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Prognostic Factors for Upper Tract Transitional Cell Carcinoma: A Retrospective Review of 66 Patients

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OBJECTIVE: We assessed the prognostic factors on recurrence and disease-specific survival of patients treated for upper tract transitional cell carcinoma (TCC).

METHODS: Data on 66 patients who were treated for upper tract TCC in a single centre over a 13-year period were analysed. Mean follow-up time was 49.2 months. Fifty-five out of 66 (83.3%) underwent nephroureterectomy with excision of a bladder cuff. Four (6.1%) patients had nephrectomy alone while three (4.5%) had renal-sparing surgery. Four patients did not receive surgery due to advanced age and other comorbidities. Age, sex, tumour location, stage and grade were analysed as prognostic factors for disease recurrence and disease-specific survival using log rank univariate analysis.

RESULTS: Disease recurrence occurred in 45 (68.2%) patients at a median time of 11.0 months. Recurrences were found in the bladder in 27.3%, the contralateral renal pelvis in 4.5%, local retroperitoneum in 19.7%, distant sites in 13.6%, with simultaneous local and distant metastases occurring in 3.0%. Tumour stage was the only significant prognostic factor for recurrence. Presence of extraurothelial recurrence, stage and grade were significant prognostic factors for disease-specific survival.

CONCLUSION: Tumour stage was the most consistent predictor of both disease recurrence and survival. These findings would guide the need for any adjuvant chemoradiotherapy. [*Asian J Surg* 2008;31(1):20–4]

Key Words: cancer, neoplasm, recurrence, survival, urothelium

Introduction

Upper tract transitional cell carcinoma (TCC) is a relatively uncommon urological cancer. Renal pelvis TCC accounts for approximately 10% of all renal tumours and about 5% of all urothelial tumours.[1] Ureteric tumours are even less common, with one fourth the incidence of renal pelvis tumours.[2] This study reviewed the clinical presentation, evaluation and treatment outcomes. We aimed to identify the significant prognostic factors for recurrence and disease-specific survival in patients treated in one centre with prolonged follow-up.

Patients and methods

Patient characteristics

A retrospective review of patients treated for upper tract TCC at Singapore General Hospital from January 1990 to October 2002 was conducted. Sixty-six patients were identified using surgical logs and histopathology records.

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Clinical data and recurrence status were obtained by review of all pertinent medical records up to May 2005.

Preoperative investigations performed

Intravenous urogram (IVU), computed tomography (CT) scan, retrograde pyelogram (RPG) and rigid/flexible ureterorenoscopy (URS) with or without biopsy were used for preoperative diagnosis. Most patients had more than one modality of investigation. IVU and CT scan were done in 49 (74.2%) and 50 (75.8%) patients, respectively. RPG and URS were done in 27 (40.9%) and 29 (43.9%) patients, respectively.

Treatment modalities

Sixty-two patients underwent some form of operative treatment. Nephroureterectomy with removal of a bladder cuff was the most frequently performed procedure, accounting for 55 (83.3%) cases. Out of these 55 patients, 41 underwent open surgery while 14 underwent laparoscopic surgery. Four (6.1%) patients underwent nephrectomy. Another three (4.5%) patients underwent renal-sparing procedures because of serious comorbidities, distal ureteric tumour location or impaired renal function. The remaining four patients did not receive any definitive surgery due to advanced age or significant medical comorbidities.

Six patients received adjuvant radiotherapy: one had T3 disease with positive lymph nodes; two had T3 disease with positive resection margins (at the ureteric and bladder cuff resection lines); and three had T4 disease. Five patients received adjuvant chemotherapy: two had T3/T4 tumours; two had T3 tumours with positive lymph nodes; and one had T3 tumour, positive lymph nodes and positive bladder cuff resection margin. One patient received both adjuvant chemotherapy and radiotherapy for T4 disease and positive lymph nodes with positive ureteric resection margin.

