DOI: 10.4081/aiua.2022.2.138

ORIGINAL PAPER

# Variant histologies of urothelial carcinoma: Does it change the survival outcomes in patients managed with radical cystectomy?

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***Summary*** *Objective: To investigate the impact of variant histologies (VH) of urothelial carcinoma (UC) on survival outcomes after radical cystectomy (RC).*
*Materials and methods: Data from 181 patients with UC treated with RC between January 2013 and December 2019 at a single tertiary care referral center were retrospectively accessed. All RC specimens were assigned by genitourinary dedicated pathologists. 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.*
*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 and DS 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. However, after adjusting for confounders, such as, demographics characteristics, comorbidities and pathological features, VH were not associated with any survival outcomes.*
*Conclusions: Our study evidenced the high incidence of bladder cancers with VH. Although clearly associated with features of more aggressive behavior, VH had not any significant impact in survival expectancies when all confounders are adjusted in multivariate analyses.*

KEY WORDS: *Urothelial carcinoma; Variant histology; Radical cystectomy.*

Submitted 2 April 2022; Accepted 16 April 2022

## INTRODUCTION

Bladder cancer is the tenth most common cancer worldwide, accounting for 3% of all new cases worldwide (1). *Urothelial carcinoma* (UC) is the commonest histology of bladder cancer. However, due to its known propensity for divergent differentiation, the 2004 *World Health Organization* (WHO) classification of tumors of the urinary system recognized a wider spectrum of *variant histologies* (VH) (2). One of its aims was increase the awareness for 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% (3) and, although the presence of VH has been associated with a more aggressive behavior, conclusive data on their effect on survival outcomes are currently not well stablished. The optimal therapeutic management of this patients is based in expert opinion and so, no strong recommendations in this respect can be done. Therefore, this is the first Portuguese-based cohort to report the oncological and survival outcomes after *radical cystectomy* (RC) in patients with VH, comparing against patients with *pure urothelial carcinoma* (PUC).

## MATERIALS AND METHODS

A retrospective review was done using an electronic data search of all patients submitted to *radical cystectomy* (RC) between January 2013 and December 2019 in our Institution. The procedures were approved by the *Institutional Internal Review Board*. Overall, 240 consecutive patients were identified. Exclusion criteria were: lymph node or distant metastasis on initial staging (n = 43), pure non-urothelial carcinomas (n = 8), no transurethral resection of bladder tumor prior to RC (n = 5) and lost in follow-up or insufficient data (n = 3).
A multidisciplinary team reviewed all patients preoperatively with chest, abdominal and pelvic *computed tomography* (CT) or *magnetic resonance imaging* (MRI) if TC was contraindicated. Open RC with pelvic node dissection was performed by a team of urologists using standard techniques. All RC specimens were assigned by genitourinary dedicated pathologists and histological type was classified according to the 2004 WHO classification of tumors of the urinary system (2). Pathological stages were classified according to 2010 *American Joint Committee on Cancer* (AJCC)/*Union International Contre le Cancer* (UICC) *Tumor, Node, Metastasis* (TNM) staging classification (7th edition) (4). Only VH on RC specimens were included. For the purpose of this study, we didn't discriminate the amount of VH on the specimen and assumed that any component of VH would drive outcomes. VH with less than 10 cases were classified as other variants and more than one VH on the RC specimen as mixed variants.

No conflict of interest declared.

Patients were followed-up, at least, every 6 months for the first 2 years and then yearly with a clinical review, complete blood count and serum chemistry evaluation and CT or abdominal and pelvic ultrasonography plus chest x-ray. Additional investigation (e.g., bone scan, PET-CT, urine cytology, neocystoscopy) was performed when clinically indicated.

We aimed to prove that patients with VH had worst survival outcomes, defined as *overall survival* (OS), *disease-specific survival* (DSS) and *recurrence-free survival* (RFS), in comparison with patients with PUC. Recurrence was defined as the evidence of any locoregional or distant metastasis on imaging follow-up. Evidence of disease progression in patients with positive surgical margins was not consider as recurrence, rather persistence of disease.

