

Evaluation, management and outcome of upper urinary tract transitional cell carcinoma – A five year single center experience

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ABSTRACT

Aims and Objectives: To review a single centre experience in the evaluation, management and outcome of upper tract transitional cell carcinoma. **Materials and Methods:** We reviewed 18 cases over five years from January 2010 to October 2015 with a median follow up of 18 months. Patient characteristics including age, sex, symptoms and signs were reviewed. All patients were evaluated with ultrasound and contrast enhanced computerized tomography. Tumour details including location, laterality, grade and stage was noted based on pathological findings. **Results:** The mean age of the patients included was 57 years. Most common presentation was haematuria (72%). Most common location of the tumours was renal pelvis (50%), followed by ureter (39%) and tumours in both renal pelvis and ureter in 11%. Concomitant bladder involvement was seen in 17% of the patients. Nephroureterectomy with excision of bladder cuff was the most common surgery performed (78%). 11% of the patients underwent renal sparing surgery and two other patients underwent nephroureterocystoprostatectomy. Morbidity rate was 22% and recurrence was seen in 16% of the patients. **Conclusion:** Transitional cell carcinoma of the upper tract is a rare tumour which is known for its multicentricity and recurrence. Nephroureterectomy with excision of bladder cuff has been the gold standard for the management, although endosurgical and tumour sparing surgery in selected cases have proven to be equally efficacious. Tumour grade and surgical procedure performed are independent risk factors for recurrence.

Key words: Renal tumors, Ureteric tumors, Transitional cell carcinoma, Upper tract transitional cell carcinoma, Recurrence

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INTRODUCTION

Transitional cell carcinoma of the upper urinary tract is an uncommon disease encountered by the urologist, accounting for 5-10 % of renal tumors and only 5-6% of urothelial tumors. Tumors of the ureter are an even rarer entity accounting for only 25% of the urothelial tumors.¹ Upper tract transitional cell carcinoma is known for its multiplicity and recurrence. Nephroureterectomy with excision of ipsilateral bladder cuff has been considered to be the gold standard for the management of these tumors. However the advent of laparoscopy and advances in semirigid and flexible instrumentation has

opened the door for conservative approaches to manage this tumor. The overall survival rate at five years is around 65%.² We herein reviewed our five year experience in the evaluation management and outcome of 18 patients surgically managed for transitional cell carcinoma of the upper tract.

MATERIALS AND METHODS

We retrospectively reviewed patients who were surgically treated for upper tract transitional cell carcinoma at M S Ramaiah medical college from January 2010 to October

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2015. A total of 18 patients were traced using medical records. Clinical data was obtained reviewing patient files and operative logs. Patients were followed up with physical examination, cystoscopy and upper tract imaging every three months for the first year and once in six months for the next two years. The median follow up was 18 months ranging from one to 60 months.

Patient characteristics including age, sex, symptoms and signs were reviewed. All patients were evaluated with ultrasound and contrast enhanced computerized tomography. A select few cases were further evaluated with Magnetic resonance Imaging and ureterorenoscopy. Tumor details including location, laterality, grade and stage was noted based on pathological findings. Operative logs were reviewed and the type of surgery, duration, intraoperative blood loss and complications were appraised. Postoperative complications and recurrence of tumor were assessed.

RESULTS

Patient characteristics and tumor details are described in Table 1. A total of 18 patients diagnosed with upper tract transitional cell carcinoma were included in our study. The mean age of the patients included was 57 years ranging from 41-70 years. Male to female ratio was 2:1.

Majority of the patients presented with hematuria (72%). The other symptoms of presentation were flank pain (22%), dysuria (5%), and urinary tract infection (11%). One patient presented with a palpable mass per abdomen. Urinary cytology was positive for malignant cells in four patients (22%)

Ultrasound was the initial investigating modality used. Contrast enhanced computerized tomography was the main investigating modality used to assess tumor location, invasion, lymph nodes and metastasis (Figure 1). In doubtful cases, magnetic resonance urography (3 cases) (Figure 2a) or ureteroscopy (2 cases) with brush biopsy (Figure 2b) was used to confirm the diagnosis.

Most common location of the tumors was the renal pelvis accounting for nearly 50% of the tumors. Transitional cell carcinoma of the ureter was seen in 39%, one patient of which had tumor occupying the entire length of ureter (Figure 3). 11 % of the tumors were present in both renal pelvis and ureter. Concomitant bladder involvement was seen in three patients (Figure 4).