Grade and stage distribution

The pathological stage and grade were available for 65 patients. Six (9.2%) patients had grade 1 disease, 27 (41.5%) had grade 2 disease, and 32 (49.2%) had grade 3 disease. Seven patients (10.8%) had Ta disease, 15 (23.1%) had T1 disease, eight (12.3%) had T2 disease, 26 (40%) had T3 disease, and nine (13.8%) had T4 disease. A statistically significant correlation was evident when comparing disease grade (grades 1 and 2 *vs.* grade 3) and stage (Ta and T1 *vs.* T2, T3 and T4): low-stage disease corresponded with low grade, while high-stage disease had predominantly high-grade disease (Fisher's exact test, $p = 0.001$). None of those with pTa, pT1 or pT2 primary tumours had nodal or distant metastatic disease either at presentation or during follow-up. Of the 15 (22.7%) patients with nodal or metastatic disease, 10 had pT3 tumours and five had pT4 tumours.

Statistical method

Survival analysis was performed to assess the predictive value of prognostic factors including age (greater *vs.* less than/equal to the population mean of 69), sex (male *vs.* female), tumour location (renal pelvis *vs.* ureter), tumour grade (1 *vs.* 2 *vs.* 3) and stage (Ta *vs.* T1 *vs.* T2 *vs.* T3 *vs.* T4) with regard to disease recurrence and disease-specific survival. In addition, the impact of urothelial versus extraurothelial recurrence on disease-specific survival was also compared. The American Joint Committee on Cancer TNM stage classification was used.[3] Data were entered into a statistical database (SPSS version 13.0; SPSS Inc., Chicago, IL, USA) and subjected to univariate survival analysis. Kaplan-Meier curves were created and compared using the log rank test.

Results

Patient characteristics and clinical features are outlined in Table 1. The male to female ratio was 2:1. Most patients were in their sixth and seventh decades of life at diagnosis. Eighty-two percent of patients had gross haematuria at presentation. A prior history of bladder TCC was noted in six (9.1%) patients. Nine (13.6%) patients had synchronous bladder TCC when the upper tract tumour was diagnosed. All were unilateral at presentation. Median follow-up of these patients was 35.3 months (mean, 49.2 months; range, 1–158.5 months).

Of the 12 patients who received chemotherapy and/or radiotherapy, overall outcome was poor. Eight of them died of the disease with a median survival of 20.0 months. Ten patients had recurrence with a median time to recurrence of 3.6 months.

Recurrence

Disease recurrence occurred in 45 (68.2%) patients (Table 2). The median time to recurrence was 11.0 months (range, 1–117.0 months). The most common site was the bladder, accounting for 18 (27.3%) cases. Three (4.5%) cases recurred in the contralateral renal pelvis. Thirteen (19.7%) patients had local recurrences in the retroperitoneum, occurring

Table 1. Characteristics of 66 patients with upper tract transitional cell carcinoma (TCC)

	n (%)
Sex	
Male	44 (66.7)
Female	22 (33.3)
Mean age, yr (range)	69 (33–92)
Presenting complaints*	
Macroscopic haematuria	54 (81.8)
Loin pain	6 (9.1)
Palpable mass	5 (7.6)
Incidental diagnosis on imaging	4 (6.1)
Microscopic haematuria	3 (4.5)
Surveillance for previous bladder TCC	3 (4.5)
Side	
Right	34 (51.5)
Left	32 (48.5)
Primary tumour location	
Renal pelvis	34 (51.5)
Upper- and mid-ureter	9 (13.6)
Lower third ureter	17 (25.8)
Renal pelvis and ureter	6 (9.1)
Prior history of bladder TCC	6 (9.1)
Synchronous bladder TCC	9 (13.6)

*Some patients presented with more than one complaint.

Table 2. Sites of tumour recurrence over a mean follow-up of 35 months in 66 patients

	n (%)
Bladder	18 (27.3)
Local retroperitoneum	13 (19.7)
Metastases	9 (13.6)
Contralateral renal pelvis	3 (4.5)
Both local and metastatic recurrences	2 (3.0)
Total recurrences	45 (68.2)

at a median time of 10.1 months. Metastatic recurrences developed in nine (13.6%) patients at a median time of 3.9 months. In two (3.0%) patients, there were both local and metastatic recurrences. On log rank univariate analysis of possible prognostic factors, tumour stage was the only significant prognostic factor for recurrence ($p < 0.001$). The Kaplan-Meier recurrence-free survival curve by tumour stage is shown in Figure 1.

