Impact of Variant Histology on Survival and Response to Chemotherapy in Patients with Upper Tract Urothelial Carcinoma

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INTRODUCTION

- Upper tract urothelial carcinoma (UTUC) is a rare genitourinary malignancy that represents only 5-10% of all urothelial malignancies.
- While the majority of these cancers will be derived from urothelium (urothelial carcinoma, UC), variant histology (VH) is reported in < 5% of these cases.
- VH has been shown to be a predictor of adverse outcomes in muscle-invasive bladder cancer
- In UTUC, VH has been shown to be a poor prognostic indicator largely in single or multi-institutional studies

OBJECTIVE

- To identify prognostic and treatment factors for variant histology of UTUC using a nationwide database
- To analyze the effect of adjuvant chemotherapy on overall survival.

METHODS

- The National Cancer Database (NCDB) was queried for all cases of UTUC from 2004-2016.
- Patients with other cancer diagnoses, metastasis, and/or diagnosis on autopsy were excluded.
- Kaplan-Meier and Cox proportional hazards regression were used to identify independent predictors of overall survival.

Table 1 Median survival of variant histology (months from diagnosis)

	n (% of all VH)	Median survival (95% CI)
Micropapillary	46 (4)	44.2 (28.5 - 60.0)
Sarcomatoid	201 (18)	11.5 (8.3 - 14.7)
Squamous	419 (38)	26.3 (13.1 - 39.6)
Adenocarcinoma	307 (28)	108.4 (79.1 - 137.7)
Small cell	91 (8)	12.8 (9.7 - 15.8)
Other	29 (3)	18.3 (5.9 - 30.1)

RESULTS

Table 2 Demographic and clinical characteristics of the study cohort

Variable	UC n = 27,737 (%)	VH n = 1,093 (%)	p-value
Age			<0.001
< 50	1,058 (4)	88 (8)	
50 - 59	3,429 (12)	171 (16)	
60 - 69	7,412 (27)	265 (24)	
70 - 79	9,213 (33)	361 (33)	
≥ 80	6,625 (24)	208 (19)	
Gender			0.284
Male	15,883 (57)	608 (56)	
Female	11,854 (43)	485 (44)	
Race			0.001
White	25,319 (91)	970 (89)	
Black	1,194 (4)	74 (7)	
Other	936 (3)	41 (4)	
Unknown	288 (1)	< 10	
Charlson/Deyo Score			0.053
0	18,928 (66)	756 (69)	
1	6,457 (23)	240 (22)	
>1	2,982 (11)	97 (9)	
Type of Facility			0.064
Academic/Research	10,133 (37)	429 (40)	
Community Cancer	2,262 (8)	94 (9)	
Comprehensive	11,277 (41)	397 (37)	
Other	3,869 (14)	15 (14)	
Grade			<0.001
Unknown	3,963 (14)	165 (15)	
Low	8,363 (30	372 (34)	
High	15,411 (55)	556 (51)	
T stage (pathologic)			<0.001
Tx	13320 (48)	379 (35)	
≤T1	4,575 (16)	140 (13)	
T2	2319 (8)	73 (7)	
≥T3	7523 (27)	495 (46)	
N stage (pathologic)			<0.001
Nx	15,906 (57)	582 (53)	
N0	10,160 (37)	374 (34)	
N+	1,680 (6)	137 (13)	
M stage (clinical)			<0.001
Mx	22,569 (92)	942 (86)	
M0	1,366 (5)	62 (6)	
M1	802 (3)	89 (8)	

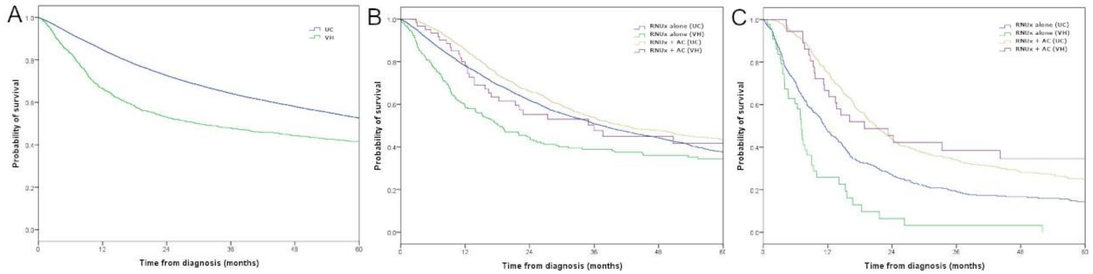

Figure 1. Kaplan-Meier curves detailing survival of patients with upper tract urothelial carcinoma. (A) Overall survival stratified by histology – urothelial carcinoma (UC) vs variant histology (VH). (B) Survival of ≥pT2N0/XM0/X patients after radical nephroureterectomy (RNUx) stratified by adjuvant chemotherapy (AC) and histology. (C) Survival of pN+M0/X patients after RNUx stratified AC and histology.

Table 3 Overall survival of upper tract urothelial carcinoma compared to variant histology by stage (months from diagnosis)

	Urothelial		Variant Histology		
	Mean (95% CI)	Median (95% CI)	Mean (95% CI)	Median (95% CI)	p-value
Overall	81.7 (80.6 - 82.7)	67.5 (65.5 - 69.5)	68.1 (63.3 - 73.0)	30.0 (22.3 - 37.8)	<0.01
≤T1	94.7 (93.4 - 96.0)	94.0 (91.1 - 96.8)	88.5 (81.4 - 95.5)	78.1 (55.8 - 100.3)	0.003
≥T2	65.0 (63.0 - 67.0)	38.2 (36.2 - 40.3)	55.5 (48.5 - 62.6)	22.1 (16.2 - 28.0)	<0.01
N+	40.4 (37.0 - 43.7)	17.1 (15.9 - 18.4)	25.2 (17.6 - 32.8)	9.4 (7.1 - 11.6)	0.001
M+	19.7 (17.1 - 22.3)	8.8 (7.7 - 10.0)	20.9 (13.9 - 27.9)	6.7 (3.9 - 9.6)	0.925

- On multivariable cox proportional hazards analysis, **VH was associated with worse overall survival** when compared to UC (HR 1.341, 95% CI 1.196 – 1.504)
- Patients who were ≥pT2N0/XM0/X or pN+M0/X after RNUx appeared to benefit from adjuvant chemotherapy across both UC and VH with improved overall survival (HR 0.817, 95% CI 0.754 – 0.884)

CONCLUSIONS

- Variant histology of the upper urinary tract is associated with later stage at presentation and worse survival when compared to UC when adjusted for stage.
- Adjuvant chemotherapy may be beneficial in a subset of these patients with advanced disease

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