

CANCER-SPECIFIC SURVIVAL IN PATIENTS WITH UPPER TRACT UROTHELIUM CARCINOMA AFTER RADICAL NEPHROURETERECTOMY

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Abstract

Introduction: Identifying prognostic factors is essential for proper postoperative patient monitoring with upper urinary tract carcinoma, that would contribute to the decision-making process regarding the application of adjuvant chemotherapy after radical nephroureterectomy.

Aim: To investigate demographic, clinical, and pathological prognostic factors of cancer-specific survival (CSS) for upper urothelial tumors.

Methods: A retrospective cohort study was conducted including 342 patients who underwent radical nephroureterectomy. Kaplan-Meier method and Log-Rank test were used to assess survival. Cox regression analysis was used to determine the impact of different factors on cancer-specific survival after radical nephroureterectomy.

Results: The study cohort consisted of 342 patients, with a mean follow-up time after radical nephroureterectomy of 32.5 (6-154) months. The 5-year CSS was 64% for this patient cohort. During the follow-up period, a total of 128 (37.4%) patients died, including 92 (28.2%) patients who died due to urothelial carcinoma. Multivariate analysis showed that the pathological stage of the primary tumor (HR, 11.1; 95% CI 3.64-33.8; $P=0.001$), presence of positive lymph nodes (HR, 2.04; 95% CI 1.05-3.94; $P=0.03$) and preoperative anemia (HR, 3.50; 95% CI 2.02-6.08; $P=0.001$) were independent predictors significantly associated with worse CSS. Patients

with disease stage $\leq$ pT2 had significantly better CSS compared to patients with disease stage $\geq$ pT3 ($P=0.001$, Log-Rank test). The average CSS for patients with positive lymph nodes (pN+) was 22.1 ± 5.1 months (95% confidence interval from 12.1-32.2).

Conclusion: Preoperative anemia, pathological disease stage, and presence of positive lymph nodes are significant independent prognostic predictors of CSS in patients who underwent radical nephroureterectomy (RNU).

Keywords: upper urothelial tumors, cancer-specific survival, prognostic factors, radical nephroureterectomy

Introduction

Upper tract urothelial carcinoma is a rare tumor. These tumors account for approximately 5% of urothelial carcinomas, while 95% are urothelial carcinomas of the urinary tract¹. In Western countries, the incidence of upper tract urothelial carcinoma is 1-2 new cases per 100,000 population¹. The highest incidence is in patients in their seventies and eighties^{1,2}.

The well-known prognostic factors for upper tract urothelial carcinomas include pathological stage and disease stage, lymphovascular invasion (LVI), patient age, *carcinoma in situ* (CIS), macroscopic appearance of the tumor, tumor necrosis, and molecular markers^{2, 3-6}. However, the significance of the location of the primary upper urothelial tumor (pyelum compared to ureter) for the prognosis of patients undergoing radical nephroureterectomy (RNU) is still unknown. The most significant predictor affecting patient survival after RNU is the pathological stage of urothelial carcinoma^{2,7}. The ways of spread for upper tract urothelial carcinoma are primarily through direct invasion (*via mucosa*), through blood or lymphatic vessels. The 5-year cancer-specific survival (CSS) is greater than 90% for pTa/pT1 stage disease, while for pT3 and pT4 stage disease, the 5-year CSS is 30-50% and 10-20%, respectively⁷⁻⁹. Independent prognostic factors for disease recurrence and CSS include LVI. The 5-year survival rate is 30% for patients with positive lymph nodes^{9, 10-12}.

Multifocality of upper urinary tract tumors refers to the presence of two or more tumors in the upper urinary tract. Multifocality is present in more than 30% of upper urinary tract urothelial carcinomas^{13, 14}. It has been shown that the multifocality of upper urinary tract tumors harms survival without disease recurrence¹³. The prognostic significance of the multifocality of upper urinary tract carcinoma has also been pointed out by Navarro and colleagues⁹. Patients with multifocal upper urinary tract carcinoma have a three times higher risk of cancer-specific mortality compared to patients with solitary upper urinary tract carcinoma. Multicenter studies conducted in France and Japan have shown that multifocal upper urinary tract carcinomas are independent predictors of CSS^{15, 16}.

