Factors impacting survival in patients with upper tract urothelial carcinoma undergoing radical nephroureterectomy

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Introduction: *This study aims to assess the influence of different prognostic factors on survival of upper tract urothelial carcinoma (UTUC) managed by nephroureterectomy and to investigate whether these factors have an independent prognostic significance.*

Materials and methods: *A retrospective review of institutional databases from two teaching hospitals identified 269 consecutive patients with UTUC managed with nephroureterctomy between 1985 and 2005. Mean follow up was 80.6 months (median 70.3 months). Follow up was completed until January 2009. Tumor location and other clinicopathological variables were analyzed regarding survival. Data accrued included age, gender, tumor characteristics (pT stage, grade, lymph node status), tumor location, use of chemotherapy and period of diagnosis. Tumor location was divided into two groups (renal pelvis and ureter) based on the location of the tumor.*

Results: *Five year and 10 year overall survival estimates for this cohort were 71.3% and 40.0% respectively. According to tumor location, survival was 73.6% and 47.0% for the renal pelvis versus 67.8% and 32.3% for the ureter, respectively (log rank test: $p = 0.027$). In multivariate analysis, among the clinicopathological variables, T stage was the most significant prognostic factor ($p < 0.001$). Nodal involvement ($p = 0,005$), high grade ($p < 0.001$), first period of diagnosis ($p < 0.001$) and ureteral tumor location ($p = 0.003$) were significantly associated with lower survival rates. Prognosis of UTUC improved over time: survival was significantly better during the last period of diagnosis (2001-2005) ($p < 0.002$).*

Conclusions: *Tumor location and diagnostic period should be considered as an independent prognostic factor for upper tract transitional cell carcinoma.*

Key Words: upper tract urothelial carcinoma, nephroureterectomy, tumor location, prognosis

Introduction

Tumors of the renal pelvis and or the ureter are relatively uncommon; accounting for approximately 5% of all urologic malignancies.[1] The incidence of upper tract tumors is increasing, but whether this increase is real or is related to improved endoscopy, imaging, and surveillance methods is not well quantified. As for tumors of the bladder, upper tract urothelial tumors occur most commonly in the sixth and seventh decade and appear more frequently in men than in women with a sex ratio of approximately 3:1.[2]

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Primary tumor classification, pathologic grade, lymph node status, and extent of surgery have been identified as significant prognostic factors in patients with upper tract urothelial carcinoma (UTUC).[3-6] Another potential prognostic variable is the location of the tumor within the upper urinary tract and the cohort period of diagnosis. Although tumors within the renal pelvis are two to three times more common than ureteral lesions,[7,8] studies have suggested that ureteral disease confers a worse prognosis[9-10] others suggested no prognostic difference between ureteral and renal pelvis disease,[11-13] while no data in the literature exists about the trend over time of the prognosis of UTUC treated by nephroureterectomy.

Therefore, and in order to overcome these limitations, we decided to set up a database and to collect all the relevant information in two teaching hospitals with an important recruitment of patients.

Materials and methods

We retrospectively reviewed the medical records, including radiology and pathology data, of 269 consecutive patients treated surgically with nephroureterectomy for UTUC between October 1985 and October 2005 at two teaching hospitals. Patients with distant metastasis at diagnosis were excluded. One hundred and ninety-six men and 73 women formed the basis of the current study. Surgery was performed with curative intent in all cases. Nephroureterectomy with bladder cuff removal was the common procedure. All pathology reports were reviewed and pathological staging was assessed according to the 2002 TNM staging system. The staging was done according to the main papillary tumor independently of the presence of Tis. Whenever there were multiple tumors, the staging was done according to the tumor with the higher stage. Tumors were graded according to the 1973 WHO classification. After surgery patients were followed with routine blood tests, urine cytology, cystoscopy, chest x-ray, abdominopelvic computerized tomography and bone scan according to the surveillance protocol or as clinically indicated. Follow up was completed until the first of January 2009. This study complies with national regulation for retrospective clinical studies.

To compare the outcomes for different locations, lesions were categorized as 161 renal pelvis and 108 ureteral cases. The trend over time for each location of UTUC was also analyzed by dividing the study period into three groups on the basis of year of diagnosis: (1985-1995), (1996-2000), and (2001-2005).

