ORIGINAL ARTICLE

Primary Urothelial Carcinoma of the Ureter: 11-Year Experience in Taipei Veterans General Hospital

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Background: Urothelial carcinoma of the upper urinary tract is relatively rare, occurring in 5% of all urothelial tumors. Ureteral urothelial carcinoma is even less common than that of the renal pelvis, accounting for about 25% of all upper urinary tract tumors. The aim of this study was to evaluate the clinical behavior, survival, recurrence and prognostic information of primary ureteral urothelial carcinoma from our 11 years of experience at the Taipei Veterans General Hospital.

Methods: We retrospectively reviewed 111 patients with ureteral urothelial carcinoma who had been treated in our hospital between January 1993 and December 2003. Tumor staging was according to the 2002 AJCC TNM classification and stage groupings. Patients with stage 0a and stage 0is were categorized as stage 0a/is, and patients with pathologic T stage pTa and pTis were categorized as pTa/is for statistical analysis. The Kaplan-Meier method was used for survival analysis.

Results: There were 69 males and 42 females, with a mean age of 70.5 ± 9.4 years at diagnosis. Of the 111 patients, 5 presented with stage 0a/is, 38 with stage I, 23 with stage II, 21 with stage III, and 24 with stage IV. Nephroureterectomy with bladder cuff excision was performed in 78 patients, 12 patients received segmental resection of the ureter, 4 received ureteroscopic laser coagulation, and 17 underwent chemotherapy or radiotherapy or both. Tumors were located on the left side in 53 patients, on the right in 53, and bilaterally in 5. The most frequent initial presenting symptom was gross hematuria (65%). The mean postoperative follow-up period was 49.3 months. Disease recurrence in the nephroureterectomy group occurred in 36 patients (46.2%), with 17 (21.8%) at the urinary bladder, 2 (2.6%) at the retroperitoneum, 1 (1.3%) at the contralateral ureter, 6 (7.7%) with distant metastases to the lung, bone, distant lymph nodes or liver, and 10 (12.8%) at multiple sites. The 5-year cancer-specific survival rate was 100% for pTa/is, 95.2% for pT1, 69.4% for pT2, and 43.8% for pT3. All 3 pT4 cases died of cancer in a median of 12 months. Significant prognostic factors for cancer-specific survival by univariate analysis were pT (p = 0.00001), stage (p = 0.00001), type of treatment (p = 0.00001) and grade (p = 0.0001). On multivariate analysis, only stage (p = 0.0001) and grade (p = 0.014) were significant for cancer-specific and overall survival. Stage (p = 0.0001), pT (p =0.0001) and grade (p = 0.026) were also significant prognostic factors of recurrence in multivariate analysis.

Conclusion: Our experience showed that patients with pTa/is and pT1 tumors treated with radical surgery have excellent prognoses. Tumor stage and grade are the only significant prognostic factors for both cancer-specific and overall survival. [*J Chin Med Assoc* 2005;68(11):522–530]

Key Words: carcinoma, prognosis, transitional cell, ureteral neoplasms

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Introduction

Urothelial carcinoma of the upper urinary tract is relatively rare, occurring in 5% of all urothelial tumors.[1] Ureteral carcinoma is even less common than that of the renal pelvis, accounting for about 25% of all upper urinary tract tumors.[2,3] An unusually high incidence of upper urinary tract urothelial carcinoma has been reported in Taiwan, with the incidence of renal pelvis transitional cell carcinoma varying from 15.4% to 83.3%.[4] Many publications have provided the survival, recurrence and prognostic factors of urothelial carcinoma of the ureter together with that of the renal pelvis. However, different behaviors of urothelial carcinoma of the renal pelvis and ureter have been reported in terms of tumor invasion and prognosis.[5] Ureteral urothelial carcinoma is associated with a higher local or distant recurrence rate than urothelial carcinoma of the renal pelvis. The aim of this study was to evaluate the clinical behavior, survival, recurrence and prognostic information of primary ureteral urothelial carcinoma from our 11 years of experience at the Taipei Veterans General Hospital

Methods

We retrospectively reviewed the medical records of 135 consecutive patients who had been treated at our institution for urothelial carcinoma of the ureter between January 1993 and December 2003. After exclusion for synchronous tumor involvement of the renal pelvis and those without complete medical documents, 111 patients were included for analysis. Demographic data, presenting symptoms, previous history of urinary bladder or upper urinary tract urothelial carcinoma, tumor location, treatment modality, time to recurrence, and outcome were recorded.

