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Prognostic Value of the Anatomical Location of Upper Urinary Tract Urothelial Carcinoma

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ABSTRACT

INTRODUCTION: The prognostic significance of pyelum versus ureteral urothelial carcinomas is controversial. The objective of the study was to evaluate the prognostic value of the anatomical location of transitional cell carcinoma (TCC) in the upper urinary tract.

METHODS: We retrospectively analyzed data from 51 patients with upper urinary tract TCC (UTTCC) from a single institute. Patients were treated surgically between 1995 and 2007. Tumor location and other clinicopathological variables were evaluated regarding cancer recurrence and survival. Recurrence and cancer-specific survival probabilities following tumor resection were analyzed using the Kaplan-Meier method and log rank test. Univariate and multivariate analyses were performed using Cox proportional hazards regression model.

RESULTS: Mean patient age was 69.5 years (range, 25-87 years); median follow-up was 43.8 months (range, 37-142 months). TCCs were in the pyeleum or the calyx (n = 33), the ureter (n = 9), and in both locations (n = 9). There was no significant difference between the number of patients with transmural tumor growth (pT3-pT4) in the proximal ureter or pyelum (41%) when compared with distally located tumors (18.2 %) (P = .30). The majority of the patients (67%) had pT2 or pT3 primary tumors. None of the patients with Ta/cis, T1, or T2 primary tumors had nodal or distant metastatic disease, either initially or during follow-up. Median overall and disease-specific survivals were 37.9 months and 40.1 months, respectively. The repartition of tumor stage and grade was similar in the pyelum pelvis and the distal ureter (P = .06 and P = .46, respectively). The tumor location did not significantly affect the 3-year bladder recurrence rate (P = 0.83). The disease-specific survival rates were 88.2% for patients with tumors in both the pyelum and distal ureter locations. There was no significant impact of UTTCC location on 3-year survival.

CONCLUSION: Tumor location does not appear to be an independent prognostic factor for patients with UTTCC. Patients with pyelum or distal ureter TCC with the same tumor grade and stage had the same risk of bladder cancer recurrence and survival. We recommend the same surveillance protocol regardless of the tumor location.

KEYWORDS: Upper urinary tract; Transitional cell carcinoma; Prognosis; Recurrence; Survival rate

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Abbreviations and Acronyms

CT, computed tomography
TCC, transitional cell carcinoma
UTTCC, upper urinary tract transitional cell carcinoma

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INTRODUCTION

Upper urinary tract transitional cell carcinoma (UTTCC) is a relatively uncommon disease, accounting for approximately 5% to 10% of all renal tumors and 5% to 6% of all urothelial tumors [1]. Tumors of the pyelum pelvis are 3 to 4 times more common than ureteral transitional cell carcinoma (TCC) [2].

Potential prognostic factors and recurrence patterns after surgical treatment have been systematically discussed for this disease in many studies [3-5]. Widely accepted risk factors consist of the pathological stage of the primary tumor, tumor grade, lymph node status, and the presence of distant metastases [1,5-9]. However, several others have been proposed with some conflicting results. The location of the primary tumor (pyelum vs ureter) represents one of these controversial risk factors.

Because prognosis is highly variable, UTTCC should be considered a heterogeneous disease based on different tumor locations (pelvis vs ureter) and invasion patterns (renal parenchyma, peripelvic fat and periureteral fat) [10]. In the present study, we investigated whether the anatomical location of the tumor has prognostic value for UTTCC.

METHODS

We retrospectively reviewed the radiology and pathology medical records of all patients treated surgically for UTTCC between February 1995 and June 2007 at our department.

Patient Database

Exclusion criteria were a history of upper urinary tract urothelial tumor or urothelial tumor combined with another malignancy, distant metastasis at diagnosis, and UTTCC with concomitant invasive bladder TCC. Tumors that were located in the ureteral ostium and resectable from within the bladder were excluded from the analysis and considered as bladder tumors.

We determined patient and tumor characteristics, presentation, treatment, and the impact of traditional prognostic factors and tumor location on recurrence and survival. Tumor location was documented from radiological and endoscopic studies and from the specimen. Location was categorized as: (1) renal calyx, (2) renal pyelum (Figure 1), (3) proximal ureter (from ureteropyelum junction down to the ureter at the upper level of the sacrum), (4) midureter (from the upper level of the sacrum down to the crossing of the common iliac artery) (Figure 2), or (5) distal ureter (intrapelvic) (Figure 3). Bladder tumors were considered concomitant when diagnoses were made within 3 months prior or after the UTTCC diagnoses.