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. The Kaplan-Meier method was used to estimate OS, DFS and RFS and differences between groups were assessed using log-rank test. Multivariable Cox proportional hazards regression analysis tested the effect of VH on recurrence, *disease specific* (DSM) and overall (OM) mortality after adjustment for age, gender, *body mass index* (BMI), estimated 10-year survival according to *Charlson comorbidity index* (CCI), time to RC, *neoadjuvant chemotherapy* (NAC), pathological T and N stage, *positive surgical margins* (PSM) and *lymph vascular invasion* (LVI). All models were tested for concordance probability using Wald and Score tests. Schoenfield residual plots were used to test the proportional hazards assumption. Statistical significance was considered as $p < 0.05$.

Statistical analyses were 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*).

***Table 1.***
*Clinicopathological characteristics of cohort.*

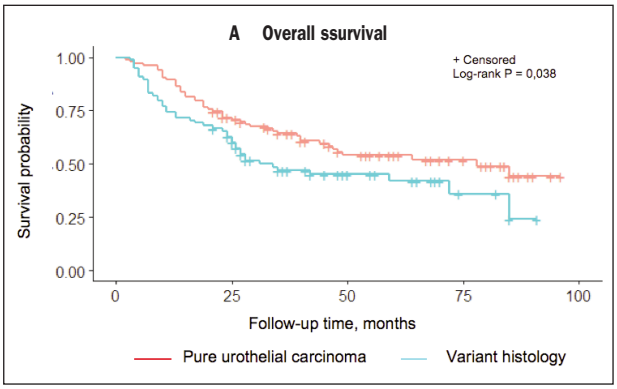
| | PUC (n = 103; 57%) | VH (n = 78; 43%) | P-value |
|---|---|---|---|
| Age. median. range (years) | 69 (62-74) | 69 (62-75) | 0.659 |
| Male gender | 88 (85%) | 67(86%) | 0.930 |
| BMI ≥ 25 | 58 (56%) | 38 (49%) | 0.311 |
| Estimated 10-year survival according CCI | 21% (2-53) | 21% (2-53) | 0.220 |
| 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<br>pTa-T1-cis<br>T2<br>T3-T4 | 22 (21.3%)<br>31 (30.1%)<br>15 (14.6%)<br>35 (34.0%) | 5 (6.4%)<br>4 (5.1%)<br>11 (14.1%)<br>58 (74.4%) | < 0.0001 |
| 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 |

*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.*

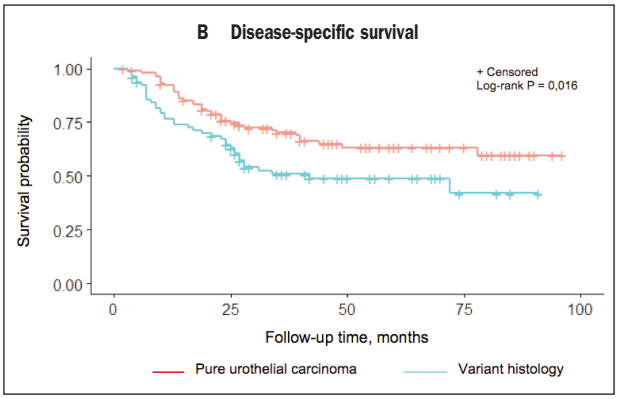
## Results

In total, 181 patients were included after meeting inclusion/exclusion criteria. Median age was 69 years [interquartile range (IQR): 62-75)] and 86% (n = 155) were male.

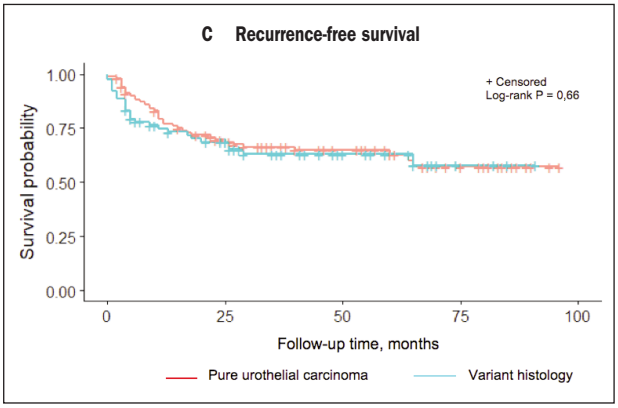
***Figure 1.***
*The Kaplan Meier analysis assessing overall survival (A), disease-specific survival (B) and recurrence-free survival (C).*
*NR – Not reached; PUC – Pure urothelial carcinoma; VH: Variant histology.*




