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Do tumor size and location affect survival in upper urinary tract urothelial carcinoma?

Üst üriner sistem ürotelyal karsinomlarinda tümör boyutu ve yerleşimi sağ kalımı etkiler mi?

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ABSTRACT

Aim: This study aimed to evaluate the effect of tumor location based on clinicopathologic features on cancer-specific survival (CSS) of patients who were treated surgically for locally/locally advanced upper tract urothelial carcinoma (UTUC).

Materials and Methods: A single-center series of 145 patients with UTUC who underwent radical nephroureterectomy between May 2010 and August 2019 were included in the study. Patients were stratified based on the location of the tumor as renal pelvis and ureter located tumor. Clinicopathologic characteristics and oncological outcomes were compared according to tumor location and CSS rates after surgery were graphically explored using Kaplan–Meier curves.

Results: At a mean follow-up time of 41.8 (4-124) months after surgery, 65 patients (44.8%) died from UTUC. Kaplan-Meier curves showed that tumor location was not associated with CSS in the analysis performed according to tumor stage, grade, and size. In the analysis that was conducted without regard to tumor location, worse CSS was found for patients with pT3 disease versus those with ≤pT2 and with high-grade tumors versus those with low-grade (p=0.025 and p=0.011, respectively).

Conclusion: Tumor location was not associated with CSS in any of the analyses. Regardless of tumor location, patients with pT3 disease and high-grade tumors, have a worse prognosis. Further studies on prognostic factors are needed to evaluate the advantages of these factors in the management of patients with UTUC.

Keywords: Cancer-specific survival; nephroüreterectomy, renal pelvis; upper tract ürothelial carcinoma; üreter.

ÖZ

Amaç: *Bu çalışma, lokal/lokal ileri üst sistem ürotelyal karsinomu nedeniyle cerrahi olarak tedavi edilen hastaların klinikopatolojik özelliklere dayalı tümör yerleşiminin kansere özgü sağkalım üzerindeki etkisini değerlendirmeyi amaçlamıştır.*

Gereç ve Yöntem: *Çalışmamıza, Mayıs 2010 ile Ağustos 2019 arasında üst üriner sistem ürotelyal karsinomu nedeniyle radikal nefroüreterektomi yapılan 145 hasta dâhil edildi. Hastalar tümörün yerleşimine göre renal pelvis ve üreter yerleşimli tümör olarak sınıflandırıldı. Klinikopatolojik özellikler ve onkolojik sonuçlar, tümör yerleşimine göre karşılaştırıldı ve ameliyat sonrası kanser spesifik sağ kalım oranları Kaplan-Meier eğrileri kullanılarak grafiksel olarak karşılaştırıldı.*

Bulgular: *Radikal nefrorüreterektomi ameliyatından sonra ortalama 41,8 (4-124) aylık takip süresinde 65 hasta (%44,8) üst üriner sistem ürotelyal karsinom tümörü nedeniyle öldü.*

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Kaplan-Meier eğrileri, tümör evresi, derecesi ve boyutuna göre yapılan analizde tümör lokasyonunun kanser spesifik sağkalım ile ilişkili olmadığını gösterdi. Tümör yerleşimine bakılmaksızın yapılan analizde, pT3 hastalığı olanlarda ≤pT2 olanlara ve yüksek dereceli tümörü olanlarda da düşük dereceli olanlara göre daha kötü kanser spesifik sağkalım değerleri bulundu (sırasıyla p=0.025 ve p=0.011).