The pathologic stage of the tumor (pT) was assessed according to the 2002 American Joint Committee on Cancer TNM classification.[6] Patients were also stratified into stage 0a or stage 0is, and stage I, II, III, or IV according to the stage groupings of the classification system. Patients with stage 0a or stage 0is were categorized as stage 0a/is, and patients with pTa or pTis were categorized as pTa/is for statistical analysis because patients with Ta and Tis were few and their disease showed similar clinical behaviors. Tumor grade was assessed according to the grading system established by the World Health Organization.[7]

Time to recurrence was defined as the period from the date of diagnosis to the time when recurrence was demonstrated. Survival time was defined as the time from the initial date of presentation to the end point, including death or censoring.

Traditional prognostic factors that were analyzed included age at diagnosis (older or younger than the patients' mean age), gender (male, female), presenting symptoms (gross hematuria, asymptomatic, lower abdominal or flank pain), pT stage (pTa/is, pT1–4), stage groupings (stage 0a/is, stage I–IV), grade (1, 2, 3), laterality (left, right, bilateral), tumor location (upper, middle, lower third of ureter, multiple sites), and type of treatment (nephroureterectomy with bladder cuff excision, nephron-sparing surgery, other nonsurgical treatment).

Univariate and multivariate analyses were performed using the Kaplan-Meier method with the log-rank test and Cox proportional hazards regression model to evaluate each prognostic factor with respect to survival and recurrence. Differences were considered to be statistically significant when p was less than 0.05.

Results

There were 69 men and 42 women (M:F, 1.6:1), with a mean age at diagnosis of 70.5 ± 9.4 years (range, 38–91 years). Patients were followed up for a mean of 49.3 months (range, 1–136 months). Histopathologic reports were available for 105 of the 111 patients; all were urothelial carcinomas.

The initial presenting symptoms included gross hematuria (72/111, 64.9%), incidental findings on physical examination (21/111, 18.9%) and lower abdominal or flank pain (18/111, 16.2%). Ureteral tumors were located on the left side in 53 (47.7%) patients, on the right in 53 (47.7%), and bilaterally in 5 (4.5%). The tumors were in the upper third of the ureter in 24 (21.6%) patients, in the middle third in 37 (33.3%), in the lower third in 36 (32.4%), and at multiple sites in 14 (12.6%). A previous history of urothelial carcinoma of the urinary bladder or contralateral ureter was present in 7 and 5 patients, respectively. Concomitant bladder urothelial carcinoma was seen in 12 patients when the ureteral tumor was diagnosed. Among these 12 patients with concomitant bladder cancer at the time of diagnosis and the 7 with a previous history of bladder cancer, 7 had recurrence at the urinary bladder during follow-up and were excluded from the group with subsequent bladder recurrence due to the high recurrence rate of bladder cancer. Tumor recurrence in the urinary bladder occurred in 30 of the 111 patients (27.0%) in

a median of 9 months (mean, 22.2 months; range, 1–100 months). The stage and grade of ureteral urothelial carcinoma in the 111 patients are shown in Table 1.