Surgical Treatment and Follow-up Examination

Standard treatment for UTTCC was radical nephroureterectomy, including removal of the ipsilateral ureter and bladder cuff at its distal extent. Dissection of regional lymph nodes around the ipsilateral great vessel was performed in patients who had enlarged nodes on a preoperative computed tomogram (CT) or in patients for whom there was suspicion of enlarged nodes on intraoperative examination. Extended lymphadenectomy was not routinely performed.

The pathologic stage and grade distributions of the tumors were available for all patients according to the TNM classification 2002 system. All tumors were graded according to the World Health Organization (WHO) grading for transitional cell carcinoma.

After surgery, a strict follow-up protocol was applied to all patients. Routine blood tests, cystoscopy, and ureteroscopy were performed every 3 months for the first 2 years, every 6 months for the subsequent 3 years, and then yearly. Chest x-ray or CT scan and upper tract imaging studies (excretory urogram or CT) were obtained yearly during follow-up. Bone scans were performed if there was suspicion of bone metastasis.

Statistical Analyses

Statistical studies were performed using SPSS version 15 (IBM Corp, Somers, NY, USA). Categorical variables were compared using the chi-square test and continuous variables were analyzed with the *t* test. Recurrence and cancer-specific survival probabilities following tumor resection were analyzed using the Kaplan-Meier method and log rank test. Univariate and multivariate analyses were performed using Cox proportional hazards regression model, with $P < .05$ considered statistically significant.

RESULTS

Patient Characteristics

There were 39 men and 12 women, with a mean age of 69.5 years (range, 25-87 years). The male to female ratio was slightly over 3:1. A total of 72.5 % of patients were smokers and 5 had a history of urinary stones. The most frequent presentation was hematuria (92.1% of cases), followed by flank pain (45%). Consultation delay was more than 18 months in 10 patients (19.6%).

A prior history of bladder TCC was noted in 5 (9.8%) patients. In 3 cases, bladder tumor and UTTCC were found simultaneously and in 15 patients the bladder tumor was found more than 3

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Figure 1. Example of a Tumor in the Renal Pyelum.
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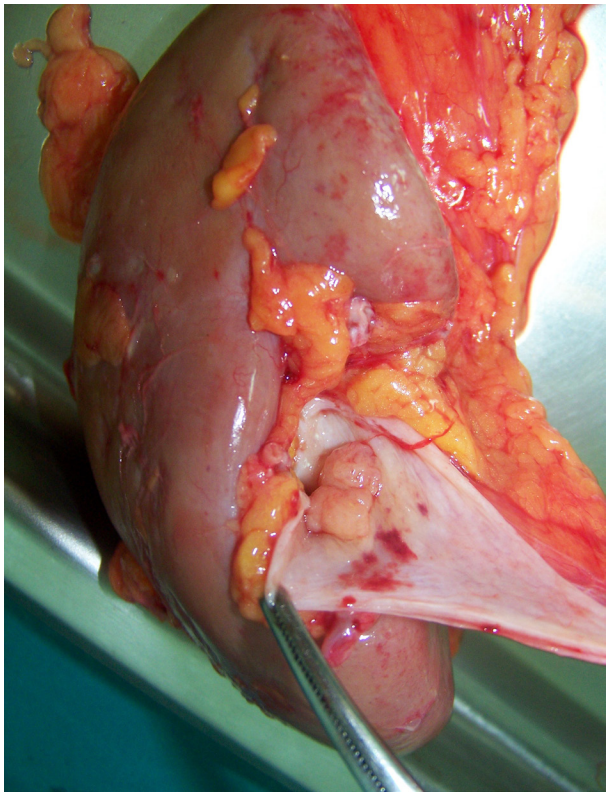