Radical nephroureterectomy with the removal of the bladder cuff is considered the gold standard in the treatment of upper urinary tract carcinoma, whether it involves tumors of the renal pelvis or ureter¹⁷.

This study aimed to investigate and determine which demographic, clinical, and pathological characteristics represent prognostic factors for cancer-specific survival for upper urothelial tumors.

Method

A retrospective cohort study was conducted, which included patients who underwent radical nephroureterectomy for upper urinary tract cancer.

The study population consisted of patients with upper urinary tract cancer (387 patients), who underwent surgery at the Clinic of Urology, University Clinical Center of Serbia in Belgrade. Surgical treatment involved RNU.

Excluded from the study were patients who had previously undergone radical cystectomy, received neoadjuvant chemotherapy, and those with contralateral upper urinary tract cancer. The final study cohort consisted of 342 patients. Data on relevant demographic, clinical, and pathological characteristics were collected through a retrospective analysis of the medical records of patients who underwent surgery for upper urinary tract cancer. Additional information not found in the medical records was obtained by telephone. The localization of the dominant tumor was used to stratify upper urinary tract cancer into tumors of the renal pelvis and tumors of the ureter. The dominant tumor was the one with the highest pathological stage of the disease. In the case of multifocal upper urinary tract cancer of the same pathological stage, the tumor with a higher pathological grade was considered the dominant tumor. The presence of two or more cancers simultaneously in any part of the upper urinary tract was referred to as the multifocality of upper urinary tract cancer.

All included patients had transitional cell carcinomas of different grades of malignancy and stages. They were

classified into three grades of malignancy (G1, G2, and G3) according to the World Health Organization (WHO) classification, and into four stages of development (T1-T4) according to the TNM (Tumor, Node, Metastasis) classification^{18, 19}.

Patients were divided based on the geographic regions they originated from, into those from the Balkan Endemic Nephropathy (BEN) area and those who do not belong to the BEN region. The region was defined as a BEN region if three or fewer patients from that area were reported to the Balkan Endemic Nephropathy patient registry. The included patients, were patients with a permanent residence in the BEN or non-endemic region from birth until the end of follow-up.

The study population was followed up for an average of 32.5 months (6-154). Patient monitoring involved urological examination and cystoscopy every three months during the first year of follow-up, and every six to twelve months thereafter. Patients whose cause of death was upper urinary tract cancer had disease progression and widespread metastases at the time of death.

Statistical analysis

χ^2 test and T-test were used for statistical analysis of demographic, clinical, and pathological characteristics. Survival analysis was performed using the Kaplan-Meier method, with the use of the Log-Rank test. Patients were followed from the time of surgery (time zero, 0) until death. Univariate and multivariate analysis (Cox regression model) was used to determine the impact of different factors on CSS after RNU. A significance level of 95% ($P < 0.05$) was defined for all tests.

Results

The study cohort consisted of 342 patients. The average age of patients with upper urinary tract carcinoma at the time of surgery was 66 years. The majority of patients were in their sixth and seventh decades of life. The clinical, demographic, and pathological characteristics of this study cohort are presented in tables 1 and 2.

The five-year CSS for this patient population was 64%. During the follow-up period, a total of 128 (37.4%) patients died, including 92 (28.2%) deaths due to upper urinary tract carcinoma. Univariate analysis revealed that preoperative pyuria (HR 1.81; 95% CI 1.18-2.76; $P=0.006$), preoperative anemia (HR 4.55; 95% CI 2.95-7.02; $P=0.001$), prior history of non-muscle invasive bladder cancer (HR 1.85; 95% CI 1.21-2.82; $P=0.004$), tumor size (HR 1.54; 95% CI 1.02-2.33; $P=0.04$), primary tumor histological grade (HR 1.62; 95% CI 1.05-2.48; $P=0.03$), primary tumor pathological stage (HR 14.7; 95% CI 6.36-33.9; $P=0.001$), lymphovascular invasion (HR 1.57; 95% CI 1.03-2.40; $P=0.004$), and presence of lymph