All patients were initially treated with surgery. Nephroureterectomy with removal of bladder cuff was the most common surgery performed accounting for nearly 78%

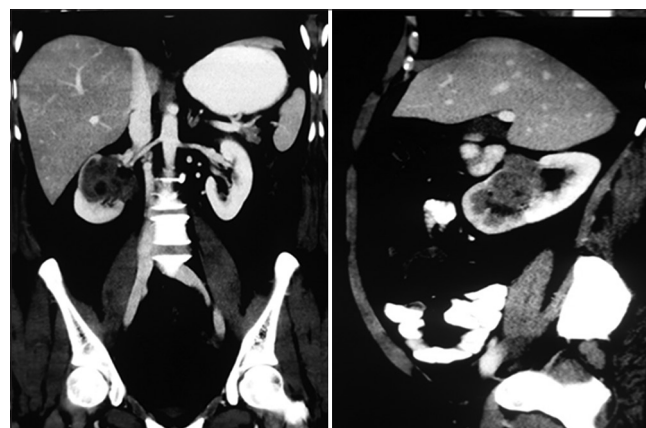


Figure 1: CT scan showing TCC of Right renal pelvis

Table 1: Patient demographics, tumor details and surgery performed					
S. no	Age	Sex	Location	Surgery	Grade
1	54	M	Renal pelvis	Nephroureterectomy	High
2	62	M	Renal pelvis	Nephroureterectomy	Low
3	41	F	Renal pelvis	Nephroureterectomy	Low
4	69	M	Lower ureter	Distal ureterectomy+boari flap	High
5	61	M	Lower ureter	Distal ureterectomy+reimplantation	Low
6	61	M	Lower ureter+bladder	Nephroureterectomy+cystoprostatectomy	High
7	42	F	Renal pelvis	Nephroureterctomy	*
8	55	F	Renal pelvis	Nephroureterctomy	Low
9	49	M	Renal pelvis and ureter	Nephroureterctomy	Low
10	57	F	Entire length of ureter	Nephroureterctomy	High
11	70	M	Renal pelvis	Nephroureterctomy	Low
12	43	M	Renal pelvis+ureter	Nephroureterctomy	Low
13	51	M	Lower ureter+bladder	Nephroureterocystoprostatectomy	High
14	56	M	Renal pelvis	Nephroureterctomy	High
15	63	F	Mid ureter	Nephroureterectomy	Low
16	59	M	Renal pelvis	Nephroureterctomy	High
17	64	F	Mid ureter	Nephroureterctomy	Low
18	64	M	Renal pelvis+bladder	Nephroureterectomy+TURBT	High

*Sarcomatoid variant of TCC

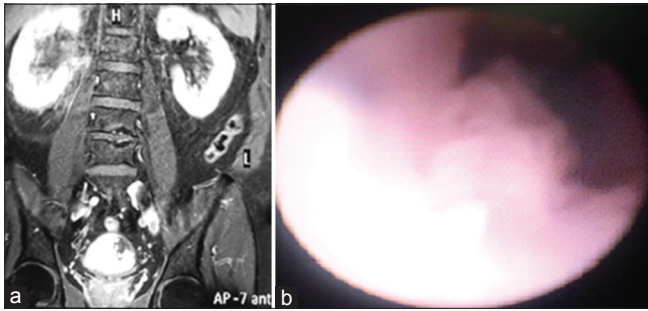


Figure 2: (a) MRI showing a right renal pelvic tumor with bladder tumor (b) ureteroscopy showing a ureteric TCC

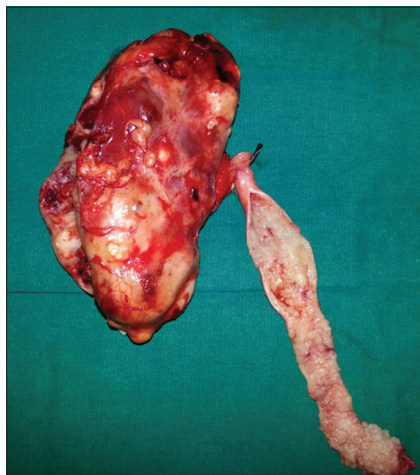


Figure 3: Tumor involving entire length of ureter



Figure 4 : Nephroureterocystoprostatectomy specimen with tumor involving bladder and lower ureter (arrow)

of the procedures. Patients with primary tumors in the renal pelvis and proximal ureter underwent this surgery. Eleven patients underwent laparoscopic nephroureterectomy along with bladder cuff excision through the incision used to retrieve the specimen. Three patients underwent open nephroureterectomy; these patients underwent transurethral resection of the intramural ureter. All patients underwent standard lymph node dissection.

