



Original Research

Impact of Variant Histology on Clinical and Pathological Outcomes in Patients with the Upper Urinary Tract Urothelial Carcinoma

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Abstract

Objectives: The objective of the study was to determine the effect of variant histology on pathological outcomes and survival in patients operated for the upper urinary tract urothelial carcinoma (UTUC).

Methods: Data of 128 patients who were operated for UTUC between 2001 and 2019 were retrospectively analyzed. Patients with pure urothelial carcinoma and patients with variant histology were compared in terms of demographics, pathological outcomes, and survival.

Results: The mean age of the patients was 65±11 years, female to male ratio was 30/98 and median follow-up period was 26.5 (1–176) months. Variant histology was detected in 14.8% of patients. Variant histology was found to be associated with surgical margin positivity, lymph node metastasis, presence of lymphovascular invasion, high tumor stage and grade (p=0.001, p=0.012, p=0.001, p=0.002, and p=0.009, respectively). Three-year cancer-specific and overall survival rates were 79.6% and 77.3%, respectively. There was no statistically significant relationship between variant histology with cancer-specific and overall survival (p=0.514 and p=0.515, respectively).

Conclusion: Variant histology of UTUC was found to be associated with locally advanced disease, but its effect on survival could not be demonstrated.

Keywords: Survival analysis, upper system transitional epithelial cell carcinoma, variant histology

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Urothelium refers to the epithelium of the urinary system, starting from the renal calyces to the urethra. While approximately 90–95% of urothelial-related malignancies originate from the bladder, the remaining 5–10% are of the upper urinary tract origin.^[1,2] Although the gold standard treatment for the upper urinary tract urothelial carcinomas (UTUCs)^[3] is radical nephroureterectomy with

bladder cuff excision, the reliability of nephron-sparing approaches has been proven in selected cases.^[4]

A large number of pre-operative and post-operative factors are used to predict the prognosis of UTUC.^[4] In recent studies, the effect of variant histology on survival in UTUC has been pointed out and suggested to be included among prognostic factors.^[5,6]

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In this study, we investigated the effect of variant histology on pathological and oncological outcomes and survival in patients operated for UTUC.

Methods

The Institutional Review Board (IRB) approval was obtained from the Hacettepe University IRB committee (Approval number: GO 21/579). The data of 128 patients who were operated for UTUC between 2001 and 2019 were analyzed retrospectively. Patients with metastasis at the time of diagnosis and those received neoadjuvant therapy were excluded from the study. All patients underwent abdominal imaging with computed tomography (CT) or magnetic resonance imaging (MRI) for diagnosis, while thorax CT was performed to assess lung metastasis. Cystoscopy was performed preoperatively to evaluate bladder tumor.

Radical nephroureterectomy was performed with bladder cuff excision. Only four patients with ureteral tumors underwent ureterectomy, bladder cuff removal, and ureteroneocystostomy. Regional lymphadenectomy was performed in patients with pathological lymph nodes on preoperative scans or patients intraoperatively exhibiting lymph node positivity. The width of the lymph node dissection was determined by the primary surgeon during surgery. Tumors were classified according to the 2009 TNM staging system. After the change in tumor ratings by the World Health Organization (WHO) in 2004, patients with a previous grade of 1–2 were categorized as low grade while those with Grade 3 were categorized as high grade. Patients were followed up with cystoscopy, urine cytology, chest X-ray, complete blood count, liver and kidney function tests, and abdominal CT/MRI scans at 3–6 month intervals for the first 2 years and then annually.

Anemia was considered for values below 12 g/dL in women and 13 g/dL in men according to the specifications of the WHO.^[7] The location of the highest T stage tumor was used to determine renal pelvis or ureter tumors. Tumor grade was used to determine the location of tumors of the same stage. Those with tumor stage Ta, CIS, and T1 were grouped as superficial tumors and those with \geq T2 as invasive tumors. In patients with multiple tumors, the tumor with the highest grade was accepted as the primary tumor. The patients were classified into two groups: Those with and without hydronephrosis according to their pre-operative imaging scans and those operated before and after 2010. Patients were evaluated according to Eastern Cooperative Oncology Group (ECOG) scoring system.^[8] All patients were divided into two groups: Those with pure urothelial carcinoma and those with variant histology.