Figure 3. Example of a Tumor in the Distal Ureter (arrow).
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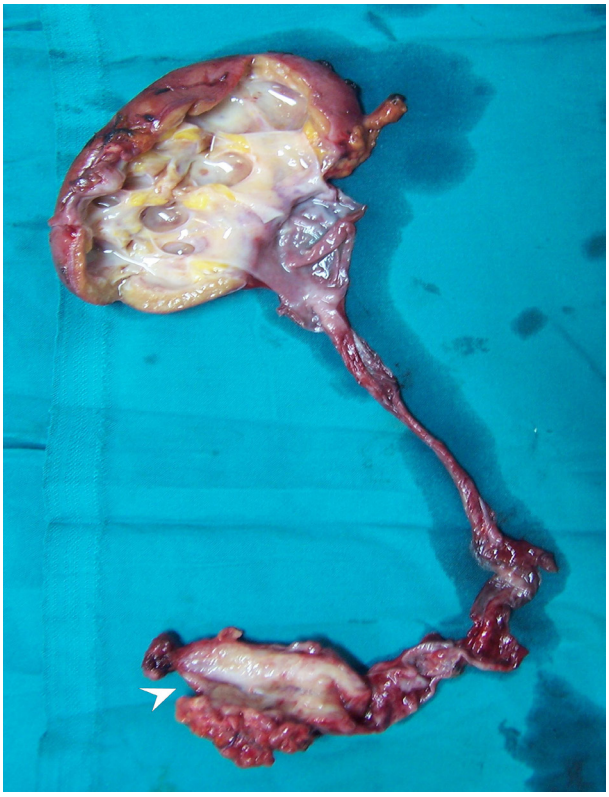

Figure 2. Example of a Tumor in the Midureter (arrow).
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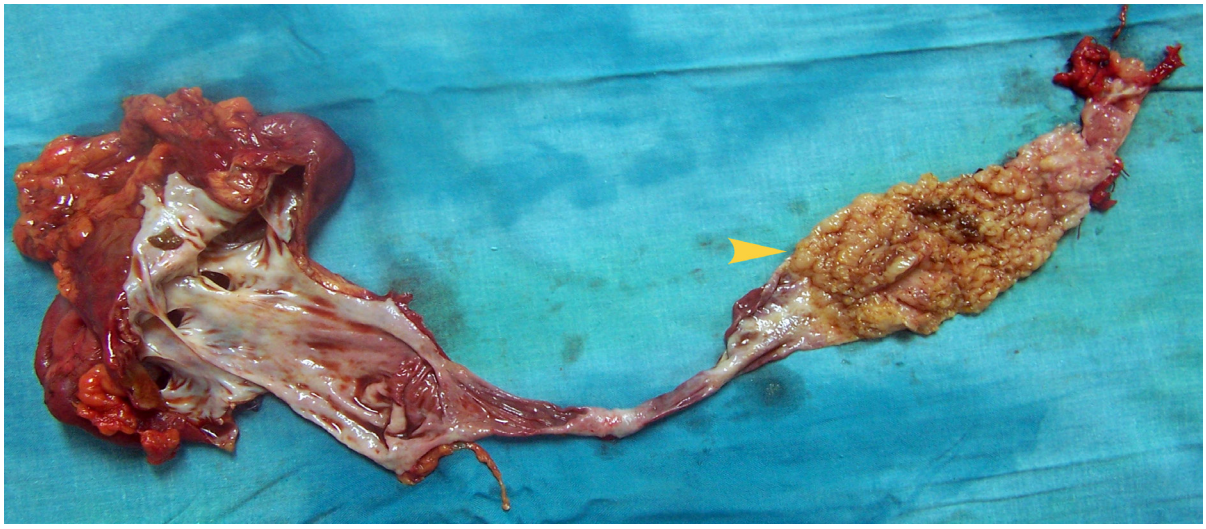

months (range, 7-60 months) after treatment of UTTCC. UTTCC was on the right side in 29 cases and on the left in 22 cases. No patient had bilateral UTTCC.

Surgical Procedure and Tumor Characteristics

In all cases, surgery was initially performed with curative intent. Nephroureterectomy with removal of a bladder cuff was the most frequently performed procedure, accounting for 39 (76.4%) patients. Seven (13.7%) patients underwent a radical nephrectomy alone (for renal neoplasm) and 5 patients (9.8%) underwent a simple nephrectomy (for a nonfunctioning kidney).

The primary tumor locations are reported in Table 1. The most common locations were the pyelum and calyx (combined) or the pyelum (alone).