Two patients who had primary tumor in the distal ureter underwent nephron sparing surgery in the form of distal ureterectomy. One of these patients needed a Boari flap to establish urinary tract continuity. Ureteric reimplantation was done in the other patient. Three patients who had concomitant bladder tumors were initially staged with Trans urethral resection of bladder tumor. Two of the patients, were diagnosed to have muscle invasive bladder tumor and underwent nephroureterocystoprostatectomy with orthotopic neobladder. The remaining patient, who had superficial bladder tumor, underwent nephroureterectomy along with transurethral resection of the intramural ureter for treatment of the primary transitional cell carcinoma of the renal pelvis.

Most of the tumors (50%) were well differentiated low grade tumors, 44% were high grade. One patient was diagnosed to have a very rare sarcomatoid variant of transitional cell carcinoma. Lymph nodes were positive in three patients (16%).

Recurrence was seen in three patients (16%) and all patients had high grade tumors and one of these patients had undergone renal sparing surgery. Two patients had recurrence in the bladder and both patients underwent transurethral resection of bladder tumor. One patient who was diagnosed to have sarcomatoid variant of transitional cell carcinoma had recurrence in the retro peritoneum and liver and she was started on gemcitabine and cisplatin based chemotherapy.

Morbidity rate in our series was 22% with 2 patients developing minor surgical site infections. One patient who underwent nephroureterocystoprostatectomy, developed urine leak from the neobladder and was managed conservatively. One patient developed urosepsis and was managed with Intravenous meropenem. No cancer related deaths were observed during the course of follow up.

DISCUSSION

Transitional cell carcinoma of the upper tract is a fairly uncommon malignancy encountered in the urological practice accounting for 5-10% of renal tumors.¹ The most common location of these tumors remains the renal pelvis. The incidence of transitional cell carcinoma in the ureter is scarce compared with the renal pelvis with a ratio of 1:3.³ Over the last 30 years, the incidence of renal pelvic tumors has remained fairly constant, however the incidence of ureteric tumors has been on the rise.¹ Similarly in our series, nearly half the patients had renal pelvic transitional cell carcinoma and an additional 11% had renal pelvic and ureteric tumors.

The peak incidence of tumors of the transitional cell tumors of upper tract is around the sixth and seventh decade of life and rarely occurs before the age of 40.¹ Males are affected three times more than females.¹ A familial incidence has been described in families with Balkan endemic nephropathy and is said to be 100-200 times more common in these patients.⁴ The other risk factors associated with upper tract transitional cell carcinoma are cigarette smoking, occupational factors analgesic abuse, coffee consumption, chronic infections and stones.^{5,6} Another risk factor associated with upper tract transitional tumors is the presence of bladder tumors. 1-4 % of the upper tract urothelial tumors are associated with bladder urothelial tumors and this risk can raise up to 20%.^{7,8} Also approximately 30 – 75% of the upper tract transitional tumors have an associated bladder tumor.^{1,9} In our series concomitant bladder tumor was seen in 16% of the patients.

A distinguishing feature of these tumors is its multiplicity which is seen in 27-36% of the cases,¹ however the incidence of bilateral tumors is low accounting for only 2-8% of the cases.^{1,10}

The most common presenting symptom of these patients is microscopic or gross hematuria seen in 75% patients, followed by flank pain (30%).¹ Seventy-two percent of our patients presented with hematuria.

Ultrasound is usually the first investigating modality used and helps to distinguish between stone and tumors. Intravenous urography can appreciate filling defects in the ureter and pelvis in 50 -70%of the tumors.¹ Computerized tomography is a better imaging modality for determining local extent of primary tumor, invasion into renal parenchyma, assess lymph node involvement and metastasis.¹¹ Magnetic resonance imaging has no added benefit over computerized tomography.¹ Urinary cytology has a minimal role in the diagnosis, with a sensitivity of less than 50% and a specificity of 90%.¹²