Of the 111 patients, 78 underwent nephroureterectomy with bladder cuff excision. The pT stage and grade in these 78 patients are shown in Table 2. Five patients had grade 1 lesions, 2 of which were pTa/is and 3 were pT1 tumors. Grade 2 lesions were present in 41 patients, 17 of which were pT2–pT4. Grade 3 lesions were observed in 32 patients, 30 of which were pT2–pT4. The disease recurred in 36 (46.2%) patients in a median of 10.5 months (range, 1–100 months). The initial recurrences occurred in the urinary bladder in 20 cases, locally in the retroperitoneal tumor bed or lymph nodes in 5, in the contralateral ureter in 3, and in distant metastases in 8. In terms of the total number of recurrence episodes, 23 patients had recurrences in the bladder, 7 had recurrences locally, 3 had recurrences in the contralateral ureter, and 15 in distant organs such as bone (3), lungs (3), distant lymph nodes (3) and at multiple sites (6) including the liver.

In patients with a solitary kidney, and in those who had a high risk of radical operation and distal ureteral tumors, nephron-sparing procedures including segmental resection of the ureter and laser coagulation of the tumor under ureteroscopy were performed in 12 and 4 patients, respectively. Of the 12 patients who underwent segmental resection of the ureter, 5 presented with grade 2 tumors while the others had grade 3 tumors; 7 (58.3%) developed recurrence in the remaining ipsilateral ureter and 2 had distant metastases. Disease recurrence occurred in 8 of the 12 patients (66.7%) in a median of 22.5 months (range, 2–57 months).

In the remaining 17 patients with advanced-stage disease or severe comorbidity or who refused surgical intervention, systemic chemotherapy, radiotherapy or both was administered. Eleven (64.7%) died of the cancer in a median of 7 months (range, 1–25 months), and 4 (23.5%) died of non-cancer causes. Nine of 21 patients with pT3 tumor had adjuvant chemotherapy, most with the MVAC (methotrexate, vinblastine, doxorubicin, cisplatin) regimen. Adjuvant radiotherapy was performed in 4 of the 21 pT3 patients. However, 8 of the 21 pT3 and all 3 of the pT4 patients did not receive a complete course of adjuvant therapy after the radical surgery due to severe side effects or refusal to receive therapy.

Table 1. Stage and grade of ureteral urothelial carcinoma in 111 patients

Stage*	Grade, *n* (%)				Total, *n* (%)
	1	2	3	Unknown	
0a/is†	2 (1.8)	3 (2.7)	0	0	5 (4.5)
I	3 (2.7)	27 (24.3)	6 (5.4)	2 (1.8)	38 (34.2)
II	0	12 (10.8)	11 (9.9)	0	23 (20.7)
III	0	4 (3.6)	17 (15.3)	0	21 (18.9)
IV	0	5 (4.5)	15 (13.5)	4 (3.6)	24 (21.6)
Total, *n* (%)	5 (4.5)	51 (45.9)	49 (44.1)	6 (5.4)	111 (100)

*Stage groupings according to the American Joint Committee on Cancer TNM classification, 2002; †Stage 0a and stage 0is are combined and categorized as stage 0a/is.

Table 2. Pathologic stage (pT) and grade of 78 patients treated with nephroureterectomy

Stage*	Grade, *n* (%)			Total, *n* (%)
	1	2	3	
pTa/is†	2 (2.6)	2 (2.6)	0	4 (5.1)
pT1	3 (3.8)	22 (28.2)	2 (2.6)	27 (34.6)
pT2	0	12 (15.4)	11 (14.1)	23 (29.5)
pT3	0	4 (5.1)	17 (21.8)	21 (26.9)
pT4	0	1 (1.3)	2 (2.6)	3 (3.8)
Total, *n* (%)	5 (6.4)	41 (52.6)	32 (41.0)	78 (100)

*Pathologic stage groupings according to the American Joint Committee on Cancer TNM classification, 2002; †pTa and pTis are combined and categorized as pTa/is.

Table 3. Five-year recurrence-free rate by pathologic stage (pT)*

Stage	Median	95% CI	5-year recurrence-free rate (%)
pTa/is	37.00	–	50.0
pT1	–	–	70.4
pT2	50.00	4.05, 95.95	49.4
pT3	15.00	0.99, 29.01	27.7
pT4	10.00	–	0

*p = 0.0214. CI = confidence interval.