Sonuç: *Tümör yerleşimi, yapılan analizlerin hiçbirinde kanser spesifik sağkalım ile ilişkilendirilmedi. Tümörün yerleşiminden bağımsız olarak, pT3 hastalığı ve yüksek dereceli tümörleri olan hastalar daha kötü bir prognoza sahip olduğu görüldü. Üst üriner sistem ürotelyal karsinomlu hastaların yönetiminde bu faktörlerin avantajlarını değerlendirmek için prognostik faktörler hakkında daha fazla çalışmaya ihtiyaç vardır.*

Anahtar Sözcükler: *Kansere özgü sağkalım; nefroüreterektomi, renal pelvis; üst sistem ürotelyal karsinomu; üreter.*

INTRODUCTION

Urothelial carcinoma is a malignancy derived from the urothelial epithelium lining the urinary tract from the renal pelvis until the urethra. Urothelial carcinoma may arise from any part of the urinary tract and bladder tumors account for 90-95% of urothelial carcinomas (1). In contrast, upper tract urothelial carcinoma (UTUC) is relatively rare and comprises only 5%-10% of all urothelial carcinomas and 5%-7% of all renal neoplasms (2). Tumors of the upper urinary tract are almost twice as common in men compared with women, with with a peak incidence occurring in the eighth decade of life (2). Although promising results have been achieved with conservative approaches in selected patients, the standard treatment for non-metastatic UTUC is radical nephroureterectomy (RNU) with bladder cuff resection.

Despite the advancement in surgical techniques and due to widespread use of neoadjuvant and adjuvant chemotherapy, the survival of patients with UTUC has significantly improved over time. Patients with UTUC have more advanced disease compared to urothelial carcinomas of the bladder and a poor prognosis with a 5 -year cancer-specific survival (CSS) of less than 50% for pT2/pT3 and less than 10% for pT4 disease (3). Many tumor-related prognostic factors have been identified to assist urologists in the decision-making phase regarding the patients' further treatment management.

There are conflicting results in the literature and there is no consensus on patient prognosis based on disease location (4, 5). This study aims to present additional data on the effect of clinicopathological characteristics based on tumor location on CSS of patients treated surgically for UTUC.

MATERIALS and METHODS

Patient Selection and Inclusion Criteria

A single-center, retrospective study was conducted. Ethics committee approval for this study was obtained from the local ethical Committee. (Date: 21.07.2022, Reference number: 22-7T/14). Our analysis looked retrospectively at outcomes for a large cohort of patients treated. All data analysed were collected as part of routine diagnosis and treatment. Patients were diagnosed and treated according to national guidelines and agreements. The study was prepared in accordance with the ethical principles of the Declaration of Helsinki. Between May 2010 and August 2019, 158 patients treated for clinically localized UTUC with renal pelvis or ureter at our institution were enrolled. Patients with a history of muscle-invasive urothelial carcinoma of the bladder or undergone radical cystectomy, previous contralateral upper UTUC, those with multifocal UTUC, non-urothelial carcinoma such as squamous cell and adenocarcinoma, and incomplete follow-up data were excluded from the study. Overall, the study focused on the remaining 145 patients. Medical files and hospital records were reviewed retrospectively to analyze the clinical and pathological data on disease-specific survival. All patients have undergone open or laparoscopic RNU with bladder cuff excision. The open RNU procedures were performed by two incisions, with a flank incision followed by a separate lower-quadrant Gibson incision. The laparoscopic RNU procedures were performed using transperitoneal laparoscopic nephrectomy followed by a separate lower-quadrant Gibson incision. Regional lymphadenectomy was performed only in patients with clinically positive lymph nodes in preoperative diagnostic evaluation.

Data Collection and Pathological Evaluation

The database included the following parameters: gender, age at diagnosis, tumor characteristics (size, grade, location, pathological stage, and lymph node status), follow-up time, and oncological outcomes. RNU specimens of 145 patients were evaluated by two experienced genitourinary pathologists and processed according to standardized procedures. Tumor

location was categorized as renal pelvis and ureter. According to tumor size, patients were categorized into two groups (<3cm and >3cm) based on the size of the threshold in previous studies (6, 7). Tumor node metastasis (TNM) classification (WHO 2016) was used for pathological staging (8).

Follow-up Protocol

Patients were followed up at 3 months and 6 months, then every 6 months for 2 years following surgery and annually thereafter. Follow-up included physical examination, laboratory tests, cystoscopic evaluation, and a thoraco-abdominopelvic computed tomography scan. CSS was determined from surgery to the last date of the patient's visit or death related to UTUC (local recurrence or distant metastasis).