| | Median (months) | 2-years OS | 5-years OS |
|---|---|---|---|
| PUC | 78 | 0.72 | 0.54 |
| VH | 31 | 0.63 | 0.42 |




| | Median (months) | 2-years DSS | 5-years DSS |
|---|---|---|---|
| PUC | NR | 0.76 | 0.63 |
| VH | 42 | 0.64 | 0.49 |




| | Median (months) | 2-years RFS | 5-years RFS |
|---|---|---|---|
| PUC | NR | 0.70 | 0.63 |
| VH | NR | 0.70 | 0.63 |

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

| | OM HR [95% CI] | P-value | DSM HR [95% CI] | P-value | Recurrence 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)<br>Likelihood ratio test: p < 0.001<br>Wald test: p < 0.001<br>Score test: p < 0.001 | | Concordance (SE): 0.795 (0.026)<br>Likelihood ratio test: p < 0.001<br>Wald test: p < 0.001<br>Score test: p < 0.001 | | Concordance (SE): 0.779 (0.031)<br>Likelihood ratio test: p < 0.001<br>Wald test: p < 0.001<br>Score test: p < 0.001 | |

*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.*

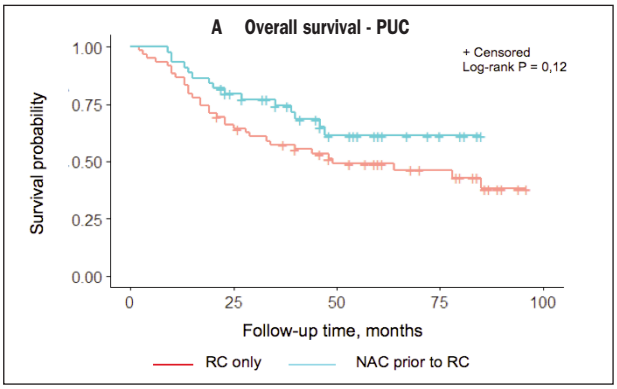
Regarding histology, 57% (n = 103) patients had PUC, whereas 43% (n = 78) patients had VH. Squamous cell differentiation (SQD; n = 29, 16.0%) was the commonest VH, followed by mixed VH (n = 18; 9.9%), micropapillary VH (MPV; n = 10, 5.5%) and others VH (n = 21; 11.6%), which comprise nested VH (n = 7; 3.9%), glandular VH (n = 5; 2.8%), sarcomatoid VH (n = 4; 2.2%), plasmacytoid (n = 3; 1.7%), microcystic (n = 1; 0.5%) and poorly differentiated (n = 1; 0.5%). Table 1 shows clinicopathological characteristics of the cohort. Patients with VH had a significantly higher pathological stage, regional lymph node metastasis, PSM and LVI, comparing to PUC patients.

The median follow-up was 35 (IQR: 18-59) months for all cases. Over that period, 50.3% (n = 91) of patients died and cancer related mortality was 40.3% (n = 73). Disease recurrence occurred in 35.4% (n = 64) of all patients. Kaplan-Meier survival analysis shows that median OS (Figure 1A) and DSS (Figure 1B) 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 1C).

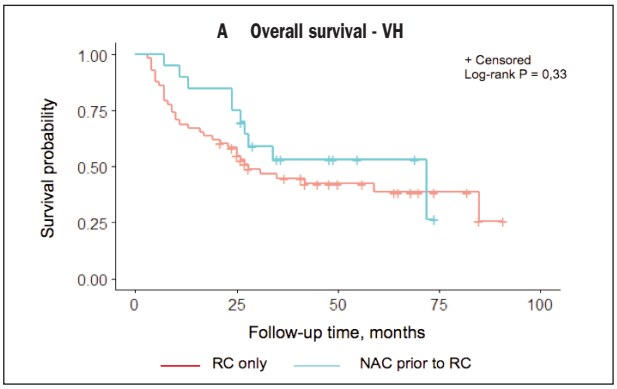
Multivariable Cox regression analyses predicting the risk of OM, DSM and recurrence are represented in Table 2. No differences were seen in these endpoints between PUC and VH patients. On the other hand, higher pathological stage, regional lymph node metastasis and PSM were all independent predictors for OM, DSM and recurrence. A significant higher proportion of patients with PUC were submitted to NAC as opposite to patients with VH (42.7% *vs* 25.3%, p = 0.017).