The main characteristics of patients with UTTCC in the pyelum, ureter, and pyelum and ureter (combined) are reported in Table 2. The characteristics of these groups were statistically comparable.

The pathologic stage and grade distributions of the tumors were available for all patients (Table 3). A strong correlation between grade and stage is apparent (P = .035). The majority (67%) of these patients had pT2 or pT3 primary tumors. None of the patients with Ta/cis, T1, or T2 primary tumors had nodal or distant metastatic disease, either initially or during follow-up.

There was no significant difference between the number of patients with tumor growth through the ureteral wall (pT3-T4) in proximal ureter or pyelum locations (41%) when compared with distally located tumors (18.2 %) (P = .30). There was no significant correlation between the tumor stage of bladder tumors and UTTCC (P = .52). Tumor location in the upper tract could not predict the presence or development of bladder cancer in the first 3 years postoperatively (9 bladder recurrence versus 2 in the pyelum and 2 in the distal ureter) (P = .40).

Tumor Recurrence and Survival Rates

The median follow-up after initial UTTCC diagnosis was 43.8 months (range, 37-142 months). At the initial relapse, 4 (7.8%) patients had local recurrence in the retroperitoneum (tumor bed, lymph node), 11 (21.5%) patients had local recurrence in

Table 2. Main Characteristics of Patients According to Upper Urinary Tract Transitional Cell Carcinoma Location (N = 51).

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Characteristic	Pyelum	Ureter	Pyelum + Ureter	*P*
Age, years				
Mean	69.7	66.1	72.1	.33
Range	25-87	53-75	59-89	
Sex, n				
Male	28	5	6	.14
Female	5	4	3	
Smoker, n	22	7	8	.38
Clinical features, n				
Hematuria	31	9	7	.17
Flank pain	12	6	5	.21
Consultation delay, n > 18 months	5	3	2	.46

Table 1. Upper Urinary Tract Transitional Cell Carcinoma (UTTCC) Location (N = 51).

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Location	n	%N
Pyleum + calyx	18	35.3
Pyelum	11	21.5
Pyelum + ureter	7	13.7
Distal ureter	7	13.7
Calyx	4	7.8
Calyx + ureter	2	3.9
Midureter	1	2.0
Distal ureter	1	2.0

Table 3. Distribution of Tumor Histologic Grade and Stage (N = 51; 5 With Double Localization).

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Tumor Stage	Grade 1	Grade 2	Grade 3	Total
Ta/cis	8	2	1	11
T1	4	5		9
T2	6	8	3	17
T3	3	9	5	17
T4			2	2
T5	21	24	11	56

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Table 4. Bladder Recurrence and Survival Rates According to Tumor Stage, Grade, and Upper Urinary Tract Location (N = 51).
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Outcome	Pyelum	Ureter	Pyelum + Ureter	*P*
Disease-specific 3-year survival, n/total n				
Ta or T1, N0 or xM0	9/9	6/6	2/2	1
T2 or T3, N0 or xM0	20/24	2/3	6/7	.78
Grade 1 or grade 2	24/27	8/8	6/6	.43
Grade 3	5/6	0/1	2/3	.46
Bladder recurrence-free at 3 years, n/total n				
Ta or T1, N0 or xM0	7/9	6/6	1/2	.20
T2 or T3, N0 or xM0	18/24	2/3	6/7	1
Grade 1 or grade 2	21/27	7/8	4/6	.83
Grade 3	4/6	1/1	3/3	.60

the bladder, and 3 (5.9%) patients had distant recurrence in the lung or liver. Two patients with local recurrence had primary grade 3 tumors.

Six patients died of disease (4 with pelvic and 2 with distal ureter UTTCC); 7 patients died of other causes. Of the 4 local failures that resulted in death, 3 patients had pelvis tumors and 1 patient had distal ureteral tumors ($P = .63$). Two of the 3 cases of distant metastasis occurred in pelvic tumors as initial failure during follow-up, and they died of the disease.

Median overall and disease-specific survival were 37.9 months and 40.1 months, respectively. The repartition of tumor stage and grade was similar in the pyelum pelvis and the distal ureter ($P = .06$ and $P = .46$, respectively). Tumor location had the same impact on survival and bladder recurrence at a given tumor stage and grade (Table 4). The tumor location did not significantly affect the 3-year bladder recurrence rate ($P = 0.83$).

