis and urine cytology were performed in all patients with preoperative imaging in form of contrast enhanced computed tomography(CT) scan of abdomen and pelvis. The patients were subjected to appropriate treatment taking into consideration the age, performance status, tumor size, location of the tumor, stage of tumor and available treatment modalities in our institute.

Out of total 16 patients, 15 patients underwent radical nephroureterectomy (RNU) with bladder cuff excision. One patient had systemic metastasis at the time of presentation and underwent palliative symptomatic treatment in view of poor performance status. Cystoscopy was done in all patients as part of protocol to see for concomitant bladder tumor.

In 13 patients nephroureterectomy was done by open surgical technique using flank incision and bladder cuff excision was done by transurethral resection of ureteral orifice using holmium: yttrium-aluminum-garnet (Ho:YAG) laser. In two patients laparoscopic nephroureterectomy along with bladder cuff excision was done. Lymph node dissection was carried out in cases where they were detected preoperatively on CT scan or were palpable during operation. The limit of lymph node dissection was up to common iliac group for pelvic and upper ureteric and up to external iliac group for lower ureteric tumors. None of our patients were subjected to adjuvant chemotherapy. Most of the patients were discharged on 5th postoperative day and catheter was removed on 10th postoperative day.

After histopathological report tumor stage was determined according to the recent version of the TNM classification. Tumor grading was done according to recent World Health Organization (WHO) classification system. All patients were kept under regular follow up during the course of present study to look for any progression of disease and to detect any local or systemic recurrences. Disease recurrence was defined as local recurrence in the tumor bed, regional lymph nodes, bladder or distant metastasis. Cystoscopy along with urine cytology were carried out 3 monthly for first year and 6 monthly for second year. Radiographic imaging for upper tract in form of CT scan was done once yearly in noninvasive tumors and 6 monthly in invasive tumors. Metastatic workup (X-ray chest, liver function, CT scan

of whole abdomen pelvis, bone scan) was performed in patients with systemic metastasis and those having high risk of progression. The age, sex, symptoms, TNM stage, tumor size, tumor location with respect to renal pelvis and ureter, tumor grade, duration of follow-up, details of bladder, local and systemic recurrences were analyzed.

Statistical analysis

Sample size Calculation

Sample size calculation is based on the results (effect sizes) from the previously published study.¹¹ The calculations are performed using PS software i.e. power and sample size calculation software. The program runs on the Microsoft Windows operating systems (Windows 95 and later). The calculation details are shown below. Thus, a sample size of 15 cases (minimum) satisfying the inclusion criteria would produce 80.0% statistical power (type II error = 0.20) and 5% type I error probability ($\alpha=0.05$) to be able to study the pre and post-operative clinicopathological features. Hence, we chose a sample size of 16.

Table 1: Sample size calculation.

Alpha Error	Sample Size (n) (Minimum)	Power
0.05 (5%)	11	75.0%
0.05 (5%)	15	80.0%
0.05 (5%)	21	85.0%
0.05 (5%)	29	90.0%

Statistical test

Values on qualitative characteristics will be shown as n (%) and the values on quantitative characteristics will be shown as mean, standard deviation, minimum and maximum as descriptive statistics. The two years cancer-specific survival and recurrence free survival is calculated using Kaplan-Meier survival analysis. The entire statistical analysis is performed using Microsoft Excel sheets and Statistical package for social sciences (SPSS; Chicago, USA) for MS Windows.

RESULTS

Present study included 16 patients of upper urinary tract tumors. The mean age was 67 years, the range was 58-80 years and the peak incidence was in 6th decade. The majority of patients were males (75%) with male to female ratio of 3/1. Smoking was common risk factor among males (75%) for developing upper tract carcinoma in present study population. The most common symptom was gross hematuria in 13 patients (81.25%) followed by flank pain in 2 patients (12.5%) and weight loss in 1 patient (6.25%). However, the yield of urine cytology was very low, 2/16 patients (12.5%).