Table 1. Clinical and demographic characteristics of the study cohort

CHARACTERISTICS	n (%)
Age, mean $\pm$ SD	66.2 $\pm$ 8.9
Sex	
Male	190 (55.5)
Female	152 (44.5)
Location	
Pyelon	201 (58.2)
Ureter	141 (41.8)
BEN	
Yes	107 (31.3)
No	135 (68.7)
Previous history of non-muscle invasion bladder tumor	
Yes	89 (26.1)
No	253 (73.9)
Anemia	
Yes	144 (42.1)
No	198 (57.9)
Piuria	
Yes	85 (24.8)
No	257 (75.2)
Total	342 (100)

Legend: BEN - Balkan endemic nephropathy

node metastasis (HR 5.83; 95% CI 3.38-10.1; $P=0.001$) were significant predictors associated with CSS (table 3). Multivariate analysis included all parameters regardless of the significance level. The multivariate analysis showed that primary tumor pathological stage (HR 11.1; 95% CI 3.64-33.8; $P=0.001$), presence of lymph node metastasis (HR 2.04, 95% CI 1.05-3.94; $P=0.03$), and preoperative anemia (HR 3.50; 95% CI 2.02-6.08; $P=0.001$) were independent significant predictors associated with CSS (table 4).

The Log-rank test showed that the cancer-specific survival (CSS) of patients with tumor stage $\leq$ pT2 was significantly better ($P=0.001$) compared to those with tumor stage $\geq$ pT3 (figure 1). The mean CSS for patients with tumor stage $\leq$ pT2 was 140.7 ± 6.3 months (95% CI 128.3-153.2). The mean CSS for patients with tumor stage $\geq$ pT3 was 55.8 ± 5.4 months (95% CI 45.2-66.6). The median survival was 93.3 ± 5.6 months (95% CI 82.1-104.5).

By using the Log-Rank test, it was found that patients with positive lymph nodes pN+ had significantly worse CSS compared to patients without positive lymph nodes pN0/pNx ($P=0.001$) (figure 2). The average CSS of patients with positive lymph nodes pN+ was 22.1 ± 5.1 months (95% CI 12.1-32.2).

Table 2. Pathohistological characteristics of the study cohort

CHARACTERISTICS	n (%)
Tumor size	
< 3 cm	150 (43.8)
> 3 cm	192 (56.2)
Tumor grade	
G1 or G2	166 (48.5)
G2	176 (51.5)
Tumor stage	
pT0, pTa, pTis	5 (1.5)
pT1	31 (9.1)
pT2	100 (29.2)
pT3, pT4	206 (60.3)
Lymph node status	
pNx	271 (79.2)
pN0	51 (14.9)
pN+	20 (5.9)
Lymphovascular invasion	
Negative	239 (69.8)
Positive	103 (30.2)
Total	342 (100)

Discussion

Radical nephroureterectomy with excision of the bladder cuff is the gold standard in the treatment of invasive upper urinary tract carcinoma². Despite the radical nature of the surgical treatment, a large number of patients develop local or distant disease recurrence^{2, 3, 20-27}. Therefore, identifying prognostic predictors in patients with upper urinary tract carcinoma is of great importance.

The significance of the localization of the primary upper urinary tract carcinoma (*pelvis versus ureter*) on disease prognosis in patients who underwent radical nephroureterectomy (RNU) is still not fully understood. It is believed that pelvicalyceal carcinoma has a better prognosis compared to ureteral carcinoma. Patients with ureteral carcinoma have a higher risk of developing local recurrence and distant metastasis¹¹. The results of this retrospective study show that pelvicalyceal carcinomas occur with significantly higher pathological stages and grades compared to ureteral carcinomas. Patients with ureteral carcinoma had a higher incidence of multifocal tumors. Additionally, patients with ureteral carcinoma had a higher incidence of a positive history of non-muscle invasive bladder tumors, which was statistically significant.