Patient survival was defined as the time between the date of surgery and the date of death from any cause. Patients, who were alive on January 1, 2009 were censored. Prognostic factors assessed were patient age, gender, pT stage, pN stage, grade, surgical margin status, adjuvant chemotherapy, period of diagnosis and tumor location.

The chi-square test or the Fischer exact test, whenever necessary, were used to study the association between categorical variables. The Mann Whitney test assessed differences in variables with a continuous distribution across dichotomous categories.

Survival probabilities after nephroureterectomy were determined using the Kaplan-Meier method. The log rank test was used to compare survival curves. Multivariate Cox proportional hazards regression models were used to study time to mortality after nephroureterectomy. Differences were considered statistically significant when $p < 0.05$. We tested the interactions between the different covariates. In all models, the proportional hazards assumption was systematically verified using a graphical method.

Results

Table 1 summarizes the clinical and pathologic characteristics of patients, stratified by tumor location. Mean follow up was 80.6 months (median 70.3 months). One hundred and ninety-six men (72.9%) and 73 women (27.1%) were included with a median age of 66.7 years. Overall, 59.8% of tumors were classified as renal pelvis and 40.2% were ureteral. The stage distribution of UTUC tumors in this cohort was 8.1% pTa, 29.7% pT1, 28.6% pT2, 24.3% pT3, and 9.3% pT4. 30.5% of patients had grade 1 urothelial tumors, 39.5% had grade 2 urothelial tumors and 30.0% has grade 3 tumors; 8.2% of patients had positive lymph nodes. More specifically, 46.0% of tumors were diagnosed during the period 2001-2005.

When comparing renal pelvis tumors and ureteral tumors, there were no differences regarding age, gender, stage, nodal status, tumor grade, surgical margin, and chemotherapy. Interestingly, the proportion of renal pelvis tumors increased significantly with time ($p < 0.001$), Table 1.

When we divided the pT stage into two subgroups of non-muscle invasive urinary carcinoma (pTa, pT1) and muscle invasive urinary carcinoma (pT2, pT3, pT4), patients with ureteral tumor were more likely to have muscle invasive carcinoma (69.5% versus 57.0%), those with renal pelvis tumor were more likely to have non–muscle invasive UTUC (43.0% versus 30.5%) ($p = 0.042$).

TABLE 1. **Clinicopathologic characteristics of the 269 patients with upper urinary tract carcinoma**

	n (%)	Ureter (108 patients)		Renal cavity (161 patients)		p value
		n	(%)	n	(%)	
Gender						p = 0.636
Female	73 (27.1)	31	(42.5)	42	(57.5)	
Male	196 (72.9)	77	(39.3)	119	(60.7)	
pT stage						p = 0.092
pTa	22 (8.1)	11	(50.0)	11	(50.0)	
pT1	80 (29.7)	22	(27.5)	58	(72.5)	
pT2	77 (28.6)	36	(46.8)	41	(53.2)	
pT3	65 (24.3)	28	(43.1)	37	(56.9)	
pT4	25 (9.3)	11	(44.0)	14	(56.0)	
pN stage						p = 0.939
pN0	247 (91.8)	99	(40.1)	148	(59.9)	
pN+	22 (8.2)	9	(40.9)	13	(59.1)	
Tumor grade						p = 0.707
1	82 (30.5)	36	(43.9)	46	(56.1)	
2	106 (39.5)	41	(38.7)	65	(61.3)	
3	81 (30.0)	31	(38.3)	50	(59.1)	
Surgical margin						p = 0.372
Negative	257 (93.7)	105	(40.9)	152	(59.1)	
Positive	12 (6.3)	3	(25.0)	9	(75.0)	
Chemotherapy						p = 0.922
No	241 (89.6)	97	(40.2)	144	(59.8)	
Yes	28 (10.4)	11	(39.3)	17	(60.7)	
Period of diagnosis						p < 0.001
1985-1995	51 (19.0)	32	(62.7)	19	(37.3))	
1996-2000	94 (35.0)	43	(45.7)	51	(54.3)	
2001-2005	124 (46.0)	33	(26.6)	91	(73.4)	
Age at diagnosis	269 (100)	Mean = 66 SD = 5		Mean = 67 SD = 7		p = 0.41

Overall 5 year and 10 year survival were 71.3% and 40.0%, respectively, Figure 1 and 2. According to tumor location, the survival rates were 73.6% and 47.0% for the renal pelvis and 67.8% and 32.3% for the ureter, respectively (log rank: p = 0.027). In univariate analysis, survival decreased with advanced pT stage (p < 0,001), high grade (p < 0.001), nodal metastasis (p < 0.001), positive surgical margin (p = 0.022), ureteral tumor location (p = 0.029), chemotherapy (p < 0.001) and period of diagnosis (p = 0.002), Table 2.