Figure 4. The 3-Year Bladder Recurrence Rate According to UTTCC Location.
doi: 10.3834/uij.1944-5784.2011.02.10f4

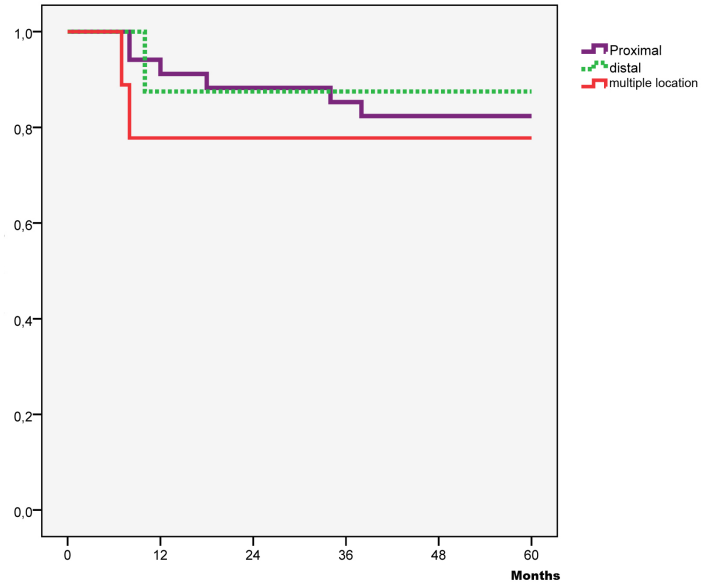

Figure 5. Disease-Specific Survival Rates for Patients With Tumors in the Pyelum or Distal Ureter.
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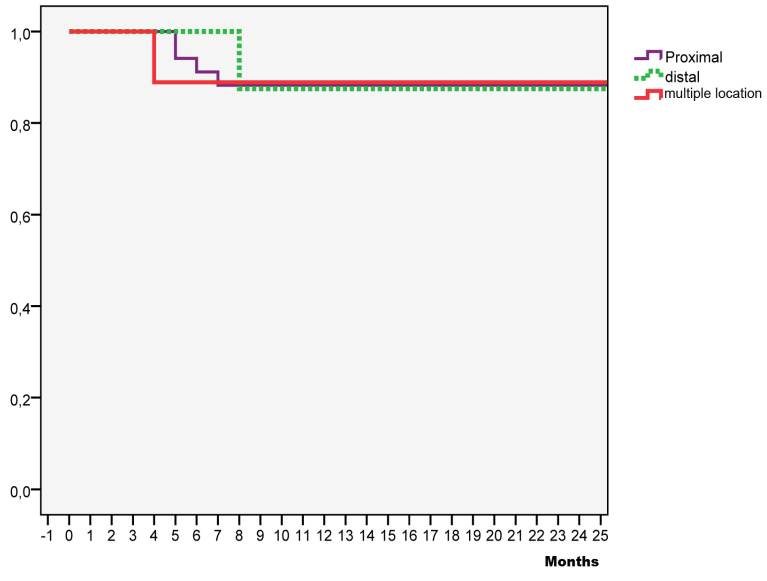

Figure 4 represents the evolution of bladder recurrence rates according to UTTCC location..

The disease-specific survival rates were 88.2% for patients with tumors in both the pyelum and distal ureter locations. Figure 5 represents the disease-specific survival rates in patients with UTTCC in the pyelum and distal ureter. There was no significant impact of UTTCC location on 3-year survival.

Noninvasive pTa and pT1 UTTCC showed survival rates that were comparable in the pyelum and the ureter. Five (out of 6) of the cancer deaths occurred in patients with stage-3 tumors; 3 of these patients had grade-3 tumors.

DISCUSSION

TCC of the upper urinary tract comprises only a minority of TCC tumors in the urinary system [11]. It is estimated that renal pelvic TCC accounts for approximately 5% of all urothelial tumors and 10% of all renal tumors [2,12]. Ureteral TCC is less common than tumors of the pyelum by a ratio of 1:3 or 1:4 [2]. In our study, this ratio was slightly less than 1:4. UTTCCs are invasive in over 50% of cases [13]. In our study, the cancers were invasive in 70.6% of the patients at presentation, perhaps because of a delay in consultation. Consultation delay was longer than 18 months in nearly 20% of the patients.