The results of this study showed a 5-year CSS of 64%, which is consistent with more recent studies and demonstrates that RNU leads to long-term disease control even in patients with locally advanced disease^{4, 7, 11, 28-30}.

Table 3. Univariate analysis of potential prognostic factors for cancer specific survival in 342 patients after surgical management of upper tract urothelial carcinoma (UTUC) (Cox regression models)

CHARACTERISTICS	UNIVARIATE ANALYSIS		
	HR	95% CI	P*
Age (age) (< 60 vs > 60)	1.57	0.92-2.65	0.09
Sex (male vs female)	1.12	0.74-1.68	0.59
Anemia (no vs yes)	4.55	2.95-7.02	0.001
Piuria (no vs yes)	1.81	1.18-2.76	0.006
The history of non-muscle invasive bladder tumor (no vs yes)	1.85	1.21-2.82	0.004
Location (pylon vs ureter)	0.87	0.57-1.32	0.51
Tumor multiplicity (unifocal vs multifocal)	1.29	0.86-1.96	0.21
Tumor size (< 3 cm vs > 3 cm)	1.54	1.02-2.33	0.04
Grade of tumor (G1 or G2 vs G3)	1.62	1.05-2.48	0.03
Tumor stage ($\leq$ pT2 vs $\geq$ pT3)	14.7	6.36-33.9	0.001
Lymph node status (pN0/pNx vs pN+)	5.83	3.38-10.1	0.001
Lymphovascular invasion (not vs yes)	1.57	1.03-2.40	0.04

Legend: P* - value of univariate analysis; CI - interval confidence; HR - hazard ratio

Table 4. Multivariate analysis of potential prognostic factors for cancer specific survival in 342 patients after surgical management of upper tract urothelial carcinoma (UTUC) (Cox regression models)

CHARACTERISTICS	MULTIVARIATE ANALYSIS		
	HR	95% CI	P*
Age (age) (< 60 vs > 60)	1.52	0.79-2.90	0.20
Sex (male vs female)	0.92	0.53-1.58	0.75
Anemia (no vs yes)	3.50	2.02-6.08	0.001
Piuria (no vs yes)	1.05	0.62-1.77	0.85
The history of non-muscle invasive bladder tumor (no vs yes)	1.08	0.64-1.82	0.77
Location (pylon vs ureter)	2.23	1.22-4.10	0.09
Tumor multiplicity (unifocal vs multifocal)	0.96	0.55-1.64	0.87
Tumor size (< 3 cm vs > 3 cm)	0.95	0.58-1.54	0.83
Grade of tumor (G1 or G2 vs G3)	0.69	0.33-1.47	0.35
Tumor stage ($\leq$ pT2 vs $\geq$ pT3)	11.1	3.64-33.8	0.001
Lymph node status (pN0/pNx vs pN+)	2.04	1.05-3.94	0.03
Lymphovascular invasion (not vs yes)	0.73	0.43-1.23	0.24

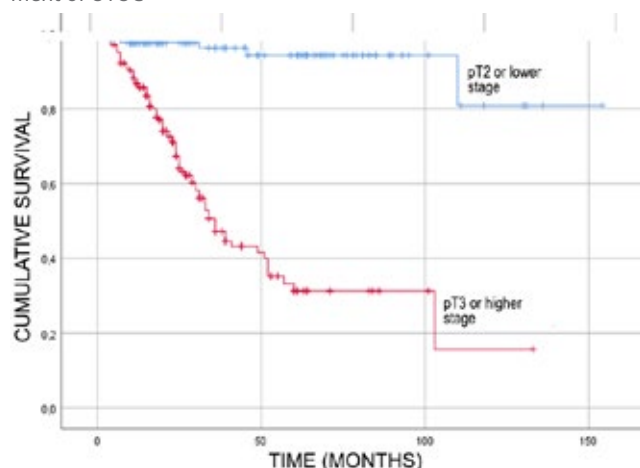
Legend: P* - value of multivariate analysis; CI - interval confidence; HR - hazard ratio