Statistical Analysis

For univariate analysis, the Chi-square test was used for nominal data, the t-test was used for parametric variables, and the Mann–Whitney U test was used for non-parametric variables. Mean \pm standard deviation is used for parametric variables, while median and range is used for nonparametric variables. Binary logistic regression analysis was used in multivariate analysis. The Kaplan–Meier method was used for survival analysis, while the log-rank test was used to assess significance in the univariate analysis. Cox regression analysis and a backward stepwise model were used for multivariate survival analysis. All statistical analyses were performed using the Statistical Package for the Social Sciences v. 24.0 (SPSS Inc., Chicago, IL, USA) software for Windows. $P < 0.05$ was considered as the statistical significance level.

Results

The mean age of the patients was 65 ± 11 years, female to male ratio was 30/98 and median follow-up was 26.5 (3–176) months. Variant histology was observed in a total of 19 patients, including squamous in nine patients (7%), micropapillary in six patients (4.7%), sarcomatoid in two patients (1.6%), and mixed in two patients (1.6%). The demographic, clinical, and pathological data of the patients are given in Table 1. When the patients were evaluated according to operation years, no difference was found among the rates of patients diagnosed with variant histology (13.5% vs. 15.8%, $p = 0.716$).

Surgical margin positivity, lymph node metastasis, lymphovascular invasion, high stage, and grade were associated with variant histology, ($p = 0.001$, $p = 0.012$, $p = 0.001$, $p = 0.002$, and $p = 0.009$, respectively). In addition, the rate of adjuvant chemotherapy was higher among the patients with variant histology ($p = 0.001$) (Table 2).

The 3-year cancer-specific survival rate was 79.6%. Age, type of urothelial carcinoma, presence of lymphovascular invasion, tumor stage, tumor grade, lymph node metastasis, adjuvant chemotherapy, tumor size, and surgical margin positivity were found to be associated with cancer-specific survival in the univariate analysis ($p = 0.003$, $p < 0.001$, $p < 0.001$, $p = 0.001$, $p = 0.001$, $p < 0.001$, $p = 0.030$, $p = 0.007$, and $p < 0.001$, respectively). Age and presence of lymphovascular invasion were also found to be significantly associated with cancer-specific survival in the multivariate analysis ($p = 0.007$, and $p < 0.001$, respectively) (Table 3).

The 3-year overall survival rate was 77.3%. Age, type of urothelial carcinoma, preoperative anemia, presence of lymphovascular invasion, tumor stage, tumor grade,

Table 1. Demographic and clinicopathological

Parameters	n (%)
Length of hospital stay (days)	6.31±0.35
Tumor size (mm)	41.02±2.24
Age	
≥65	68 (53.1)
<65	60 (46.9)
Gender	
Female	30 (23.4)
Male	98 (76.6)
Tumor Histology	
Pure Urothelial Carcinoma	109 (85.2)
Variant Histology	19 (14.8)
Squamous	9 (7)
Micropapillary	6 (4.7)
Sarcomatoid	2 (1.6)
Mix Pathology	2 (1.6)
Preoperative Hydronephrosis	
Yes	87 (68)
No	41 (32)
ECOG Score	
0-1	119 (93)
2	9 (7)
Surgical Margin	
Positive	17 (13.3)
Negative	111 (86.7)
Adjuvant Chemotherapy	
Yes	10 (7.8)
No	118 (92.2)
Lymph Node Status	
pNx-N0	115 (89.8)
pN1-2	13 (10.2)
Accompanying CIS	
Yes	28 (21.9)
No	100 (78.1)
Type of Surgery	
Open	92 (71.9)
Laparoscopic	36 (28.1)
Primary Tumor Location	
Kidney	85 (66.4)
Ureter	43 (33.6)
Lymphovascular Invasion	
Positive	38 (29.7)
Negative	90 (70.3)
Tumor Stage	
Superficial	58 (45.3)
Invasive	70 (54.7)
Tumor Grade	
Low	30 (23.4)
High	98 (76.6)
Presence of Pre-operative Anemia	
Normal	70 (54.7)
Anemic	58 (45.3)