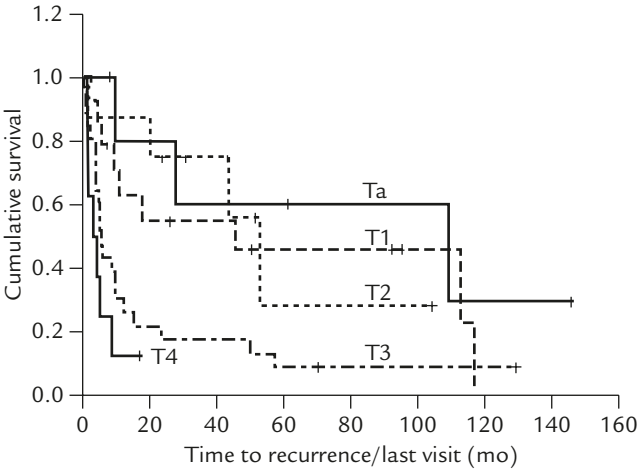

Figure 1. Recurrence-free survival by T stage.

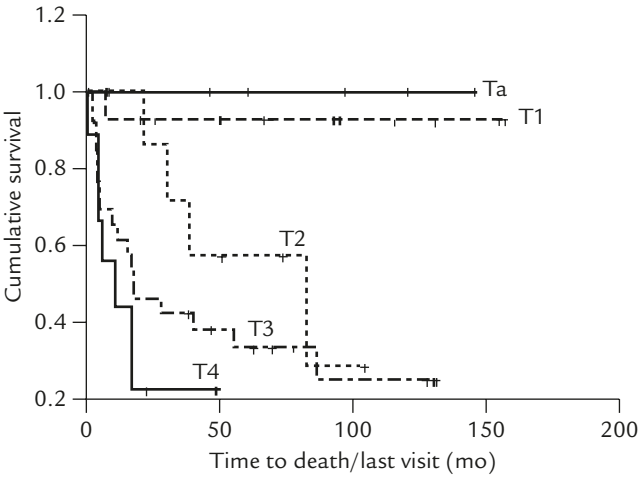

Figure 2. Disease-specific survival by T stage.

Survival

Overall median disease-specific survival was 87.0 months. On univariate log rank analysis, tumour stage ($p < 0.001$) and grade ($p < 0.001$) were both significant prognostic factors for disease-specific survival. Figure 2 shows the Kaplan-Meier disease-specific survival curves by tumour stage.

In addition, we compared the significance of urothelial recurrences (bladder and contralateral renal pelvis) with extraurothelial recurrences (local retroperitoneum or metastatic) on disease-specific survival. There was a significant difference in survival ($p < 0.001$). Of the 21 patients whose recurrences were found in urothelium, the mean disease-specific survival was 114.8 months. Of the 24 patients who had extraurothelial recurrences, the mean disease-specific survival was significantly worse at 55.2 months.

Discussion

We reviewed our experience with upper tract TCC to assess the effect of prognostic factors on disease recurrence and survival. We then compared our results with similar retrospective studies of patients with this uncommon urological malignancy.

With regard to patient and tumour characteristics, we noted that these had remained relatively constant when compared to studies in the last 20 years.[4–6] In our series, the renal pelvis remained the commonest site of occurrence of the primary tumour (51%). The bladder was the commonest site of first recurrence after an upper tract urothelial carcinoma, occurring in 40% of patients with recurrence. The longest time to recurrence in the bladder occurred as late as 57 months. These important disease characteristics continue to provide valuable insight during diagnostic and follow-up evaluations. In particular, the high incidence of bladder recurrence mandates long-term endoscopic bladder surveillance.

The overall outcome of the 12 patients who received adjuvant chemotherapy and/or radiotherapy was poor. This underlines the well-known fact that adequate surgery remains the best hope for curative treatment in patients with localized disease. As many as 40% and 14% of our patients had T3 and T4 disease, respectively, and 50% had grade 3 disease. Since T stage and grade have been repeatedly shown to be significant prognostic factors for upper tract TCC, it can be predicted that as many as half of our patients will develop early recurrence or have poor survival despite surgery. It is therefore our institution's practice to discuss these patients at multidisciplinary tumour conferences in the hope of offering them some form of adjuvant treatment post-nephroureterectomy.

