

Original article

Survival Following Kidney Sparing Management of Upper Urinary Tract Transitional Cell Carcinoma is Adversely Affected By Prior History of Bladder Cancer

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ABSTRACT

Objective: To evaluate oncological outcomes of Kidney Sparing Surgery (KSS) for upper urinary tract transitional cell carcinoma (UUT-TCC).

Patients and Methods: We performed a retrospective review of patients who underwent segmental ureterectomy or endoscopic treatment (percutaneous nephroscopy or retrograde ureteroscopy) for UUT-TCC between 1991 and 2006 at our institution. We evaluated recurrence-free and overall survival rates following KSS. There were 40 renal units in 38 patients. Three patients had bilateral synchronous disease. Mean patient age (\pm SD) was 69.8 ± 12.3 years. Eighteen (47%) patients had a prior history of bladder TCC. Sixteen (40%) segmental ureterectomies and 24 (60%) endoscopic treatments were performed. Six (16%) patients received adjuvant BCG. Grade distribution was 24 (60%) low-grade, 12 (30%) high-grade and 4 (10%) Gx. The mean follow-up was 47 months.

Results: Recurrence rate was 32.5%. The three and five-year recurrence-free survivals were 59.5% and 42.4%. Tumor location was predictive for recurrence ($p < 0.03$). The three and five-year overall survivals were 91.6% and 79.8%. Predictive variables for overall survival were tumor grade ($p < 0.008$) and stage ($p < 0.018$) and previous history of bladder TCC. There was a statistically significant correlation ($r = 0.3539$) between tumor grade and stage ($p = 0.027$).

Conclusions: KSS offers good oncological outcomes in selected patients with UUT-TCC. The tumor biology rather than the surgical approach dictates prognosis. Patients with higher stage and grade disease may be better served with a more aggressive treatment approach.

Key Words: Upper Urinary Tract, Transitional Cell Carcinoma, Endoscopic, Kidney Sparing Surgery, Ureteroscopy, Percutaneous, Survival, Recurrence

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INTRODUCTION

Upper urinary tract transitional cell carcinoma (UUT-TCC) is less common than bladder cancer, accounting for approximately 5% of urothelial malignancies and less than 10% of renal tumors¹. Radical nephroureterectomy (RNU) with excision of the ipsilateral ureteral orifice and bladder cuff has been considered the standard of care of UUT-TCC due to the high recurrence rate and multiplicity in the same renal unit and the low incidence

of bilateral disease². However, in patients with impaired renal function, solitary kidney, bilateral synchronous tumors and high surgical risk, Kidney Sparing Surgery (KSS) may be a preferred option. Developing literature suggests that select patients with normal contralateral kidney and solitary, small, low grade and stage tumors may also be considered for organ sparing approaches³. KSS of UUT-TCC encompasses a spectrum of ablative

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and endoscopic approaches aimed at organ preservation. KSS can be achieved by partial ureterectomy or endoscopic surgery.

Multiple studies have confirmed the efficacy and safety of endoscopic treatment of UUT-TCC. Tawfik and Bagley reported on the outcome of ureteroscopic management for UUT-TCC from 14 series and found a recurrence rate of 33% for 61 renal pelvic tumors and 31% for 144 ureteral tumors⁴. Tumor recurrence was most dependent upon tumor grade with 25% recurrence for grade I tumors and almost 50% for higher grade lesions⁵. Percutaneous antegrade approach, although more invasive, is preferred for more substantial tumors in the renal pelvis and proximal ureter. It provides better visualization and large caliber working instruments for larger size tumors. In a literature review of 84 patients, an overall recurrence rate of 27% was found, with tumor grade strongly predicting outcomes⁶. Recently, Roupret and colleagues noted a similar 30% recurrence rate with 5-year disease specific survival of 80%⁷.

Segmental ureterectomy is a widely accepted form of KSS. It can be applied for invasive tumors and has the added advantage of staging lymphadenectomy. However, it is mainly limited to distal ureteral tumors and occasional mid or proximal ureteral defects that can be primarily approximated.

The aim of this study was to assess the oncological outcomes of patients with primary UUT-TCC treated with KSS. KSS.

PATIENTS AND METHODS

We performed a retrospective chart review of patients who underwent segmental ureterectomy and endoscopic treatment (percutaneous nephroscopy or ureteroscopy) for UUT-TCC between January 1991 and December 2006 at Mc Gill University Health Center. The recorded data included patient demographics, tumor characteristics (stage, grade, site and focality), prior history of

bladder cancer, type of treatment, indication for surgery and adjuvant BCG instillation. We evaluated recurrence-free and overall survival rates following KSS.