UTUC: Upper Tract Urothelial Carcinoma; ECOG: Eastern Cooperative Oncology Group; CIS: Carcinoma *in situ*.

lymph node metastasis, preoperative hydronephrosis, tumor size, and surgical margin positivity were found to be significant factors for overall survival in the univariate analysis ($p=0.001$, $p<0.001$, $p=0.013$, $p<0.001$, $p=0.005$, $p=0.006$, $p<0.001$, $p=0.043$, $p=0.035$, and $p<0.001$, respectively). Age and presence of lymphovascular invasion were also found to be associated with overall survival in the multivariate analysis ($p=0.006$ and $p<0.001$, respectively) (Table 4).

Recurrence was observed in 67 patients (52.3%) during the follow-up period. No significant difference was found between the recurrence rates of patients with pure urothelial carcinoma and patients with variant histology (51.4% vs. 57.9%, $p=0.600$). The rate of patients with only bladder recurrence, with only distant metastasis and with both bladder recurrence and distant metastasis were 40.3%, 40.3%, and 19.4%, respectively. Of the bladder recurrences, 62.5% were found to be high-grade tumors. At the last follow-up, 39 patients (30.5%) died due to UTUC, while seven patients (5.5%) died due to other reasons.

Discussion

In recent years, different studies have been published in which the effect of variant histological findings on pathological and oncological outcomes in patients with urothelial carcinoma was investigated. Histologic variants of urothelial carcinoma of both the bladder and upper tract have been shown to be associated with aggressive disease.^[5,9] Therefore, this study aimed to investigate the effect of variant histology on pathological and oncological outcomes and survival in patients who were operated for UTUC.

The rate of upper urinary tract carcinoma with variant histology has been reported to range between 7.9% and 24.2%.^[10-12] Variant histology was shown to be associated with higher lymph node positivity, surgical margin positivity, presence of lymphovascular invasion, advanced stage, and grade tumors.^[11,13,14] In our study, the rate of patients with variant histology was found to be 14.8% and it was observed that there was a higher rate of lymphovascular invasion, surgical margin, and lymph node positivity in the group with variant histology. These results suggest that variant histology poses a risk factor for local aggressive disease. Consequently, it is necessary to perform radical surgery to ensure local disease control in the group with variant histology while being cautious toward nephron-sparing approaches. The review of the literature shows that there is a lack of consensus on the effect of variant histology on survival. Sakano et al.^[13] and Tang et al.^[14] stated that variant histology had no effect on survival while, on the contrary, Kim et al.^[6] and Chung et al.^[12] con-

Table 2. Comparison of demographic and clinicopathological data of patients according to urothelial carcinoma histology

