Do Variant Histologies of Urothelial Carcinoma change the survival outcome in patients managed with radical cystectomy?

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Introduction:

The tenth most common type of cancer worldwide is bladder cancer, with urothelial carcinoma (UC) being the most common histology.1 Besides pure urothelial carcinoma (PUC), which is the most common UC, a wider spectrum of variant histologies (VH) has been recognized by the 2004 World Health Organization (WHO) classification of tumors of the urinary system, due to its known propensity for differentiation.2 These variants show urothelial differentiation mixed with specific morphological phenotypes, with the squamous, glandular and micropapillary being the most common, with an incidence of 20-40%, 18% and 2-5% respectively.3

Although the presence of VH, compared to the presence of pure urothelial carcinoma has been associated with more aggressive behavior4,5, conclusive data on their effect on survival outcomes are currently not well established.

One of this work's aims was to increase the awareness of the identification of those variants on pathology specimens and, in that way, better understand its clinical and therapeutic impact. VH have been reported in 7-81% of bladder cancer.6

Methods:

From 2013 to 2019, data from 181 patients (Table 1) with urothelial carcinoma (UC) treated with radical cystectomy was retrospectively collected at a single tertiary care referral center. Overall survival (OS), disease-specific survival (DSS), and recurrence-free survival (RFS) were evaluated using the Kaplan-Meier methodology and the Cox proportional hazards regression.

Descriptive statistical analysis was performed using Pearson chi-square test to compare categorical variables and Mann-Whitney-U (2 categories) or Kruskal-Wallis (3 or more categories) tests to compare continuous variables.

Statistical analysis was conducted using SPSS Statistics® v. 24.0 (IBM Corp., Armonk, New York, United States of America) and RStudio v. 1.4.1 (Integrated Development for R. RStudio, PBC, Boston, United States of America), and a p-value < 0.05 was considered significant.

Results:

Of 181 patients, 43.1% (n = 78) had VH, with the most common being squamous differentiation (n = 29), followed by mixed variants (n = 18), micropapillary variant (N=10) and other subtypes (n = 21). The median (range) follow-up was 35 (18-59) months. Kaplan-Meier survival analysis shows that median OS (Figure 1) and DSS (Figure 2) were significantly worse for VH patients (78 vs 31 months, p = 0.038; Not Reached vs 42 months; p = 0.016). At 5 years, VH was associated with a 12% and 14% decrease in OS and DSS, respectively. No significant statistical difference between the two groups was reached regarding RFS (Figure 3). However, after adjusting for confounders, such as demographic characteristics, comorbidities, and pathological features, VH were not associated with both survival outcomes (Table 2).

Discussion:

The study revealed that the incidence of bladder cancers with VH was high. Although these variants are associated with features of more aggressive behavior, the study's results did not show a significant impact on the survival expectations of the patients when all confounders were adjusted in multivariate analysis.

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Table 1 - Clinicopathological characteristics of the cohort.

	PUC (n=103; 57%)	VH (n=78; 43%)	P value
Age, median, range (years)	69 (62-74)	69 (62-75)	0,659
Male gender	88 (85%)	67(86%)	0,930
BMI 25	58 (56%)	38 (49%)	0,311
Estimated 10-year survival according CCI	21% (2-53)	21% (2-53)	0,220
TURBT muscle invasive	79 (76,7%)	65 (83,3%)	0,542
NAC	44 (42,7%)	20 (25,3%)	**0,017**
Time to RC, median, range (weeks)	19 (10-27)	16 (10-22)	0,094
Pathological stage			
T0	22 (21,3%)	5 (6,4%)	
pTa-T1-cis	31 (30,1%)	4 (5,1%)	**<0,0001**
T2	15 (14,6%)	11 (14,1%)	
T3-T4	35 (34,0%)	58 (74,4%)	
pN+	24 (23,3%)	29 (37,2%)	**0,042**
PSM	7 (6,8%)	14 (17,9%)	**0,020**
LVI	34 (33,0%)	47 (60,3%)	**<0,0001**