None of the patients had tumor in bladder or contra lateral kidney at the time of presentation. Pathological

characteristics of all patients are described in the below representative Table 2.

Table 2: Tumor Pathology Profile.

Tumor characteristic		Number of patients
Tumor size (N=16)	1-1.9 cm	4 (25%)
	2-2.9 cm	9 (56%)
	>3 cm	3 (19%)
Tumor location (N=16)	Pelvis	9 (56%)
	Ureter	7 (44%)
Tumor side (N=16)	Right	7 (44%)
	Left	9 (56%)
Tumor necrosis (N=15)	Yes	12 (80%)
	No	3 (20%)
Lymphovascular invasion (LVI) (N=15)	Yes	4 (26.7%)
	No	11 (73.3%)
Tumor stage (%) (N=15)	T1	2 (13%)
	T2	5 (33%)
	T3	7 (47%)
	T4	1 (7%)
Tumor grade (N=15)	High	11 (73%)
	Low	4 (27%)
State of metastasis (N=16)	Non-metastatic	15 (93.75%)
	Metastatic	1 (6.25%)

Majority of them (56%) presented with tumors on left side of urinary system. The most common site was renal pelvis in 9 (56%) patients. The mean tumor size was 2.3 cm; the range was 1.4-3.1cms. In present study population, 15 patients who underwent radical nephroureterectomy (RNU), the tumor stage distribution was 13% T1, 33% T2, 47% T3 and 7% T4. Microscopically the tumors were classified into low grade and high grade. Majority of patients (73%) were of high grade variety. Tumor necrosis was seen in 80% and lymphovascular invasion was seen in 26.6% of the resected specimens.

Lymph node dissection was done in only 4 patients (26.6%) where they were grossly enlarged either on preoperative imaging or intraoperatively. Out of 4, only 2 patients (50%) showed lymph node metastasis. Disease recurred in 5 patients (33.33%) with mean of 9.2 months after radical nephroureterectomy. All recurrences were associated with high tumor stage and tumor grade.

The most common site of recurrence was in bladder which was seen in 3 patients (20%). All the three bladder recurrences were found on routine follow up check cystoscopy without any symptoms. Two patients had single tumor while one had multiple tumors. All of them underwent transurethral bladder tumor resection and were found to have Ta low grade tumors on histopathology for which 6 cycles of 120mg intravesical BCG was given and are doing well. One patient developed local recurrence after 7 months of surgery.

He was treated with 4 cycles of gemcitabine and cisplatin but he died. One patient who developed systemic recurrence in lungs was subjected to gemcitabine chemotherapy but did not tolerate. He was subsequently given palliative treatment and he died. The correlation of recurrence with tumor stage and grade have been summarized in the below table (Table 3).

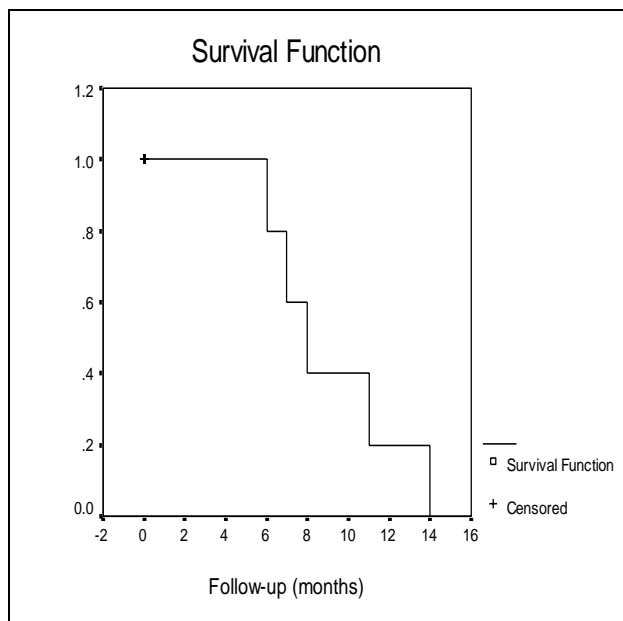
Table 3: Correlation of recurrence with tumor stage and tumor grade.