Statistical Analysis

The data were analyzed using the Statistical Package for Social Sciences, version 17.0 (SPSS, Chicago, III) program. The groups were compared using the chi-square and Mann-Whitney U tests. Kaplan-Meier survival analysis and log-rank test were used for CSS data. Statistical significance was considered as p-value <0.05.

RESULTS

145 out of 158 patients who met the inclusion criteria were included in the study. Overall, 94 patients had a renal pelvic tumor (64.8%) and 51 patients had ureteral tumor (35.2%). The mean age of the study population was 67 (34-93) years and the majority of the patients were men (116 vs 29). According to tumor size, 69 patients (47.5%) had a tumor <3cm and 76 patients (52.5%) had a tumor >3cm. When comparing renal pelvic and ureteral located tumors, there were no differences in age, gender distribution, tumor size, tumor grade, and nodal status (Table-1). Probably due to the large difference in the number of patients between the two groups, a significant difference was observed between the pathological T stages of both groups (p=0.026) and the presence of locally advanced disease (pT3) was higher in renal pelvic tumors than ureteral tumors (p=0.01).

The mean follow-up time after surgery was 41.8 (4-124) months. In this cohort, 65 patients died from UTUC, including 46 (70.7%) patients with a tumor located in the renal pelvis and 19 (29.3%) patients with a tumor located in the ureter. During the postoperative follow-up, it was observed that 33 of the patients (35.1%) with tumors located in the renal pelvis and 17 of the patients (33.3%) with tumors located in the ureter had an intravesical recurrence. When data were stratified according to pathological characteristics (pathologic stage, tumor size, tumor grade) by primary tumor location (renal pelvis versus ureter), no significant difference was found between the renal pelvis and ureteral tumors in terms of CSS (Figure-1). However, when we did not stratify the patients as tumor localization, Kaplan-Meier curves showed worse CSS for patients with pT3 disease versus those with ≤pT2 and with high-grade tumors versus those with low-grade (p=0.025 and p=0.011, respectively) (Figure-2).

Table-1. Characteristics and clinicopathological features of the patients stratified by tumor location.

Age (years)	67.8 (42-93)	65.7 (34-85)	0.293
Sex, n (%)			
Men	78 (82.9)	38 (74.5)	0.223
Women	16 (17.1)	13 (25.5)	
Tumor size, n (%)			
<3cm	58 (61.7)	33 (64.7)	0.721
>3cm	36 (38.3)	18 (35.3)	
Tumor grade, n (%)			
Low	9 (9.5)	8 (15.6.)	0.275
High	85 (90.5)	43 (84.3)	
Tumor stage, n (%)			
Ta	10 (10.6)	11 (21.5)	
T1	29 (30.8)	9 (17.6)	0.026
T2	16 (17)	21 (41.1)	
T3	39 (41.4)	10 (19.6)	
Lymph node metastasis, n (%)			
No/Nx	91 (96.9)	50 (98)	0.655
N1	3 (3.1)	1 (2)	