Legend: BMI – Body mass index; CCI – Charlson comorbidity index; LVI – Lymphvascular invasion; NAC – Neoadjuvant chemotherapy; PSM – Positive surgical margins; PUC – Pure urothelial carcinoma; RC – Radical cystectomy; VH – Variant histology
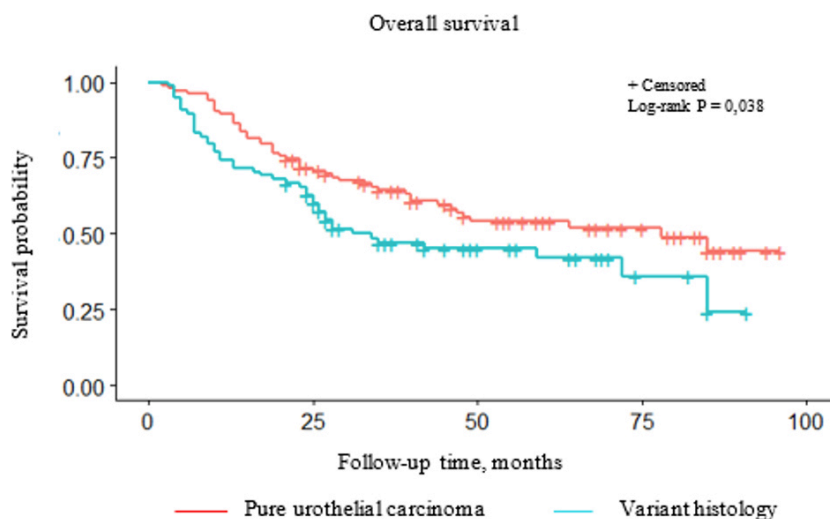
Figure 1 - The Kaplan Meier analysis assessing overall survival.
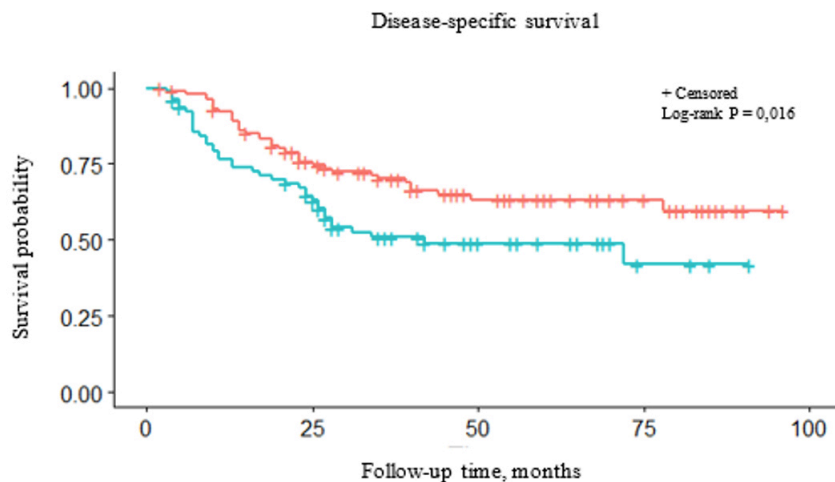
Figure 2 - The Kaplan Meier analysis assessing disease-specific survival.
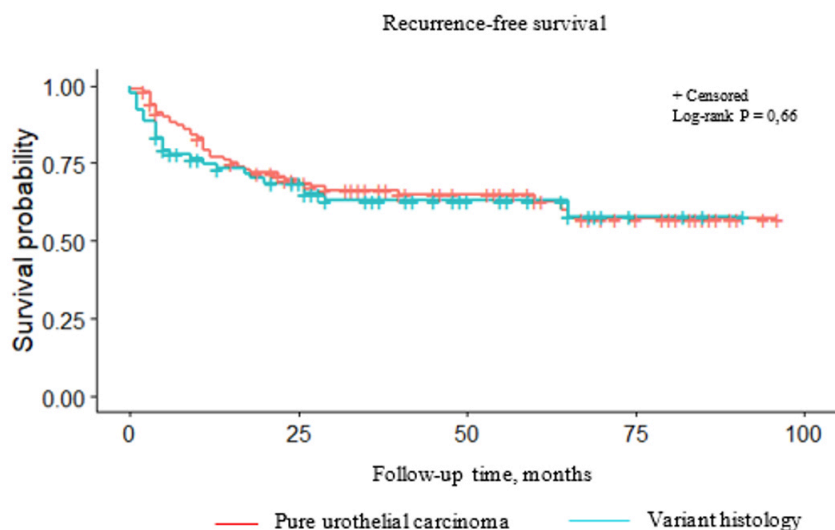
Figure 2 - The Kaplan Meier analysis assessing recurrence-free survival.