Recurrence	Tumor stage	Tumor grade
Bladder	T2	High
Bladder	T3	High
Bladder	T2	High
Local	T4	High
Lung	T3	High

In present study population of 16 patients, only 1 patient had systemic metastasis in lungs at the time of presentation. He was treated symptomatically because of advanced age and poor performance status. This patient eventually died during follow up.

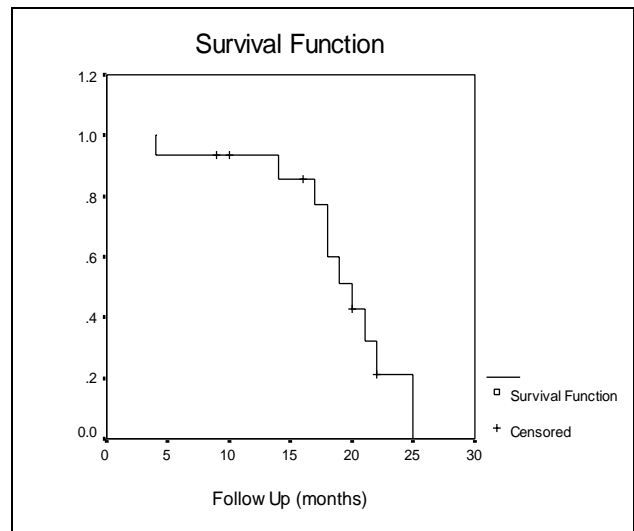
The clinical condition at final follow up of 15 patients who underwent radical nephroureterectomy was that 10(66.67%) patients were free from disease, 5 patients (33.33%) had recurrences out of which 2 died due to urothelial tumors and 3 are surviving following bladder recurrences.

During mean follow up of 16.3 months, recurrence free survival was 66.67% and cancer free survival was 86.6% after RNU (Figure 1, 2).



Mean (95% CI) of Recurrence time= 9.20 (6.33-12.07). Recurrence free survival= 66.67%

Figure 1: Recurrence free Kaplan Meir survival plot of the total patients.



Mean (95% CI) of Survival Time = 19.0 (16.0-22.0). 2 Years cancer specific survival after Radical nephroureterectomy= 86.6%

Figure 2: Cancer specific Kaplan Meir survival plot of the total patients after surgery.

DISCUSSION

Although relatively uncommon, the incidence of upper tract urothelial tumors has increased in past few decades. Considering the multifocality of these tumors and low yield of imaging techniques including endoscopy, the diagnosis and treatment has always been uncertain.

Invasive and metastatic disease is more common than in urothelial tumors of bladder. Radical nephroureterectomy (RNU) with bladder cuff excision is the gold standard treatment for upper tract cancers. Conservative treatment in form of kidney sparing surgery may be safe in some selected patients, however there exist risk of under staging, undertreatment and higher recurrence rates. To date, several contemporary, single centre series of patients treated with upper tract tumors have been published.^{12,13} While, these reports have contributed greatly to the current knowledge of the natural history and the prognostic factors important in upper tract tumors, conclusions have been limited by inhomogeneity of the study population, as related to diagnosis, patient selection, staging, pathological evaluation and treatment.

Parameters for patients in this study matched with those in literature.

Patient demographics

Age

Urothelial carcinomas of upper urinary tract are generally a disease of elderly people. These tumors peak in sixth and seventh decades of life, with mean age at initial diagnosis of about 65 years. In present study mean age was found to be 67 years.¹⁴

Sex

Most studies have found urothelial tumors of kidney and ureter to be more common in men than in women.¹⁴ In present study majority of patients were males (75%) with male to female ratio of 3:1.