Invasive diagnostic modalities include retrograde pyelography, cystoscopy, ureteroscopy and nephroscopy although the latter two have some therapeutic benefit. Retrograde pyelography has a sensitivity of about 70%.¹² Cystoscopy is usually recommended because of the high incidence of concomitant bladder tumors. Nephroscopy and ureteroscopy helps in evaluating the tumor and diagnoses with the help of cup or brush biopsy with a sensitivity of about 80% and specificity of 60%.¹² Transitional tumors of the upper tract are staged as UICC TNM classification of malignant tumours 2002 (Table 2)

Radical surgery in the form of nephroureterectomy with removal of bladder cuff has been considered the standard

Table 2: TNM classification

TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Noninvasive papillary carcinoma
Tis	Carcinoma in situ
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades muscularis
T3	(Renal pelvis) tumour invades beyond muscularis into peripelvic fat or renal parenchyma; (ureter) tumour invades beyond muscularis into periureteric fat
T4	Tumour invades adjacent organs or through the kidney into perinephric fat
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node 2 cm or less in greatest dimension
N2	Metastasis in a single lymph node (more than 2 cm but not more than 5 cm) in greatest dimension, or multiple lymph nodes, none more than 5 cm in greatest dimension
N3	Metastasis in lymph node more than 5 cm in greatest dimension
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

of care for upper tract transitional cell carcinoma because of the high incidence of multicentricity and recurrence in the distal ureteral stump (16-58%).¹ Various techniques have been described for the removal of distal ureter and bladder cuff including two separate incisions, stripping,¹³ transurethral resection of intramural ureter¹⁴ and recently the laparoscopy. In our series, eleven patients underwent laparoscopic nephroureterectomy in whom bladder cuff excision was done through an incision used to deliver the specimen and 3 patients underwent transurethral resection of the intramural ureter along with open nephroureterectomy.

Since the last three decades conservative approaches to the management of upper tract has challenged the gold standard of nephroureterectomy in the management of upper tract transitional cell tumors. Renal sparing surgery can be performed in distal ureteric tumors, tumors in solitary kidney and bilateral tumors.¹ This may not be possible in upper ureteric tumors because of the difficulty in bridging the ureteric gap. We managed to treat two cases of lower ureteric tumors with renal sparing surgery.

With the advancement in endourological technique, ureteroscopic and percutaneous techniques have been described using laser or electrosurgical techniques for the management of these tumors.¹⁵ Recurrence rates following minimally invasive surgery is high and is said to around 23-54%.¹ None of our patients were managed by endourological techniques.

The role of BCG instillation has been well established in the management of superficial bladder tumors; however

the role of BCG is still in the management of upper tract transitional tumors is still uncertain. Few reports of BCG instillation through nephrostomy tubes, ureteric catheters and by vesical urethral reflux through dubbel J catheters have been described.^{14,16} Radiotherapy has a limited role and is only considered in the local control of high grade high stage tumors and has no added survival benefit.¹⁷ The role of chemotherapy is still under trial and is mainly indicated in node positive and metastatic disease. One of our patient with sarcomatoid variant of transitional cell carcinoma received gemcitabine and cisplatin based chemotherapy

The tumor stage along with grade and the surgical procedure performed are important risk factors for recurrence.⁹ The five year disease free survival has been reported to be 100% for Ta, 91.7% for T1 and 72.6% for T2 and 40.5% for T3 tumors.¹

CONCLUSION

Transitional cell carcinoma of the upper tract is a rare tumor which is known for its multicentricity and recurrence and should be suspected in elderly patients with hematuria and hydronephrosis. Computerized tomography remains the most important diagnostic modality. Associated bladder lesions should always be ruled out. Nephroureterectomy with excision of bladder cuff has been the gold standard for the management of these tumors, although endoscopic and tumor sparing surgery in selected cases have proven to be equally efficacious. Tumor grade and surgical procedure performed are independent risk factors for recurrence. Strict follow up protocol has to be in place for all patients because of the high rate of recurrence.

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Authors Contribution:

SP - Concept and design of the study, reviewed the literature, manuscript preparation and critical revision of the manuscript; **AN** - Conceptualized study, literature search, statistically analyzed and interpreted, prepared first draft of manuscript and critical revision of the manuscript; **ABP** - Concept of study, collected data and review of study; **DR** - Conceptualized study, literature search, statistically analyzed and interpreted, prepared first draft of manuscript and critical revision of the manuscript; **PM** - Conceptualized study, literature search, statistically analyzed and interpreted, prepared first draft of manuscript and critical revision of the manuscript.

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