Similarly, in addition to advanced pT stage (p < 0.001), grade (p < 0.001), nodal metastasis (p = 0.005) and period of diagnosis (p < 0.001) as well as ureteral tumor location (p = 0.003) were independent prognostic factor in multivariate analysis, Table 3.

The overall prognosis of UTUC improved over time. The survival curve was significantly more favorable for the last period (2001-2005) than for the first (1985-1995) (p = 0.002).

Discussion

Treatment of urothelial tumors of the upper tract has traditionally been radical nephroureterectomy with bladder cuff excision. Evidence suggests that causes of upper tract urothelial carcinoma are similar to those of bladder urothelial carcinoma. Environmental factors, including cigarette smoking and exposure to industrial chemicals such as those used in the rubber and textile industries, are particularly important.

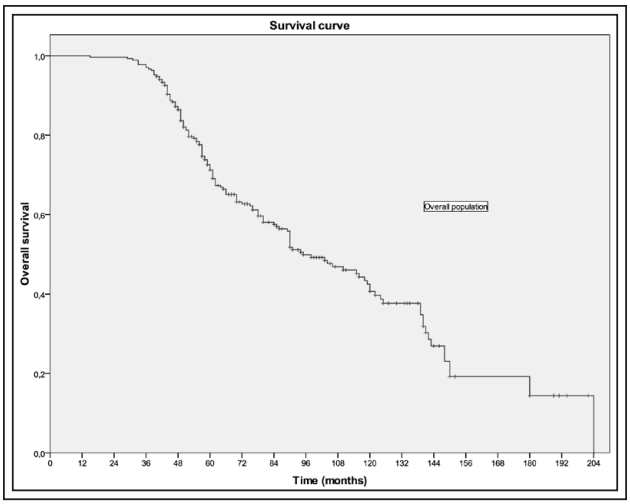

Figure 1. Survival curve - patients with upper urinary tract carcinoma (n = 269, Kaplan-Meier method).

The limited number of patients with upper urinary tract urothelial carcinoma makes organization of randomized, prospective trials rare. Consequently, outcome information has to be mainly obtained from retrospective observations. While few unbiased studies included more than 100 patients, most of them reported that outcome following nephroureterectomy was dependent on T-stage, nodal invasion and grade, with stage being the single most important determinant.[3-6,13]

Two studies (with 84 and 72 patients respectively), suggest that ureteral tumors are associated with a poorer prognosis than renal pelvis tumors.[9,10] However more recent studies reported conflicting results on the same issue. For example, Van Der Poel et al noted in their series of 149 patients that distal ureteral tumors show significantly better survival than proximal ureteral or renal pelvis tumors.[14] Meanwhile, Catto et al and others reported no prognostic difference with respect to tumor location in upper urinary tract of 146 patients[11,12,15] and 1250 patients.[13]

We investigated whether the anatomical location had real prognostic value for UTUC. Our results clearly indicate that tumor location is an independent prognostic factor. Renal pelvis tumors were associated with a higher survival rate than ureteral tumors in both univariate and multivariate analyses.

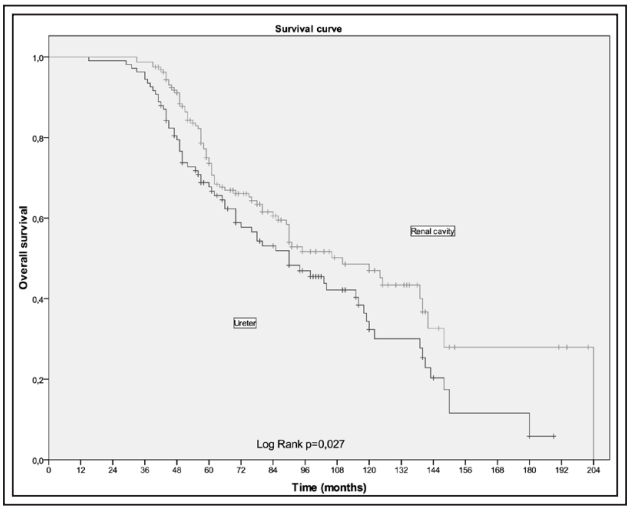

Figure 2. Survival curve by tumor location.