In this series, local recurrence was quite high (19.7%). Analysis of these 13 patients revealed that seven had T3/T4 disease, four had node-positive disease and 12 had grade 2 or 3 disease. Only one patient received adjuvant treatment after nephroureterectomy in the form of radiotherapy. After diagnosis of local recurrences, two patients underwent palliative bypass surgery for symptoms of bowel obstruction. Only one received further palliative radiotherapy. The remaining 10 patients did not receive further palliative treatment. The prognosis is dismal for these patients and the benefits of any palliative treatment should be seriously weighed against its side effects. We therefore reserve treatment only to palliate symptoms (such as bowel bypass surgery). Most of these patients would receive best supportive care.

Nine of our patients had T4 tumours. Seven of them had symptoms of gross haematuria and loin pain. Six of them underwent nephroureterectomy and the remaining patient had simple nephrectomy for palliation of their symptoms. Operative treatment for such locally advanced disease is usually non-curative. However, cytoreductive surgery in the presence of symptoms still offers the best form of palliation to the patient.

Surgery had been the mainstay of treatment for localized upper tract TCC and this was traditionally treated by radical nephroureterectomy with bladder cuff excision.[7] High recurrence rates had been noted when a less extensive operation was performed, particularly with more proximally located lesions.[8] These localized resection procedures may, however, be appropriate for patients with solitary kidney, impaired renal function or prohibitive operative risk. Unfortunately, we could not analyse the impact of these conservative forms of surgery on survival as only three patients in this series underwent renal-sparing procedures (1 patient underwent ureteric resection with re-implantation, 2 patients underwent ureteroscopic resection). However, this limitation may be mitigated by the well-known fact that tumour grade and stage are more important to patient outcome than the type of surgery.[9,10]

Localized resection techniques are also acceptable for patients with TCC of the distal ureters. Distal ureteric tumours accounted for 25% of patients in this series, second only to renal pelvic tumours. Renal-sparing surgery is preferred in patients with distal ureteric TCC which are low-grade, low-stage tumours.[5,8,11] Distal ureteric tumours tend to be smaller and less frequently invasive than their renal pelvic counterparts.[12] Many authors had therefore agreed that segmental ureterectomy and ureteral re-implantation is an acceptable treatment for urothelial tumours of the distal ureter.[13–15]

The benefits of laparoscopic techniques for nephrectomy are well-described[16,17] but beyond the scope of this study. However, it is worth noting that 14 patients in this series underwent laparoscopic surgery. This highlights the increasing role played by minimally-invasive techniques in upper tract TCC and renal tumours in general.[18] The recurrence rate appeared to be similar to conventional open surgery series.[19]

None of the quoted series studied the impact of extraurothelial recurrence. This study showed that

extraurothelial recurrence in the form of local retroperitoneal and distant metastatic deposits adversely affected survival. Whilst urothelial recurrence, most commonly found in the bladder, can be detected by cystoscopy, extraurothelial recurrence would require surveillance imaging. Regular radiological imaging must therefore be part of the routine follow-up surveillance of patients, especially those with higher-stage disease.

In a series of 252 patients, Hall et al reported that tumour stage and type of surgical procedure performed were the only significant predictors of tumour recurrence while stage and age were significant predictors of survival.[6] Badalament et al reviewed 50 patients and found, on both univariate and multivariate analyses, that stage was the only significant predictor of survival.[20] Likewise, Cozad et al reviewed 94 patients with upper tract TCC and found that stage and age were the only significant predictors of survival on multivariate analyses.[21] In our series, univariate analysis showed that tumour stage was a significant predictor of recurrence whereas extraurothelial recurrence, stage and grade were significant predictors of disease-specific survival. From these series, which number more than 50 patients each, it is apparent that tumour stage is the only consistent prognostic factor of both recurrence and survival. This would allow more definite application of appropriate adjuvant therapies for patients based on the initial histological staging. Higher-stage disease should also be followed-up more closely due to the higher rate of recurrences.

This series of 66 patients studied the prognostic significance of age, sex, tumour location, extraurothelial recurrence, grade and stage. In reported series with more than 50 patients, tumour stage was shown to be the most consistent predictor of tumour recurrence and survival. Our results reinforce this finding and will help to guide adjuvant therapies and decisions regarding follow-up period for these patients.

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