The results of the multivariate analysis showed that independent predictors of CSS can be considered preoperative anemia, pathological stage (pT) of the disease, and the presence of positive lymph nodes (N+). The prognostic significance of positive LVI was not determined, which deviates from the findings of previous studies^{5, 31}. The relationship between pathological grade and stage of the tumor concerning survival and recurrence was established by Lehmann and colleagues³². They found that the five-year CSS for patients with the pTa stage of the disease was 96.1%, while for the pT4 stage, it was 28.6%. Also, patients with the pT3 stage of the tumor do not have the same prognosis. Ciguner and colleagues found that patients with microscopic involvement of the parenchyma have significantly higher five-year CSS, without the development of metastatic disease (92%) compared to macroscopic involvement of

the surrounding tissue or involvement of the peripelvic fat tissue (8%), although they represent the same stage of pT3 disease³³.

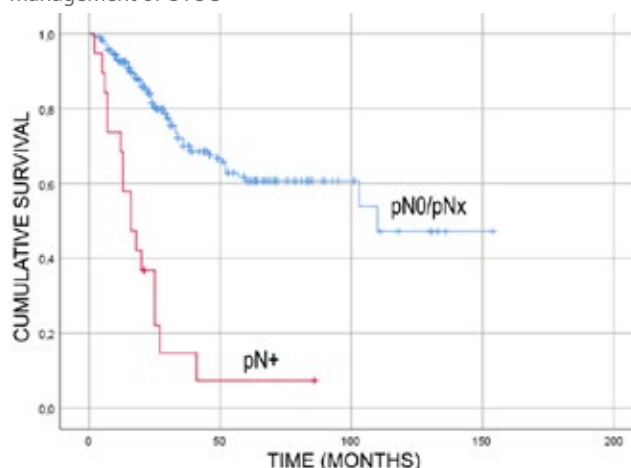
Unlike the findings of this study, Chromecki²³ found that tumor multifocality is an independent prognostic factor for both disease progression and cancer-specific mortality in patients with the localized disease treated with RNU. The difference in outcomes for patients with locally advanced disease is believed to be a result of the confusing effect of adjuvant chemotherapy. In this study, only 23% of patients received adjuvant chemotherapy, so its impact was not significant in this patient cohort. Chemotherapy in an adjuvant approach based on cisplatin is only given to patients with the pT3/pT4 stage of the disease, with or without lymphovascular invasion. There was no significant difference in patient survival based on the receipt of chemotherapy.

Figure 1. Kaplan-Meier estimates for cancer specific survival stratified according to tumor stage in 342 patients after surgical management of UTUC



We still do not have adequate data on the use of adjuvant chemotherapy in the treatment of locally advanced carcinoma of the upper urinary tract. Since these are rare tumors, the evidence is based on studies that have included less than 50 patients^{34, 35}. It is believed that adjuvant chemotherapy can achieve a remission rate of 50% but without a significant impact on patient survival³⁴. Hellenthal and colleagues³⁶ showed that chemotherapy did not affect patient survival. In a sample of 121 high-risk patients, only 22% of patients received adjuvant chemotherapy. On average, 3.1 cycles of chemotherapy were prescribed, and the

Figure 2. Kaplan-Meier estimates for cancer specific survival stratified according to lymph node status in 342 patients after surgical management of UTUC



median follow-up time was 26 months. The median survival time in the group of patients who received chemotherapy was 24 months, while in the group of patients who did not receive chemotherapy, it was 26 months. Postoperative chemotherapy had no impact on survival in high-risk patients with carcinoma of the upper urinary tract³⁵.

The limitations of this study were: retrospective design, relatively short follow-up time of patients, and the fact that the study included patients from only one institution.

Conclusion

Preoperative anemia, pathological disease stage, and the presence of positive lymph nodes are significant independent predictors of cancer-specific survival in patients who underwent RNU. Identification of prognostic factors is important to provide adequate postoperative monitoring of patients with upper urinary tract cancer, that would contribute to the decision-making process regarding the application of adjuvant chemotherapy after radical nephroureterectomy.

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