The recurrence-free survival at 5 years for each of the pT stages is shown in Table 3. In 4 patients with pTa/is tumors, 2 had recurrences in the urinary bladder at 4 and 37 months postoperatively. The recurrence-free survival curves of patients at different pT stages are illustrated in Figure 1. Two of the 3 pT4 patients had recurrences 10 and 11 months after diagnosis and 1 died of cancer 9 months after disease onset without disease relapse. In the univariate analysis, significant prognostic factors for recurrence were stage groupings (p = 0.00001), tumor grade (p = 0.0021) and type of treatment (p = 0.00001) (Table 4). In the multivariate analysis, the only significant predictors were pT stage (p = 0.0001), stage groupings (p = 0.0001) and tumor grade (p = 0.026) (Table 5).

The overall 5-year survival rate was 46.4%. The 1-, 3-, 5- and 10-year cancer-specific survival rates in the nephroureterectomy group were 92.7%, 76.2%, 69.3% and 66.3%, respectively. The 5-year cancer-specific survival rates and 5-year overall survival rates according to pT stage are shown in Table 6. The cancer-specific survival curves of patients at different pT stages are illustrated in Figure 2. All 3 pT4 patients died of disease within 12 months. Prognostic factors for cancer-specific survival by univariate analysis were pT stage (p = 0.00001), stage groupings (p = 0.00001), type of treatment (p = 0.00001) and tumor grade (p = 0.0001) (Table 7). The only factors significant for cancer-specific survival on multivariate analysis were stage groupings (p = 0.0001) and grade (p = 0.014) (Table 5).

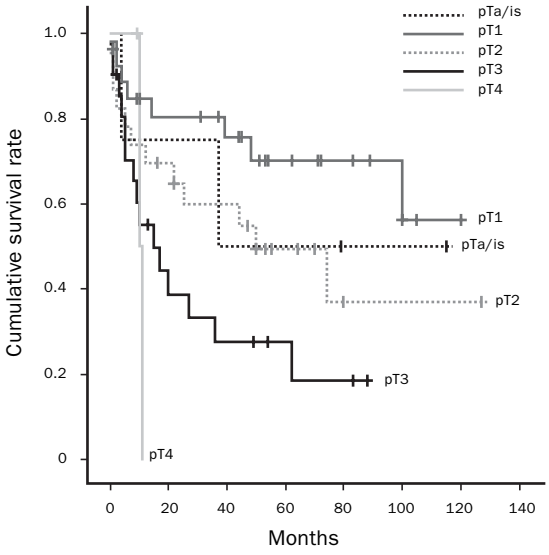

Figure 1. Recurrence-free survival curves by pathologic stage (pT).

Discussion

Urothelial carcinoma of the upper urinary tract is relatively rare, comprising 5% of all urothelial tumors.[1] Ureteral cancer is even less common than that of the renal pelvis by a ratio of 1:3 to 1:4 and is reported to exhibit significantly higher local or distant failure rates.[4,5] This study focused on urothelial carcinoma of the ureter to provide survival and recurrence information.

Among the 5 (6.4%) patients with grade 1 lesions in the nephroureterectomy group, none were staged beyond pT1. Grade 2 lesions occurred in 41 (52.6%) patients and 17 (41.5%) were pT2–pT4 tumors. Thirty of the 32 cases (93.8%) with grade 3 tumors were also staged pT2–pT4. Only 4 (5.1%) patients were pTa/is. In a study conducted by Babaian and Johnson,[8] 3 of the 31 patients (9.8%) with primary ureteral carcinoma had grade 1 tumors, 16 (51.6%) had grade 2, and 12 (38.7%) had grade 3 tumors. In a study by Heney et al[9] of 60 patients with ureteral transitional cell carcinoma, 9 (15%) patients had grade 1 tumors and 17 (28.3%) had stage 0 tumors. In a large series of 252 patients with upper urinary tract transitional cell carcinoma, 15.4% of patients presented with pTa/is and 9.3% were grade 1 tumors.[3] Compared with these series, our series demonstrated a relatively lower percentage of grade 1 and pTa/is tumors. In addition, we found a correlation between grade and pT stage, i.e. that tumors at a lower stage tended to be lower grade tumors while those at a higher stage tended to be higher grade tumors (Table 2), as has been identified in most of the previous series.