Several prognostic factors for UTTCC have been identified. Initial tumor stage, grade, multifocality, and extent of surgery have been documented as major prognostic factors [4,5,9]. The impact of tumor location on prognosis is a controversial issue [4,5,14-17]. Proximal (upper ureter, pyelum, and calix) and distal (distal ureter) UTTCCs are commonly reported as the same entity, but increasingly more papers are concluding to different entities [18,19].

Unfortunately, medical literature on the prognostic value of location is scarce. We conducted a PubMed (U.S. National Library of Medicine) database search of literature between 1990 and 2009 using the key words *upper urinary tract*, *urothelial carcinoma*, *location*, and *prognosis*. We found only 10 articles dealing with UTTCC location as prognostic factor. Three groups of investigators (with a range of 72 to 138 patients) reported significantly higher progression and/or cancer-specific mortality rates in patients with primary ureteral TCC [4,11,14]. Akdogan et al [15] found that 62% of ureteral and 43% of renal pelvic ureteral carcinomas were muscle-invasive and that ureteral location was associated with a poor outcome. Park et al [11] reported that renal pelvic tumors were related to significantly higher survival rates than ureteral tumors for stage pT3. A possible reason was that the kidney parenchyma may function as a determinant of anatomical disease spread [20]. Thus, renal pelvic tumors invading the renal parenchyma had a significantly better prognosis than those invading peripelvic or ureteral fat. As a consequence, local failure of pT3 tumors invading peripelvic or ureteral fat was more common than that of tumors invading the renal parenchyma [11]. Others have explained the differentially worse outcome of ureteral tumors by the lack of a periureteral fat layer (its outermost layer is the adventitia) when compared with the pyelum. However, these studies were limited by a relatively small sample size.

A radical surgical approach including meticulous lymphadenectomy may be therapeutic in patients with invasive ureteral TCC [14]. Two studies confirmed the prognostic value of complete node dissection for UTTCC [8,21]. On the other hand, Iborra et al [22] found higher progression rates after pyelum carcinoma when compared with more distally located cancers after endoresection. They reported higher recurrence rates with renal pelvic UC than ureteral UC when treated conservatively.

van der Poel et al [16] reported that distal ureteral tumors resulted in significantly better survival than proximal ureteral or renal pelvic tumors. Other studies showed a worse prognosis for patients with pyelum cancer when compared with more distal ureter cancer [14,23]. The more aggressive behavior of proximally located tumors may be due to late detection. Although pyelum tumors may be less readily detected due to a lack of obstructive symptomatology, the distally located tumors are diagnosed earlier due to early tumor bleeding and lumbar pain. Another explanation may be the differences in anatomy between the proximal and distal upper tract. More distal parts of the ureter contain a thicker outer muscular layer when compared with proximal parts of the ureter [24]. The distal ureter is covered by 3 muscular layers, whereas the more proximal parts of the ureter contain only 2 relatively thin interlacing layers [16,25]. In the present study, there was no significant difference between proximal and distal ureteral UTTCC for patients with stage pT2 or greater cancers.

Finally, other investigators have reported conflicting results regarding a difference in outcomes (disease progression and/or mortality) according to tumor location [5,7,9,16,17].
Our results indicated that tumor location is not an independent prognostic factor. Renal pelvic tumors resulted in the same survival rate as ureteral tumors on univariate and multivariate analyses, in opposition to results from a previous report [14]. In our study, we found no difference in UTTCC behavior with respect to location after being balanced for stage and grade.

Our study has several limitations. It is a retrospective analysis of a relatively small population of patients from a single institution. A power analysis was not conducted. Therefore, the sample size may not have been adequate to draw conclusions regarding statistical significance. The follow-up period was relatively short. Additional studies are needed to confirm the results.

CONCLUSIONS

Tumor location does not appear to be an independent prognostic factor for patients with UTTCC. Patients with pyelum tumors in the present study had the same risk of bladder cancer recurrence and survival as patients with lesions in the distal ureter that had the same tumor grade and stage. We recommend the same surveillance protocol regardless of the tumor location.

Conflict of Interest: none declared.

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