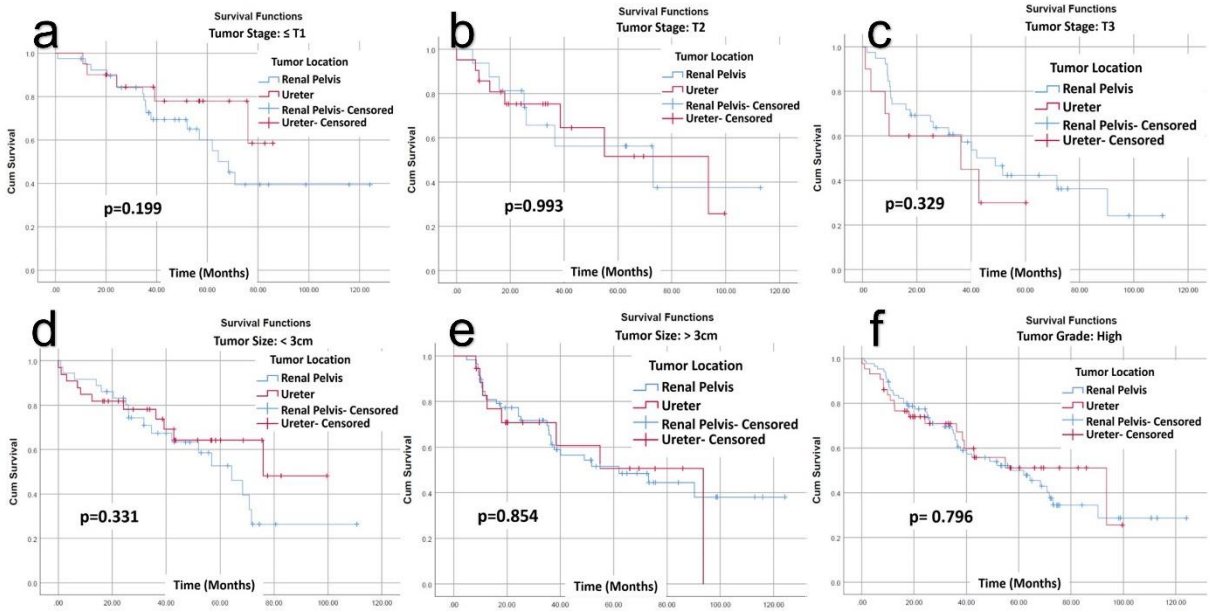

Figure-1. Kaplan-Meier survival curves for cancer-specific survival stratified by tumor location (According to; a: ≤T1 stage, b: T2 stage, c: T3 stage, d: tumor size < 3cm, e: tumor size > 3cm, f: high grade tumor)