Table 4. Univariate analysis of potential prognostic factors for recurrence

Variable	Mean ± SE	Median	%	*p*
Age (yr)				0.7262
< 70.5	53.65 ± 7.96	23.00	39.62	
> 70.5	53.62 ± 7.57	40.00	47.46	
Gender				0.9562
Male	54.44 ± 7.26	27.00	43.48	
Female	49.97 ± 7.47	36.00	44.19	
Symptoms				0.2782
Hematuria	55.43 ± 7.12	36.00	45.21	
Asymptomatic	62.85 ± 11.43	40.00	47.62	
Pain	36.47 ± 11.31	4.00	33.33	
pT				0.2727
pTa/is	55.80 ± 22.21	37.00	40.00	
pT1	59.29 ± 8.09	40.00	49.02	
pT2	66.24 ± 12.05	74.00	50.00	
pT3	26.95 ± 6.42	15.00	24.00	
pT4	26.57 ± 14.92	11.00	57.14	
Stage groupings				0.00001
0a/is	55.80 ± 22.21	37.00	40.00	
I	72.90 ± 8.79	100.00	58.97	
II	69.12 ± 12.22	74.00	52.17	
III	29.97 ± 7.07	15.00	23.81	
IV	14.82 ± 6.33	–	29.17	
Grade				0.0021
1	91.40 ± 12.16	–	80.00	
2	68.40 ± 8.45	74.00	52.94	
3	28.36 ± 4.87	15.00	30.00	
Laterality				0.8351
Left	55.88 ± 8.09	23.00	41.51	
Right	53.49 ± 7.62	39.00	46.30	
Bilateral	18.90 ± 6.63	22.00	40.00	
Tumor location				0.1585
Upper 3rd of ureter	62.93 ± 11.41	62.00	50.00	
Middle 3rd of ureter	34.66 ± 7.43	14.00	36.84	
Lower 3rd of ureter	69.39 ± 10.01	40.00	52.78	
Multiple	36.96 ± 12.06	20.00	28.57	
Type of treatment				0.00001
Radical	65.97 ± 6.68	50.00	50.00	
Nephron-sparing	34.50 ± 7.98	23.00	33.33	
Other	7.10 ± 2.83	–	27.78	

pT = pathologic stage; SE = standard error.

Table 5. Multivariate analysis of potential prognostic factors for recurrence and cancer-specific survival

Variable	Recurrence			Cancer-specific survival		
	p	RR	95% CI for RR	*p*	RR	95% CI for RR
Age	0.299	0.985	0.957, 1.014	0.655	1.009	0.970, 1.051
Gender	0.764	0.919	0.531, 1.592	0.696	1.196	0.488, 2.932
Symptoms	0.764	1.057	0.737, 1.515	0.973	1.009	0.608, 1.673
pT	0.0001	0.399	0.264, 0.602	0.103	1.749	0.892, 3.428
Stage groupings	0.0001	2.750	1.863, 4.058	0.0001	2.789	1.828, 4.256
Grade	0.026	1.880	1.079, 3.276	0.014	2.936	1.247, 6.913
Laterality	0.837	0.951	0.586, 1.542	0.657	1.187	0.557, 2.526
Tumor location	0.475	1.112	0.831, 1.486	0.708	1.095	0.681, 1.761
Type of treatment	0.584	1.171	0.665, 2.065	0.059	0.283	0.076, 1.051

CI = confidence interval; pT = pathologic stage; RR = risk ratio.

Table 6. Five-year cancer-specific survival and overall survival by pathologic stage (pT)

Stage	5-year cancer-specific survival			5-year overall survival rate		
	Median	95% CI	Survival rate (%)	Median	95% CI	Survival rate (%)
pTa/is	–	–	100	–	–	100
pT1	–	–	95.2	–	–	66.4
pT2	–	–	69.4	–	–	61.5
pT3	37	2, 72	43.8	37	21, 53	31.6
pT4	12	7, 17	0	12	7, 17	0
p		0.00001			0.00001	

CI = confidence interval.