There were 38 patients with 40 renal units. The male to female ratio was 3:1. The median age of patients was 72 years (32-88 yrs). Eighteen (47%) patients had a prior history of bladder TCC. The primary tumor was located in the kidney, ureter or both in 11 (27.5%), 28 (70%) and 1 (2.5%) of renal units, respectively. Three (8%) patients had bilateral UUT-TCC at the time of diagnosis. Unifocal disease was found in 29 (72.5%) and multifocal disease in 11 (27.5%) renal units.

Pathologic grade was available for 36 tumors and pathologic stage was available for 32 tumors. Tumor grade was not available in four patients because of insufficient tissue for pathological examination (3 patients treated with laser fulguration and one treated with double-J stenting and BCG instillation). Twenty four (60%) tumors were low grade, 12 (30%) high grade and the remainder unknown (Gx). Twenty three (57.5%) tumors were superficial (CIS, Ta, T1), 7 (17.5%) invasive (T2, T3) and 8 (20%) had undetermined stage (Tx).

Follow-up of the UUT was conducted with intravenous pyelography (IVP) or retrograde pyelography with selective urine cytology at 6-month intervals. Computed tomography (CT) scan and other imaging studies were performed as indicated clinically. Diagnostic ureteroscopy was performed if imaging studies were suspicious for recurrence or if urine cytology was positive. Follow-up of the lower urinary tract was performed with cystourethroscopy and urine cytology every 3 months.

Univariate analysis using the log-rank test was performed to assess the predictive value of potential prognostic factors. Kaplan-Meier curves were generated for recurrence-free and overall survival. Stage versus grade correlation was done using Spearman's rank correlation test. Missing data were censored.

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Table 1: Clinical characteristics of 38 patients and 40 renal units

	n (%)
Male	28 (74%)
Female	10 (26%)
Median age (yrs) (range)	71 (32-88)
Prior bladder TCC	18 (47%)
Tumor side	
Right	23 (57.5%)
Left	17 (42.5%)
Tumor site	
Kidney	11 (27.5%)
Upper Ureter	6 (15%)
Lower Ureter	20 (50%)
Upper and Lower Ureter	2 (5%)
Kidney and Ureter	1 (2.5%)
Tumor focality	
Unifocal	29 (72.5%)
Multifocal	11 (27.5%)
Synchronous bilateral UUT-TCC	3 (8%)

Table 2: Indication and treatment of UUT-TCC in 40 renal units

Indication	
Elective	26 (65%)
Imperative	14 (35%)
Solitary Kidney	5 (12.5%)
Surgical Risk	5 (12.5%)
Bilateral Disease	4 (10%)
Treatment	
Partial Ureterectomy	16 (40%)
Endoscopic management	24 (60%)
Ureteroscopy	18 (45%)
Percutaneous	5 (12.5%)
JJ and BCG instillation	1 (2.5%)

RESULTS

Indications and treatment approaches are summarized in (Table 2). There were 26 (65%) electively treated tumors and 14 (35%) imperative indications such as solitary kidney, high surgical risk and bilateral disease. Twenty four (60%) tumors underwent endoscopic treatment and 16 (40%) had segmental ureterectomy. Of ureteral tumors treated endoscopically, sixteen were fulgurated with Holmium laser and 2 were resected.

Six (15%) renal units received adjuvant 6-weekly BCG after initial endoscopic treatment. The indication for BCG instillations was high-grade tumors in two cases and incomplete resection in five cases. Four units received intravesical BCG instillations with double pigtail catheter insertion and two units received percutaneous BCG instillations via nephrostomy tube. None of the patients received adjuvant systemic chemotherapy.

Recurrence-free survival was calculated from the day of initial treatment to the day of diagnosis of the first recurrence in the same renal unit. Disease recurrence occurred in 13 (32.5%) renal units. The mean and median times to recurrence were 31.8 and 17 months, respectively (range 1 to 139 months). The three and 5-year recurrence-free survivals were 59.5% and 42.4%, respectively. Nine recurrences were located at the same site as the initial tumor, two recurred at a lower level and two recurred at a higher level. Recurrence was multifocal in three patients. Treatment at recurrence was endoscopic management in five units, nephroureterectomy in 4 units, segmental ureterectomy in one patient and palliative therapy in one patient. Two patients were treated at an outside institution at the time of recurrence. Fifteen (40%) patients had bladder TCC recurrence, 5 (13%) of which were de novo bladder recurrences after UUT-TCC treatment.