TABLE 2. **Cox univariate analysis**

Variables	HR	CI 95%	p value
Location			
Renal cavity	1		0.029
Ureter	1.443	1.03-2.00	
Gender			
Female	1		0.475
Male	1.148	0.79-1.68	
Age (years)			
≤ 67	1		0.584
> 67	1.099	0.78-1.54	
pT stage			
pTa	1		< 0.001
pT1	2.144	0.835-5.490	
pT2	2.296	0.91-5.82	
pT3	9.057	3.62-22.05	
pT4	17.396	6.51-46.230	
pN Stage			
pN0	1		< 0.001
pN+	3.16	2.01-4.98	
Grade			
G1	1		< 0.001
G2	2.65	1.56-4.50	
G3	5.45	3.22-9.20	
Margin			
Negative	1		0.022
Positive	2.46	1.14-5.33	
Chemotherapy			
No	1		< 0.001
Yes	4.127	2.49-6.84	
Period of diagnosis			
2001-2005	1		0.002
1996-2000	1.20	0.76-1.89	
1985-1995	2.17	1.34-3.52	

TABLE 3. **Multivariate analysis of overall survival**

	p value	HR	95% CI	
			Inferior born	Superior born
Period of diagnosis				
2001-2005	< 0.001	1		
1996-2000		1.338	0.841	2.127
1985-1995		2.925	1.779	4.809
pT stage				
pTa	< 0.001	1		
pT1		2.311	0.884	6.041
pT2		2.412	0.905	6.220
pT3		6.004	2.336	15.432
pT4		10.974	3.954	30.454
pN stage				
pN0	0.005	1		
pN+		2.025	1.234	3.324
Grade				
G1	< 0.001	1		
G2		2.173	1.258	3.754
G3		3.157	1.789	5.573
Location				
Renal cavity	0.003	1		
Ureter		1.663	1.183	2.337

Patients with ureteral tumor were more likely to have muscle invasive carcinoma whereas those with renal pelvis tumor were more likely to have non-muscle invasive UTUC. These findings may be due to the fact that there is a thinner adventitial wall for the ureteral tumors to invade. When these and other variables were considered in multivariable models, tumor location represented a statistically significant independent prognostic factor. Thus, the worse prognosis of ureteral tumors is not completely explained by the greater frequency of invasion of the muscular layer for these tumors.

The overall prognosis of UTUC improved over time. The period of diagnosis represented a statistically significant independent prognostic factor. The real cause of this better prognosis over time has to be studied better using what we call in public health an age-period-cohort effect studies.

To date, all studies of tumor location as a possible prognostic factor have been retrospective and mostly based on a short follow up with no fixed date of point.

Some limitations to the current study need to be mentioned. This is inherent problems of retrospective studies. First, it was not completely possible to guarantee that biases which usually arise in retrospective studies could all be removed. Data were collected by chart review at participating institutions, thus introducing variability in the interpretation of study variables. However, all these charts were reviewed by only one investigator, on the basis of a predetermined registration grid, and the few cases for which the information available from the charts was not sufficiently detailed were discussed within the restricted group responsible for this study. This should have limited interobserver variability. Furthermore, given the important potential of recruitment of the above mentioned institutions, it was possible to limit to only two units the number of hospitals considered, which also limited variability in case management and quality of medical files. Of course, some residual variability may still remain, regarding case management, surveillance procedures and patient follow up. In this respect, it should also be mentioned that pathology specimens were not subjected to a centralized review. Nevertheless, pathological misclassification for the types of tumors studied seems improbable. Finally we have to mention that this study reports an overall survival and not a cancer specific survival.

Conclusion

We demonstrated that tumor location and diagnostic period are an independent prognostic factor for upper tract transitional cell carcinoma. Patients with ureteral tumor were more likely to have muscle invasive carcinoma; those with renal pelvis tumor were more likely to have non-muscle invasive UTUC. However, as demonstrated by multivariate analysis, invasion of the muscular layer did not completely explain the difference in prognosis between the two tumor locations.

Therefore, we recommend to adjust the follow up strategy for patients treated for ureteral tumors, in order to improve early detection and subsequent treatment of tumor relapse or metastasis, hopefully leading to an enhanced prognosis and to realize a more robust age-period-cohort studies in order to prove the effect of period of diagnosis on prognosis. □

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