Smoking

Cigarette smoking is considered one of the important risk factors for developing urothelial carcinomas of upper urinary tract just like bladder tumors. The risk correlates with number of cigarettes smoked, the duration of smoking and the degree of inhaled smoke. This risk has been observed in both sexes.

In present study, though 56% of patients were smokers, all of them were males which is in contrast to literature due to community barrier. Whether higher incidence of urothelial tumors of upper urinary tract in males could be explained by the smoking habits or environmental factors require a collaborative study from multiple centre's across India.

Clinical presentation

Patients with urothelial tumors of upper tract usually seek care because of gross hematuria (80%), flank pain (20%) and palpable mass (10%).¹⁵ Few patients may present with metastatic disease with systemic presentation.

In present study, 81.25% of patients presented with gross hematuria which correlates with the literature. One patient presented with metastasis at the time of presentation. There were no incidental cases in present study. In Western countries, due to availability of advanced technology and awareness, there has been increase in number of incidental cases.

Investigations

In present study all patients were investigated by urine cytology and CT scan. The yield of urine cytology was 12.5% despite having high tumor grade and stage. 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. Since majority of our patients presented with gross hematuria and were diagnosed with high tumor stage on preoperative CT scan, ureteroscopy was not done in our patients.

Treatment

Except for one patient presenting with metastatic disease at the time of presentation, 15 patients were treated with radical nephroureterectomy. Since majority of our patients presented with high tumor stage, radical surgery instead of conservative treatment was done. Conservative

surgery may be offered in low stage, low grade disease, solitary kidney and bilateral cases.¹⁶ However, use of such conservative treatment should be approached with caution by the patient and the surgeon, given the high recurrence rates and the necessity for vigilant and often invasive urinary tract surveillance.¹⁷

Tumor characteristics

Tumor stage

In upper tract disease, around 60 % of tumors are invasive at diagnosis compared with only 15% of bladder tumors.⁷ The thin muscle layer of renal pelvis and ureter may allow earlier penetration of upper tract tumors than seen in bladder cancers. All our patients were detected with symptoms. 13% of our patients had pT1 stage while 33% had pT2, 47% had pT3 stage and 7% had pT4 stage. A large institutional study by Margulis et al, demonstrated patients with 24% pTa, 24% pT1, 19% pT2, 30% pT3 stage and 3% pT4 stage.^{18,19} Thus, in present study patients presented with higher pathological tumors stage and majority of them had invasive disease at the time of presentation. Many patients of upper urinary tract tumors have been described to present with lower T stage in western literature.^{19,20} This could be explained by improved imaging and rigorous search for the cause for microscopic hematuria. There are hardly any data available on Indian patients on upper tract urothelial tumors. In one of the Indian studies by Radhakrishnan et al around 50% patients had T3 stage which correlates with present study.¹¹ As there is no extensive evaluation and investigation in Indian scenario, it is not surprising that our patients present very late in course of the disease. There exists a good correlation between tumor stage and patient outcome. As the stage is considered the most important prognostic factor, early detection would improve the survival in this disease.²⁰

Tumor grade

Tumor grade is another important factor which correlates with survival. However, there have been several studies for and against the grade as a prognostic marker.^{18,21} Tumors of high grade are more likely to invade into underlying connective tissue, muscle and the surrounding tissues. In this study majority of patients had high grade tumors (73%). In a large institutional study, 63.7% of patients were found to have high grade tumor.¹⁸