When we looked for the effects of NAC in survival outcomes, although no statistically significant difference was seen, patients submitted to NAC of both groups had better OS, DSS and RFS compared to patients undergoing RC only (Figure 2).

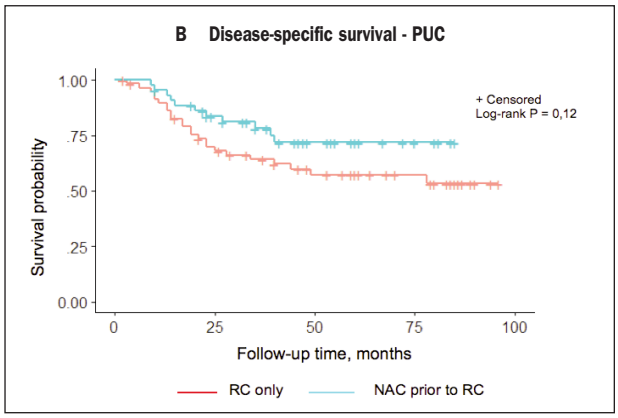
***Figure 2.***
*The Kaplan Meier analysis assessing OS (A), DSS (B) and RFS (C) in patients with PUC and VH stratified for NAC.*
*NR – Not reached; PUC – Pure urothelial carcinoma; VH: Variant histology.*



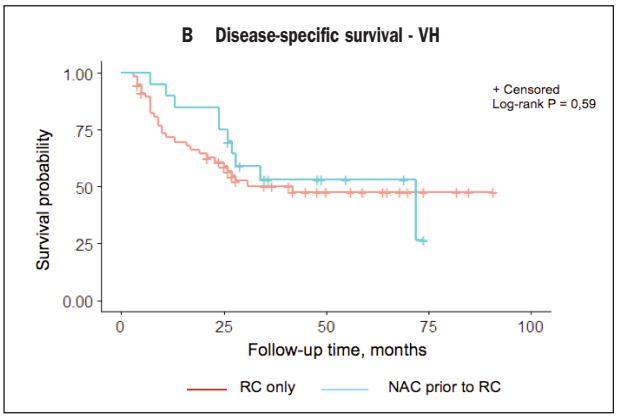

| | Median (months) | 2-years OS | 5-years OS |
|---|---|---|---|
| RC only | 49 | 0.66 | 0.49 |
| NAC prior to RC | NR | 0.80 | 0.61 |



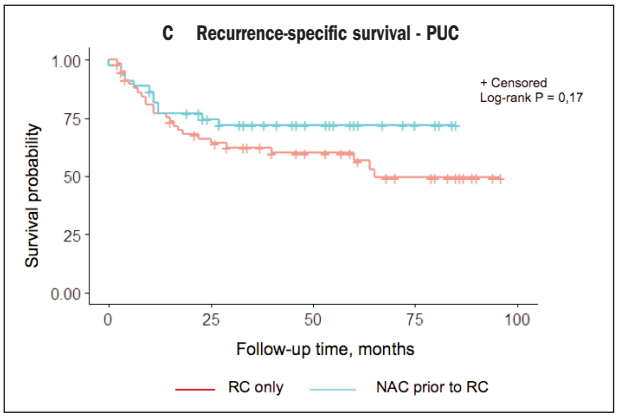

| | Median (months) | 2-years OS | 5-years OS |
|---|---|---|---|
| RC only | 28 | 0.59 | 0.39 |
| NAC prior to RC | 72 | 0.75 | 0.53 |