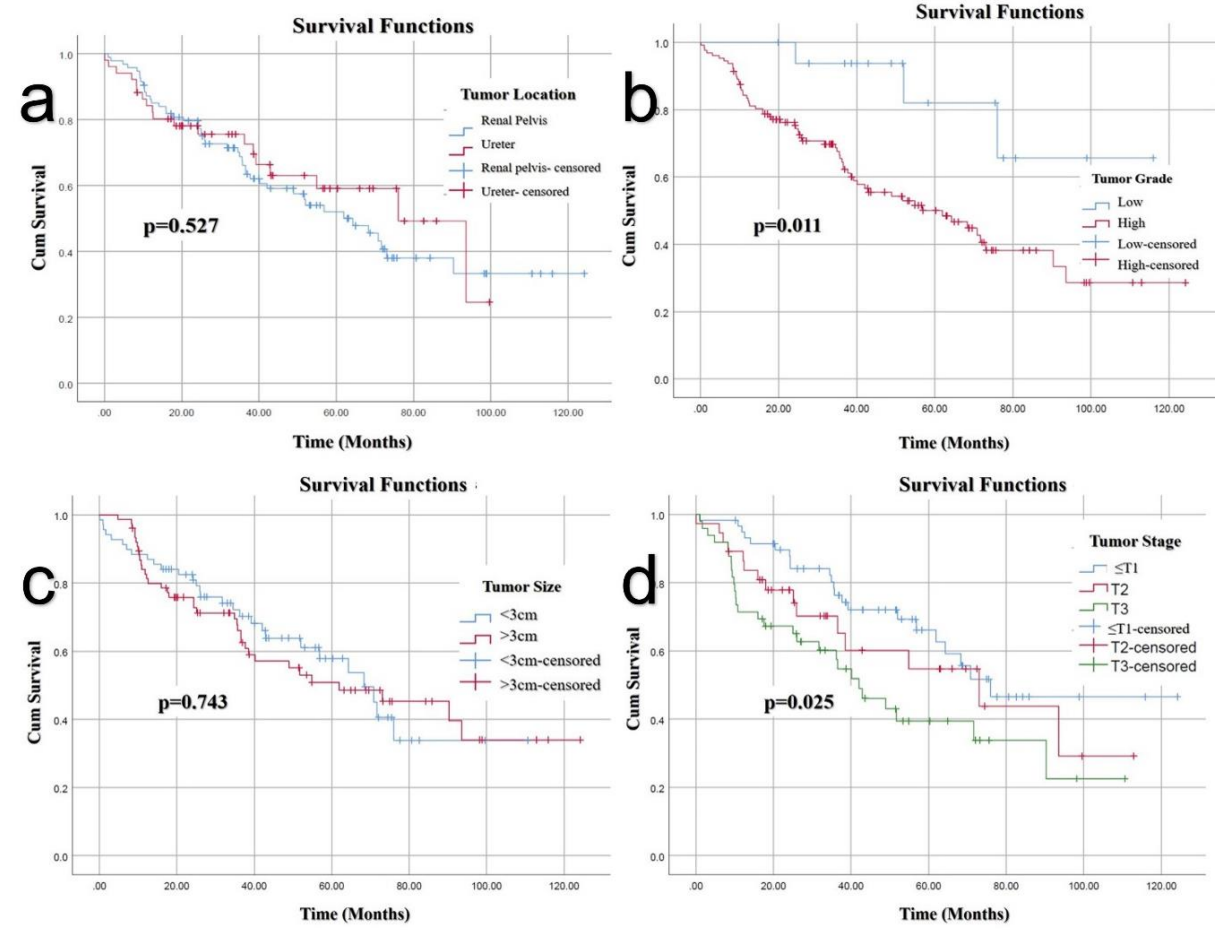

Figure-2. Kaplan-Meier survival curves for cancer-specific survival stratified by tumor charecteristics (According to; a: tumor location, b: tumor grade, c: tumor size, d: tumor stage).

DISCUSSION

There is a long debate on the influence of the tumor location (ureter versus renal pelvis) on the prognosis of patients with UTUC. A conclusive statement about the effect of tumor location on UTUC prognosis cannot be made due to a lack of prospective studies. In the current series of 145 patients with UTUC, we investigated the CSS rates and pathological factors that affect the CSS of patients who underwent standard surgical treatment after diagnosis of UTUC and we did not detect a significant difference in UTUC CSS when stratifying patients to their pathological characteristics by ureteral and renal pelvis tumor location.

To date, several prognostic models have been developed for UTUC and are used for clinical decision-making for optimal management (9-11). These models can be used in the post-treatment setting to predict disease recurrence or CSS. In a study, they tested the prognostic value of pathologic characteristics such as pT stage, lymph node metastasis, lymphovascular invasion and they developed models predicting the individual probabilities of CSS after RNU. They found 81.5% accuracy for predicting CSS and characteristics were independently associated with cancer-specific mortality (9). Similarly, a unique and optimized nomogram composed to predict CSS after RNU by combining the two largest multicenter data, T stage was found as the most important univariable predictor of CSS (10). An online nomogram was developed to provide an accurate estimate of the individual risk of cancer-specific mortality, and performed well across a wide range of threshold probabilities using decision curve analysis, and also underlined a requirement of a novel molecular marker (11). The accuracies of two post-operative nomograms for 5-year CSS were found to be 81% and 78%, respectively (12, 13).

The effect of tumor location on the prognosis of patients with UTUC is still discussed in the literature with conflicting results. Although tumor size is not included in the prognostic factors defined for UTUC in the up-to-date European Association of Urology UTUC guidelines (14). Several studies indicate tumor location as an independent predictor factor on CSS (15,16). In a study, Park et al. stated that pelvic tumors have a better prognosis in patients with pT3 disease compared to tumors in the ureter and suggested that this difference may be due to the protective role of the renal parenchyma (17). In another study conducted similarly, they stated that the tumors in the distal ureter had a better prognosis than the more proximal tumors, and declared that the factor leads this was the urothelium in the distal ureter was surrounded by thicker muscle tissue than the urothelium tissue in the proximal ureter and pelvis (18). In the present study, there was no difference in CSS between the renal pelvis and ureteral tumors. Since most of the studies investigating the effect of tumor location on prognosis are retrospective studies, a determinative decision can be only achieved with multi-center prospective studies.