Lymphovascular invasion and tumor necrosis

The presence of lymphovascular invasion is an adverse predictor of survival and usually is associated with high stage and high-grade disease.²² As with bladder and other solid organ cancers, lymphovascular invasion is the presumed mechanism that leads to regional lymph node and to systemic hematogenous metastasis. Kikuchi et al reported a large international, 13 centre collaborative study of upper tract urothelial tumor patients who

underwent radical nephroureterectomy and found the prevalence of lymphovascular invasion was 24%. Lymphovascular invasion correlated with tumor stage, grade and tumor necrosis.²³ In study by Margulis et al it was seen in 25% of patients.¹⁸ In present study lymphovascular invasion was found in 26.6% of the resected specimens. Tumor necrosis is another prognostic factor and is associated with high tumor stage and grade.²⁴ In present study tumor necrosis was found in 80% of patients and most of them had high tumor stage and grade. A study by Radhakrishnan et al showed tumor necrosis in 83.3%.¹¹

Lymph nodes

Role of formal lymph node dissection in upper tract tumors on long term survival is somewhat conflicting. Although advocated by some, studies have shown that removing lymph nodes does not have any positive effect on survival. In recent analysis of large number of patients by Roscigno et al, only 25.4% positive nodes were noted.²⁵ Similarly, Margulis et al showed positive nodes in 23% of patients who underwent lymph node dissection thus reflecting lack of standardization, lack of templates and lack of knowledge of ‘landing sites’ for upper urothelial tumors. In present study lymph node positivity was 50%. This could be explained by selective indication for node dissection and late presentation in the course of the disease.¹⁸

Recurrence

Strict follow-up of UC-UUT patients after surgical treatment is mandatory to detect any bladder recurrence, contra lateral upper tract recurrence, local recurrence, and distant metastases. When RNU is performed, local recurrence is rare, and the risk of distant metastases is directly related to the adverse prognostic factors like tumor stage, grade, lymphovascular invasion and others. In present study there were 5 recurrences after radical nephroureterectomy (33.3%). A study by Cleveland clinic showed recurrences in range of 37%. All our recurrences had higher stage and grade at the time of presentation.²⁶ The incidence of bladder tumor after treatment of upper tract tumor is around 20-70 %.⁵ Bladder recurrence after upper tract tumors occurs earlier than the reverse, at a median of 21 months. This is example of multifocal nature of urothelial tumor. Out of 5, 3 recurrences were in the bladder (20%). All our patients of bladder recurrences presented within 14 months with mean duration of 11 months. All the bladder recurrences were of low grade and low stage. This pattern and incidence of bladder recurrence is similar to the pattern described in the western studies. An Indian study by Radhakrishnan et al had bladder recurrences in range of 20% which correlates with present study.¹¹ Bladder recurrences in present study did not present with any symptoms, which makes regular check cystoscopy very important. 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. Isolated local recurrence after RNU occurred in 6.6% of patients in present study which further supports role of radical surgery in upper tract urothelial tumors. In a very large study by Margulis et al, the recurrence free survival is reported around 69%. In present study recurrence free survival after radical nephroureterectomy was 66.67%.¹⁸

Cancer specific survival

Table 4: Cancer specific survival rates.

Authors and References	No. of patients	Follow up (months),	Cancer specific Survival (%),
Gill ²⁶	42	11	97
Manabe ²⁷	58	14	85
Shalhav ²⁸	17	43	77
Present Study	16	16.3	86.6

Cancer specific survival in upper tract tumors depends on tumors staging and are summarized in the below mentioned table (Table 3). In present study after RNU the cancer specific survival at 2 years was 86.6% which correlates with that in the literature.

CONCLUSION

Upper urinary tract urothelial tumor is a rare disease and hence it presents a different set of challenges for urologist. Indian literature on this disease is scarce. In present study conducted on Indian patients, majority of patients presented late and were having high stage and grade at the time of diagnosis. Invasive disease was more common in comparison with the western literature. Radical nephroureterectomy is still the gold standard treatment. Conservative treatment should be considered only in cases with renal insufficiency like bilateral tumors or tumor in a single functioning kidney. Recurrences in bladder are common and it is important to detect and treat them early.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Patel B, Batra R, Utaal MS, Batra P. Clinico-pathological profile of patients with upper tract TCC: a single centre experience. *Int Surg J* 2018;5:2869-75.