	Pure Urothelial Carcinoma	Variant Histology	P
Length of Hospital Stay (days)	6±3.4	7.9±1.4	0.052
Tumor Size (mm)	40.1±25.1	46.2±26.7	0.337
Age			
≥65	54 (49.5%)	14 (73.7%)	0.052
<65	55 (50.5%)	5 (26.3%)	
Gender			
Female	29 (26.6%)	1 (5.3%)	0.043
Male	80 (73.4%)	18 (94.7%)	
Preoperative Hydronephrosis			
Yes	71 (65.1%)	16 (84.2%)	0.100
No	38 (34.9%)	3 (15.8%)	
ECOG Score			
0–1	102 (93.6%)	17 (89.5%)	0.518
2	7 (6.4%)	2 (10.5%)	
Surgical Margin			
Positive	10 (9.2%)	7 (36.8%)	0.001
Negative	99 (90.8%)	12 (63.2%)	
Adjuvant Chemotherapy			
Yes	5 (4.6%)	5 (26.3%)	0.001
No	104 (95.4%)	14 (73.7%)	
Lymph Node Status			
pNx-N0	101 (92.7%)	14 (73.7%)	0.012
pN1-2	8 (7.3%)	5 (26.3%)	
Accompanying CIS			
Yes	22 (20.2%)	6 (31.6%)	0.268
No	87 (79.8%)	13 (68.4%)	
Type of Surgery			
Open	75 (68.8%)	17 (89.5%)	0.064
Laparoscopic	34 (31.2%)	2 (10.5%)	
Primary Tumor Location			
Kidney	71 (65.1%)	14 (73.7%)	0.467
Ureter	38 (34.9%)	5 (26.3%)	
Lymphovascular Invasion			
Positive	26 (23.9%)	12 (63.2%)	0.001
Negative	83 (76.1%)	7 (36.8%)	
Tumor Stage			
Superficial	39 (35.8%)	0 (0%)	0.002
Invasive	70 (64.2%)	19 (100%)	
Tumor Grade			
Low	30 (27.5%)	0 (0%)	0.009
High	79 (72.5%)	19 (100%)	
Presence of Pre-operative Anemia			
Normal	62 (56.9%)	8 (42.1%)	0.233
Anemic	47 (43.1%)	11 (57.9%)	

ECOG: Eastern Cooperative Oncology Group; CIS: Carcinoma *in situ*; Bold values indicate statistical significance.

cluded that variant histology was a significant factor on survival. Zamboni et al.^[11] carried out a multicenter study with 1610 patients and evaluated the impact of variant histological subtypes on survival, in which they reported the sarcomatoid variant as the only subtype affecting survival. In our study, variant histology was found to be associated with survival in the univariate analysis, but this

association could not be demonstrated in the multivariate analysis. The dissimilarity of the study results was attributed to the difference between patient populations. Due to these uncertainties, studies with a longer follow-up period and a higher number of patients are needed to determine the effect of variant histology on survival.

Platinum-based chemotherapy is recommended for patients

Table 3. Multivariate analysis of factors affecting cancer-specific survival

Parameters	Univariate analysis		Multivariate analysis	
	3-year CSS	P	HR (95% CI)	P
Age				
<65	77.7%	0.003	0.370 (0.178–0.766)	0.007
≥65	68.3%			
Gender				
Female	72.6%	0.095	-	-
Male	69.3%			
Type of Urothelial Carcinoma				
Pure	85.6%	<0.001	0.735 (0.291–1.855)	0.514
Variant	19.6%			
Preoperative Hemoglobin Level				
Normal	76%	0.060	-	-
Anemic	63.1%			
Lymphovascular Invasion				
Yes	27.6%	<0.001	0.156 (0.057–0.430)	<0.001
No	88.5%			
T Stage				
Ta/CIS/T1	84.5%	0.001	1.167 (0.439–3.104)	0.757
T2/T3/T4	62.2%			
G Stage				
Low	95.8%	0.001	0.253 (0.031–2.054)	0.198
High	79.6%			
Primary Tumor Location				
Kidney	70.2%	0.838	-	-
Ureter	70.4%			
Lymph Node Metastasis				
Nx-N0	76.1%	<0.001	1.013 (0.347–2.959)	0.981
N1-N2	24.2%			
Adjuvant Chemotherapy				
Yes	37.5%	0.030	1.611 (0.580–4.479)	0.360
No	74.3%			
ECOG Score				
0–1	73.6%	0.350	-	-
2	51.9%			
Pre-operative Hydronephrosis				
No	83.7%	0.208	-	-
Yes	66%			
Tumor Size				
≤3 cm	84%	0.007	0.653 (0.302–1.414)	0.280
>3 cm	63.4%			
Surgical Margin				
Negative	81.1%	<0.001	0.400 (0.143–1.116)	0.080
Positive	9.4%			