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Table 3: Univariate analysis of potential prognostic factors for recurrence and overall survival

Variable	Recurrence		Overall Survival	
	Hazard Ratio (95% CI of ratio)	p value	Hazard Ratio (95% CI of ratio)	p value
Age (>70 vs. ≤70 years)	1.98 (0.71-5.55)	0.2	2.6 (0.36-18.53)	0.34
Sex (Male vs. Female)	0.76 (0.22-2.62)	0.66	3.59 (0.33-38.74)	0.29
Bladder TCC (Prior BT vs No Prior BT)	2.33 (0.78-6.92)	0.13	29.38 (3.35-257.9)	0.002*
Indications (Imperative <i>n</i> =14 vs. Elective <i>n</i> =26)	1.52 (0.47-4.88)	0.48	3.91 (0.4-38.04)	0.24
Stage (Invasive, <i>n</i> =7 vs. Superficial, <i>n</i> =23)	0.67 (2-2.26)	0.52	17.26 (1.6-186.3)	0.018*
Grade (High, <i>n</i> =12 vs. Low, <i>n</i> =24)	2.21 (0.71-6.86)	0.17	27.85 (2.33-333.4)	0.008*
Focality (Multifocal, <i>n</i> =12 vs. Unifocal, <i>n</i> =28)	0.72 (0.23-2.27)	0.58	3.25 (0.35-29.72)	0.29
Location (Kidney, <i>n</i> =12 vs. Ureter, <i>n</i> =28)	4 (1.19-13.53)	0.03*	0.27 (0.03-2.74)	0.27
BCG (no BCG, <i>n</i> =33 vs. BCG, <i>n</i> =7)	3.4 (0.74-15.6)	0.12	2.18 (0.14-34.54)	0.58
Surgical Procedure (Endoscopic, <i>n</i> =24 vs. Partial Ureterectomy, <i>n</i> =15)	1.28 (0.46-3.58)	0.64	0.321 (0.05-2.3)	0.26

Univariate analysis of studied prognostic factors for recurrence-free survival is shown in Table 3. Tumor location was a significant predictive factor for recurrence ($p < 0.03$). Age, sex, indication for surgery, tumor stage, grade, focality, surgical procedure and adjuvant BCG were not statistically significant. Tumor location within the kidney (renal pelvis or calyx) portended a higher risk of recurrence compared to ureteral location (HR 4; 95% CI 1.19-13.53). The recurrence rates were 50% and 25% for kidney and ureteral locations. Five-year recurrence-free survival for kidney and ureteral locations was 29% and 49%, respectively ($p < 0.03$). Tumor grade did not reach significance, but the recurrence rates for high versus low grade tumors were 50% and 29%, respectively.

Overall survival time was calculated from the day of treatment to the last known follow-up or death date. There were 4 deaths, 3 from metastatic TCC and one from cardiac arrest during bypass surgery. The disease-specific survival rate was 92.1%. The three and 5-year overall survivals were 91.6%

and 79.8% (Fig. 1). Median survival was not yet reached. Mean and median follow-up times were 47 and 32 months, respectively (range 1-219 months).

Univariate analysis of studied prognostic factors for survival is shown in (Table 3). There was a significant difference in overall survival when stratified by tumor stage ($p < 0.018$), grade ($p < 0.008$) and history of bladder TCC before detection of UUT-TCC ($p < 0.002$). Age, sex, indication for surgery, tumor focality and location, surgical approach and adjuvant BCG were not significant. Fig.1 shows Kaplan-Meier curves of significant variables. Survival rates were 100% and 79% for superficial (Ta, T1) and invasive (T2, T3) tumors, respectively. Five-year estimated overall survival was 100% for superficial (Ta, T1) and 53.6% for invasive (T2, T3) tumors. The survival rates for low and high-grade tumors were 100% and 75%.