In the postoperative period, the pathologic tumor stage has a crucial role in classifying the prognosis and treatment strategies of patients with UTUC. Several meta-analyses, including large and multi-institutional studies, have confirmed the prognostic value of common pathological factors (i.e., tumor stage, size, and grade, size and lymph node metastasis) (19, 20). According to these studies, patients with pTa/pT1 disease have a 5-year CSS rate of >90%, whereas patients with pT4 UTUC have a rate of 20% CSS (21, 22). In our cohort, at a mean follow-up of 41.8 months, we found that CSS rates were 45.7%, 59.4% and 40.8% for ≤pT1, pT2 and pT3, respectively. When we classified the CSS rates according to the pathological stage as renal pelvis and ureter, no significant difference was found.

It is controversial the role of tumor size as a prediction for CSS after RNU. In the current EAU guideline, it has been accepted that the size of the tumor detected in the preoperative period is below or above 2 cm and that it is one of the parameters in the risk classification of non-metastatic UTUC patients (14). In a study investigating the effect of tumor size in the postoperative period that included 932 patients who underwent RNU, the patients were divided into 4 groups with tumor sizes of <1cm, 1-2 cm, 2-3, and >3cm and in accordance with current EAU guidelines for risk stratification, demonstrated the 2-cm cutoff tends to be the most effective in distinguishing patients with ≥ pT2 UTUC (23). In the current literature, studies are showing that increasing tumor size is an adverse prognostic factor for CSS (24). In contrast, the size of the tumor had no impact on CSS, according to a study with fewer patients than other studies (25). In our study with a

median tumor size of 3.3 cm, a cut-off of 3 cm was chosen. We stratified the groups as tumor size as <3 cm and >3 cm both according to tumor location and in the cohort and we did not find a significant difference between the groups in terms of CSS.

The grade of the tumor is a well-known predictor of outcomes in malignancies as it is definitely associated with cancer aggressiveness and the stage of the tumor. Several studies have found that tumor grade is a prognostic factor for survival of patients with UTUC (26, 27). In the review which 116 studies have been evaluated, the importance of this was also underlined (19). In our cohort, when the renal pelvis and ureter located tumors were compared as low and high-grade, no difference was found between both groups, but a significant difference was observed in the comparison of low and high-grade tumors independent of tumor location, comparable to other studies.

Our study has some important limitations. First and foremost, a retrospective examination of a database from a single-center was used in the study. Second, adjuvant chemotherapy administered to patients with T3 disease may induce a selection bias. Third, the outcomes are limited by the relatively short median follow-up time that prevented the observation of long-term survival outcomes. Fourth, lack of information about adjuvant treatments such as chemotherapy or radiotherapy administered to patients with pT3 may influence survival. Finally, no standard lymph node dissection was performed in this study, however its role remains uncertain whether lymph node dissection during RNU independently improves survival in patients with UTUC (28).

CONCLUSIONS

In our study, we did not find any difference in CSS by tumor size, grade, and pathological stage between patients with renal pelvic tumor and ureteral tumor. In the analysis performed without stratifying the patients as tumor localization, we found that the prognosis was worse in those with higher tumor grade and stage in line with the literature. Although there is no RCT yet, it has been shown in phase 2 and 3 studies that neoadjuvant and adjuvant chemotherapies have a positive effect on prognosis, especially in patients with >pT2 and high-grade tumors. These findings highlight the cruciality of good evaluation of the patients with high-grade and >pT2 UTUC in terms of suitability for chemotherapy to have a better prognosis.

Conflict of interest: The authors in the study admit that there is no conflict of interest.

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