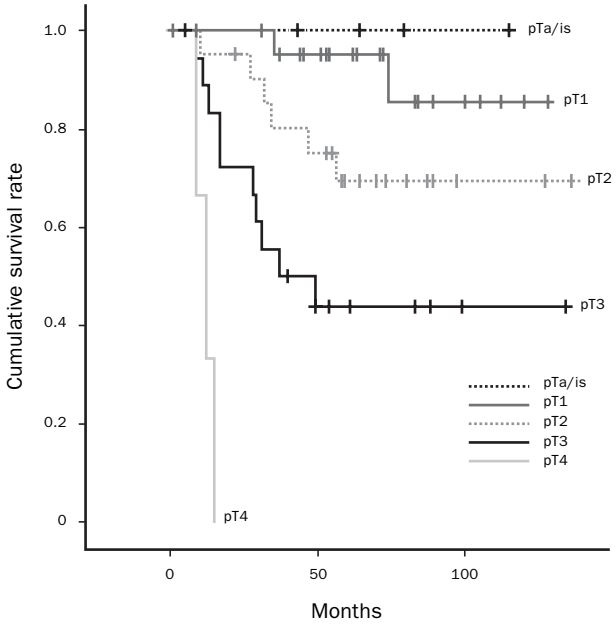

Figure 2. Cancer-specific survival curves by pathologic stage (pT).

Nephroureterectomy with bladder cuff removal remained the gold standard treatment for upper urinary tract urothelial carcinoma, because of the high recurrence rate in the remaining distal ureter of 16–58% and the multicentricity on the same side (15–44%).[3,10,11] Seventy-eight of our patients underwent this radical surgery and achieved a 5-year recurrence-free survival of 50% for pTa/is, 70.4% for pT1, 49.4% for pT2 and 27.7% for pT3. The low 5-year recurrence-free rate for pTa/is is attributable to the small case number of this group. The 5-year cancer-specific survival rates were 100% for pTa/is, 95.2% for pT1, 69.4% for pT2 and 43.8% for pT3. The 5-year survival rate for each stage of the Heney et al[9] series was 100% for stage 0, 95% for stage A, 82% for stage B, 29% for stage C and 0% for stage D. Mills and Vaughan[12] reported their experience with 53 cases of carcinoma of the ureter and showed the 5-year overall survival rate for each stage to be 100% for stage 0, 80% for stage A, 50% for stage B, 33.3% for stage C and 6.7% for stage D. Many previous studies on transitional cell carcinoma of both the renal pelvis and ureter were also

Table 7. Univariate analysis of potential prognostic factors for cancer-specific survival

Variable	Mean ± SE	Median	%	*p*
Age (yr)				0.1824
< 70.5	102 ± 8	–	72.92	
> 70.5	86 ± 8	–	63.64	
Gender				0.5968
Male	92 ± 8	–	66.13	
Female	93 ± 8	–	70.73	
Symptoms				0.0945
Hematuria	96 ± 7	–	69.23	
Asymptomatic	99 ± 9	–	80.00	
Pain	58 ± 11	47	50.00	
pT				0.00001
pTa/is	–	–	100	
pT1	101 ± 7	–	78.26	
pT2	106 ± 11	–	72.73	
pT3	71 ± 13	37	52.17	
pT4	16 ± 9	9	14.29	
Stage groupings				0.00001
0a/is	–	–	100	
I	121 ± 5	–	94.12	
II	109 ± 10	–	76.19	
III	77 ± 13	49	57.14	
IV	26 ± 7	15	22.73	
Grade				0.0001
1	–	–	100	
2	118 ± 6	–	84.09	
3	73 ± 9	37	54.17	
Laterality				0.9116
Left	87 ± 8	–	63.83	
Right	97 ± 8	–	70.59	
Bilateral	100 ± 20	–	80.00	
Tumor location				0.0758
Upper 3rd of ureter	102 ± 11	–	78.26	
Middle 3rd of ureter	73 ± 11	74	53.13	
Lower 3rd of ureter	101 ± 8	–	77.14	
Multiple	77 ± 16	–	61.54	
Type of treatment				0.00001
Radical	101 ± 6	–	70.42	
Nephron-sparing	65 ± 10	–	93.33	
Other	33 ± 10	10	35.29	

pT = pathologic stage; SE = standard error.