There were 4 complications as a result of KSS. One patient had stenosis of the ureteric orifice after ureteroscopic resection of

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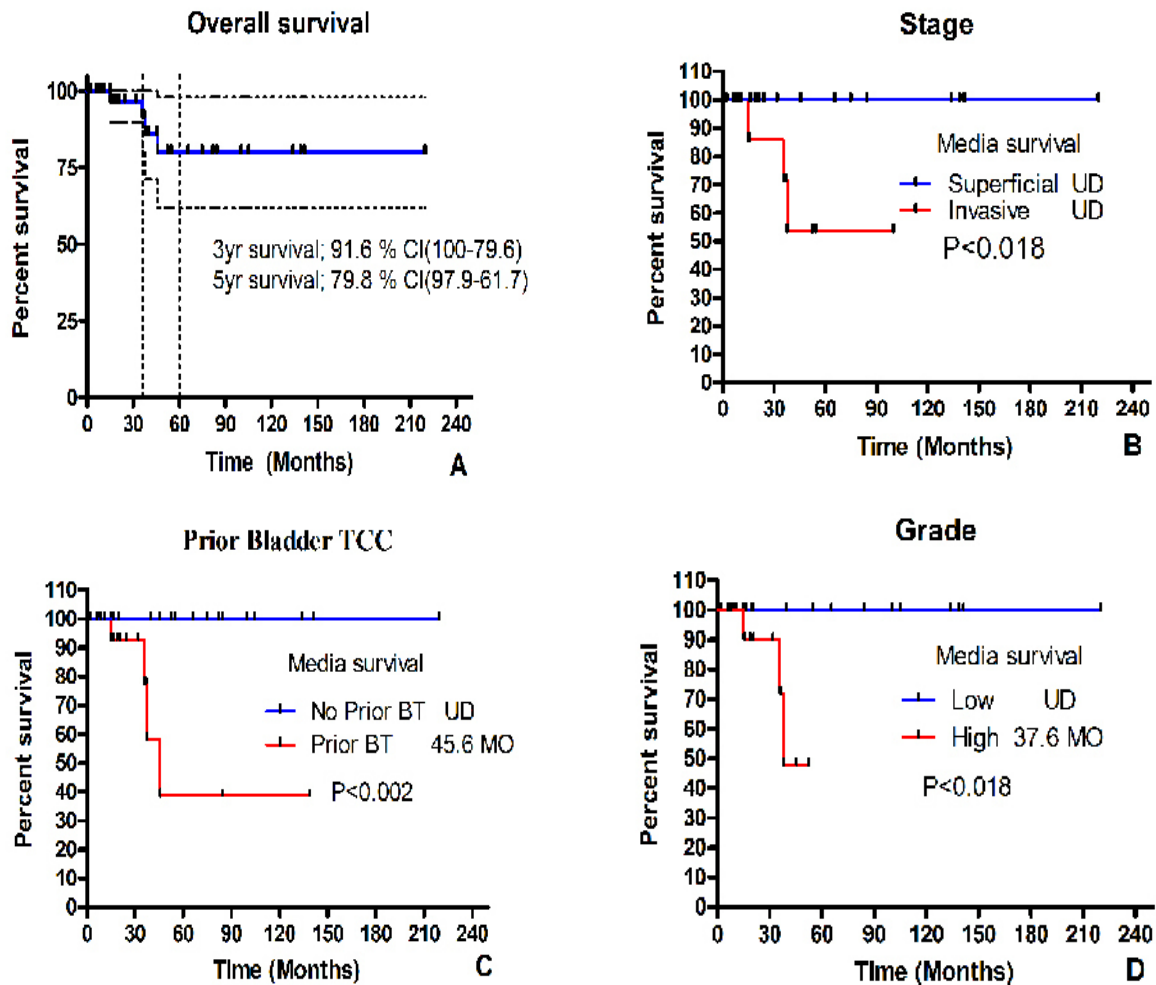


Fig. 1: (A) Overall survival. (B) Stratification of survival by tumor stage ($p < 0.018$). (C) Stratification of survival by prior history of bladder TCC ($p < 0.002$). (D) Stratification of survival by tumor grade ($p < 0.008$).

ureteral TCC that was treated by endoscopic dilatation. One patient had a stricture of the ureteropelvic junction in a single kidney after percutaneous resection of renal pelvic tumor, which resulted in renal failure and hemodialysis. Systemic tuberculosis occurred after the third installation of BCG following percutaneous resection of renal pelvic TCC in one patient. BCG installations were stopped and the patient received medical treatment for TB. Another patient with a single kidney lost its function after percutaneous resection and BCG installation and was referred for hemodialysis.