Table 2 - Multivariable Cox regression analyses predicting de risk of overall mortality (OM), disease-specific mortality (DSM), and recurrence

	OM		DSM		Recurrence	
	HR [95% CI]	**P value**	**HR [95% CI]**	**P value**	**HR [95% CI]**	**P value**
Age	0.99 [0.95;1.03]	0.55	0.99 [0.95;1.04]	0.76	0.98 [0.93;1.02]	0.34
Gender (male ref.)	0.74 [0.37;1.50]	0.41	0.86 [0.41;1.79]	0.68	0.92 [0.39;2.16]	0.85
BMI 25						
(<25.0 ref.)	0.65 [0.42;1.02]	0.06	0.63 [0.38;1.04]	0.07	0.71 [0.42;1.24]	0.23
Time to RC	1.00 [0.99;1.01]	0.18	1.00 [0.99;1.01]	0.65	1.00 [0.99;1.01]	0.79
NAC	0.76 [0.45;1.30]	0.32	0.80 [0.44;1.46]	0.47	0.95 [0.51;1.80]	0.88
Estimated 10-y survival CCI	0.99 [0.98;1.01]	0.27	0.99 [0.98;1.01]	0.69	0.99 [0.98;1.01]	0.26
pT3 (pT0-T2 ref)	3.30 [1.81;6.01]	< 0.001	4.67 [2.24;9.78]	< 0.001	3.51 [1.77;6.93]	< 0.001
pN+	1.97 [1.16;3.34]	0.01	1.93 [1.07;3.47]	0.03	32.54 [1.41;4.60]	< 0.001
PSM	1.99 [1.10;3.61]	0.02	2.35 [1.26;4.39]	0.007	0.08 [0.01;0.61]	0.01
LVI	1.54 [0.88;2.68]	0.13	2.03 [1.17;3.71]	0.02	1.93 [1.05;3.55]	0.03
PUC (ref)	-	-	-	-	-	-
VH	0.83 [0.52; 1.33]	0.44	0.91 [0.54; 1.53]	0.72	0.75 [0.42; 1.35]	0.33
Squamous	0.68 [0.36;1.31]	0.25	0.77 [0.38; 1.56]	0.47	0.72 [0.32; 1.59]	0.41
Micropapillary	0.58 [0.24;1.42]	0.23	0.63 [0.25; 1.58]	0.32	0.78 [0.28; 2.18]	0.64
Mixed	0.86 [0.41;1.81]	0.69	1.01 [0.46;2.24]	0.97	0.66 [0.35; 2.14]	0.38
Others	1.24 [0.64;2.41]	0.52	1.40 [0.46; 2.24]	0.39	0.66 [0.26; 1.69]	0.75
	Concordance (SE): 0.761 (0.026) Likelihood ratio test: p < 0.001 Wald test: p < 0.001 Score test: p < 0.001		**Concordance (SE): 0.795 (0.026)** Likelihood ratio test: p < 0.001 Wald test: p < 0.001 Score test: p < 0.001		**Concordance (SE): 0.779 (0.031)** Likelihood ratio test: p < 0.001 Wald test: p < 0.001 Score test: p < 0.001	

Legend: BMI – Body mass index; CCI – Charlson comorbidity index; LVI – Lymphvascular invasion; NAC – Neoadjuvant chemotherapy; PSM – Positive surgical margins; PUC – Pure urothelial carcinoma; RC – Radical cystectomy; VH – Variant histology

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