available for comparison of the survival and recurrence rates.[3,5,13,14] The 5-year recurrence-free rate reported by Hall et al[3] was 73% for Ta/cis, 76% for pT1, 59% for pT2, and 40% for pT3. The 5-year disease-specific survival rate by tumor stage in several studies range from 70% to 100% for pTa/is, 91% to 100% for pT1, 73% to 88% for pT2, and 41% to 61.9% for pT3.[3,13,14] However, the calculation of recurrent survival rate did not take recurrence in the urinary bladder into account. In a study conducted in southern Taiwan by Lee et al[15] in 1996, the 5-year survival rate was 100% in patients with stages 0 and A upper urinary tract carcinoma, and 82%, 67% and 33%, respectively, for stage B, C and D lesions.

Contrary to other experience, the present study showed similar or lower survival rates by stage for 2 reasons. Firstly, ureteral urothelial carcinoma has been reported to be more invasive, with higher local and distant failure rates, than renal pelvis carcinoma. While our patients all had carcinomas of the ureter, most other studies involved tumors of both the ureter and renal pelvis. Secondly, there was a lower rate of completion of adjuvant systemic chemotherapy or radiotherapy in our patients. Eleven of the 24 patients (45.8%) with pT3 or pT4 tumors did not receive a complete course of adjuvant systemic chemotherapy or radiotherapy due to either severe side effects of the therapy or patient refusal. Recurrence in the contralateral ureter following radical surgery occurred in 3 patients in the current study (3.8%), as compared with 2.5% and 2.9% in the studies of Krogh et al[10] and Charbit et al,[16] respectively.

A high incidence of ipsilateral recurrence (23–54%) after partial ureterectomy has been reported,[11] and this was seen in our study in which 7 of the 12 patients (58.3%) who were treated with segmental resection of the ureter had ipsilateral tumor recurrence in the remaining urothelium. Zoretic and Gonzales,[17] however, reported that only 1 of their 16 patients (6.3%) who underwent segmental resection of the ureter had ipsilateral tumor recurrence in the renal pelvis (after a mean follow-up of 56 months). They concluded that the indications for segmental resection should be: (1) low-grade, low-stage transitional cell carcinoma; (2) solitary kidney with a ureteral tumor; (3) bilateral synchronous ureteral tumors; (4) poor renal function; and (5) high-risk patients. However, there are arguments against conservative surgery regarding the difficulty in excluding coexisting tumors on the same side and in determining stage-1 and grade-1 tumors by intraoperative biopsy.[18]

Tumor grade and stage have traditionally been reported as being major prognostic factors in patients with upper urinary tract transitional cell carcinoma.[2,3] Some series have reported that age,[3] gender[19] and location in the renal pelvis[5] are negative prognostic factors, but these have not been confirmed.[11] Based on our findings, the prognostic factors for cancer-specific survival by univariate analysis were pT, stage groupings, type of treatment and tumor grade. The only factors significant for cancer-specific survival on multivariate analysis were stage groupings and grade. Significant prognostic factors of recurrence, by univariate analysis, were stage groupings, tumor grade and type of treatment. Only stage groupings, grade and pT were significant predictors of tumor recurrence by multivariate analysis. Our findings corresponded with previous reports on traditional prognostic factors.

From our 11-year experience in treating 111 patients with primary ureteral urothelial carcinoma, we conclude that pTa/is and pT1 stage tumors treated with radical surgery have an excellent prognosis. Tumor stage and grade are the only significant prognostic factors for both cancer-specific and overall survivals.

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