Among the 40 renal units initially treated by KSS, four kidneys were removed due to tumor

recurrence. Three units were treated initially with partial ureterectomy and one was treated endoscopically. Two nonfunctioning kidneys were left in place. The final kidney sparing rate was 85%.

There was a statistically significant correlation ($r = 0.354$) between tumor grade and stage ($p = 0.027$).

DISCUSSION

Multiple therapeutic options are available for the management of UUT-TCC. RNU with bladder cuff is considered the gold standard treatment. According to the National

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Comprehensive Cancer Network guidelines, KSS is the preferred option for low grade, mid and distal ureteral TCC and second line option for low grade, renal pelvic and upper ureteral TCC⁸. The European Association of Urology guidelines on TCC do not provide clear recommendations about KSS⁹. To our knowledge, there are no published guidelines on UUT-TCC from the American Urological Association or the Canadian Urological Association.

Several reports advocate the use of KSS for UUT-TCC in patients with solitary kidney, bilateral tumors, renal insufficiency and in patients with high risk for major surgery. The latter are considered imperative indications for KSS. However elective KSS is being performed successfully in patients with small, low grade and low stage tumors^{3,4}. Elective KSS in selected patients is justified by the fact that prognostic factors for recurrence and survival are tumor related irrespective of the treatment modality⁴. Several case series suggested that outcomes of KSS in appropriately selected patients were no different than the gold standard RNU^{4,10}.

In our study, we report the oncological outcomes of 38 patients who underwent KSS for 40 renal units. We acknowledge the limitations of this retrospective non-randomized single center cohort study. However, the strengths of the study include a fair number of patients and systematic and comprehensive analysis of potential predictors of both recurrence and survival. Clinical characteristic are similar to those reported by others^{2, 10, 11}. Prior history of bladder TCC was found in 18 (47%) patients. This figure is higher than reported by previous series (16%-19%)^{2, 11}. Fifteen (40%) patients developed bladder recurrence after KSS, only 5 (13%) of which were *de novo* bladder recurrences. Fujimoto et al¹², reported a similar incidence of bladder recurrence after UUT-TCC treatment. In other series bladder TCC recurrences were as low as 16.7%

and as high as 51%^{2, 7}. We think that those patients could be served better with routine endoscopic surveillance, however, there were no guidelines for follow-up of such patients in our institution.

In this series, the 3- and 5-year recurrence-free survivals were 59.5% and 42.4%, respectively. Ipsilateral recurrence of the disease was 32.5%. This recurrence rate is similar to that reported in previous series¹³. The risk of ipsilateral recurrence after KSS ranges from 7% to 70%^{2, 7, 10-12, 14}. In the current study the recurrence rate for low grade disease was 29% and for high grade disease was 50% (p NS). Zincke and Neves¹⁴ reported only 5% recurrence for grade 1-2 ureteral TCC and 50% recurrence for higher grades. However, Keely et al, reported 26% recurrence rate for grade 1-2 and 44% in higher grades⁵.

In this series, we established tumor location as a predictor of recurrence following KSS. Five-year recurrence-free survival for pelvicalyceal system and ureteral TCC was 29% and 49% respectively ($p < 0.03$). Similarly, Iborra et al reported tumor location in the renal pelvis as a significant predictive factor for tumor recurrence¹³.

Five-year overall survival after KSS was reported in a range from 56% to 91.7%^{7,11, 12, 15}. In the current study the 3- and 5-year overall survivals were 91.6% and 79.8%. Prognostic predictors for overall survival were tumor stage, tumor grade and bladder TCC prior to detection of UUT-TCC (Table 3). Five-year overall survival was 100% in pTa and pT1 and 53.6% in pT2 and pT3 stages. These results are comparable to those reported by Zungri et al., 100% in pTa, 95.8% in pT1 and 33.3% in pT2¹⁵. We found a 100% survival rate in low grade disease and 75% in high grade disease, which is in accordance with other reports^{11,14}.

There was a strong correlation between grade and stage of UUT-TCC ($p < 0.027$).

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Most low grade tumors were non-invasive, which is in agreement with published data^{2,16}.

CONCLUSION

KSS offers good oncological outcomes in selected patients with UUT-TCC. The tumor biology rather than the surgical approach dictates prognosis. Renal location portends a higher risk of recurrence compared to ureteral location. Long term, thorough surveillance is required, since recurrence of the disease may occur as late as five years. Prior history of bladder cancer negatively affects survival in a highly significant manner. Patients with higher stage and grade disease may be better served with a more aggressive treatment approach.

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