CSS: Cancer-specific survival, ECOG: Eastern Cooperative Oncology Group, Bold values indicate statistically significance.

with variant histology.^[4] However, glomerular filtration rate levels decrease to chronic kidney disease levels in a significant number of these patients after radical nephroureterectomy.^[3,15] Consequently, effective chemotherapeutic regimens can-

not be applied to these patients. Therefore, the administration of neoadjuvant chemotherapy can be considered in the foreground. Early adjuvant chemotherapy is important in patients who do not receive neoadjuvant chemotherapy. Consistently,

Table 4. Multivariate analysis of factors affecting overall survival

Parameters	Univariate analysis		Multivariate analysis	
	3-year OS	P	HR (95% CI)	P
Age				
<65	79.5%	0.001	0.386 (0.194–0.765)	0.006
≥65	59.8%			
Gender				
Female	73.5%	0.117	-	-
Male	66.6%			
Type of Urothelial Carcinoma				
Pure	76.1%	<0.001	0.750 (0.315–1.785)	0.515
Variant	16.2%			
Pre-operative Hemoglobin Level				
Normal	73.6%	0.013	0.460 (0.210–1.011)	0.053
Anemic	61.1%			
Lymphovascular Invasion				
Yes	26.1%	<0.001	0.128 (0.038–0.340)	<0.001
No	86.4%			
T stage				
Ta/CIS/T1	83%	0.005	0.936 (0.390–2.245)	0.881
T2/T3/T4	59.7%			
G Stage				
Low	83.4%	0.006	0.823 (0.256–2.640)	0.743
High	64.2%			
Primary Tumor Location				
Kidney	66.9%	0.548	-	-
Ureter	71%			
Lymph Node Metastasis				
Nx-N0	75.3%	<0.001	1.285 (0.464–3.559)	0.630
N1-N2	24.2%			
Adjuvant Chemotherapy				
Yes	37.5%	0.072	-	-
No	71.9%			
ECOG Score				
0–1	71.3%	0.208	-	-
2	34.6%			
Preoperative Hydronephrosis				
No	83.7%	0.043	0.456 (0.197–1.053)	0.066
Yes	63.1%			
Tumor Size				
≤3 cm	82.2%	0.035	0.845 (0.412–1.735)	0.647
>3 cm	61.2%			
Surgical Margin				
Negative	78.5%	<0.001	0.523 (0.190–1.434)	0.208
Positive	9.4%			

OS: Overall survival; ECOG: Eastern Cooperative Oncology Group; Bold values indicate statistically significance.

the patients with variant histology received a higher rate of adjuvant chemotherapy in our study.

The greatest limitation of our study is its retrospective structure, relatively low number of patients and short follow-up

period. Second, subgroup analysis could not be performed in terms of oncological and pathological outcomes among variant histological subtypes due to the limited number of patients. The heterogeneous structure of the group may

have led to differences in oncological and pathological outcomes. Another important point is that variant pathology can be overlooked in the pathological evaluation of the upper urinary tract tumors. Shah et al. reported that variant histological findings might be overlooked in patients with urothelial carcinoma during the pathological examination.^[16] The initial pathologist did not report any findings of variant histology in the 44% of the patients included in the study. Pathology specimens could not be re-evaluated since our study covered a period of 18 years. However, the fact that there was no significant difference between patients diagnosed with variant histology by years minimizes this limitation. At the same time, the long study period contributes to our study in determining the effects of urothelial carcinoma histology in long-term follow-up.

Conclusion

Variant histology was detected in approximately 15% of the patients upon pathological examination. Although variant histology was significantly associated with negative pathological outcomes, it was found to have no effect on survival. Radical surgery is required in patients with variant histology for local disease control since they more frequently present with aggressive pathological findings.

Disclosures

Ethics Committee Approval: Hacettepe University Non-interventional Clinical Researches Ethics Board 04.05.2021 GO 21/579.

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Conflict of Interest: None declared.

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