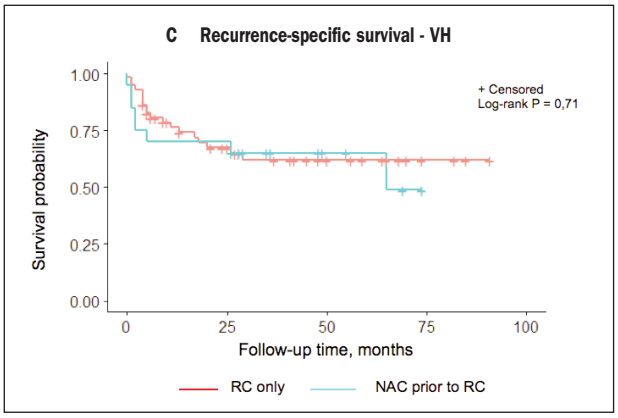

| | Median (months) | 2-years DSS | 5-years DSS |
|---|---|---|---|
| RC only | NR | 0.70 | 0.57 |
| NAC prior to RC | NR | 0.84 | 0.72 |




| | Median (months) | 2-years DSS | 5-years DSS |
|---|---|---|---|
| RC only | 42 | 0.61 | 0.48 |
| NAC prior to RC | 72 | 0.75 | 0.53 |




| | Median (months) | 2-years RSS | 5-years RSS |
|---|---|---|---|
| RC only | 65 | 0.66 | 0.57 |
| NAC prior to RC | NR | 0.75 | 0.72 |




| | Median (months) | 2-years RSS | 5-years RSS |
|---|---|---|---|
| RC only | NR | 0.67 | 0.62 |
| NAC prior to RC | 65 | 0.70 | 0.65 |

## Discussion

Over the last decade, an increasing number of studies has been published about VH and its clinical significance.

This trend is not the result of an increase in true prevalence of VH, but rather the result of a growing awareness and recognition of VH after the 2004 WHO classification of urothelial carcinomas, updated in 2016 (2, 5). As an example, *Linder et al.* re-reviewed all pathological specimens of patients submitted to RC between 1980 and 2005 and concluded that, of 1211 patients initially diagnosed with PUC, 33% were reclassified as VH (6). Similarly, *Shah et al.* reported that 44% of VH weren't documented by referral institutions, being then recognized by central pathology rereview (7).

We report that 43% of patients had VH, with SQD (16%), mixed VH (9.9%) and MPV (5.5%) being the most common variants. Although the frequency of VH reported in our cohort is superior of those reported in largest series published in the past few years, which have found prevalences of VH between 17-32%, VH subtypes proportions is in concordance, being SQD and MPV between the most common variants reported (8-11).

In our study, VH were significantly associated with predictors of more aggressive disease comparing with PUC, such as, higher pathological stages, higher rates of regional nodal involvement, higher rates of LVI and PSM. The key question is to know if whether these VH pathological findings translate in worse survival outcomes.

For the entire cohort, the 5-year OS and DSS were 49% and 57%, respectively, which were in line with a recent review, where the 5-year OS is between 36-48% for patients with non-metastatic muscle-invasive disease (12). When we looked for survival differences between VH and PUC patients, we found that patients with VH had significantly worst OS and DSS in comparison with PUC patients, with a decrease of 12 and 14% in 5 year-OS and DSS, respectively. However, after adjusting for cofounders, such as, demographics characteristics, comorbidities and pathological features, VH didn't reach statistical significance to infer it as a predictor of survival, namely, OM and DSM. The same results in multivariate Cox analyses continued to be truth when we stratified VH into subgroups, such as, SQD, MPV, mixed VH and other VH. We also didn't find any differences in uni- or multivariate analyses regarding recurrences when comparing both groups.

It probably contributes the fact that we didn't consider as recurrence patients with PSM (significantly higher in VH group) that had disease progression over the follow-up period. To date, the evidence with regard to survival outcomes in this subset of patients is based in retrospective series, with heterogenous results in stablish if whether or not VH is a true predictor of worse survival outcomes. *Xylinas et al.* reported that VH were significantly associated with more advanced tumor stages, lymph node metastasis, LVI and PSM, which as a negative effect in univariate analyses of DSS and RFS of patients with non-PUC and non-SQD variants. However, no differences were seen in multivariate Cox regression analyses (8).

*Soave et al.* stated identical results, with higher disease-specific mortality in VH patients in univariate analyses, but no differences when adjusting for cofounders (13). *Sefik et al.* concluded, in a study with nearly the size of ours, that, although patients with variant histology (especially SQD variant) have proportionally higher T stage compared to non-VH, there weren't significant differences for DSS and OS (14). In contrast, Stroman et al found that patients with VH had higher probability of death of all and disease-related causes, even after adjusting for cofounders, with HR 1.86 (95% CI: 1.21-2.85) and HR 1.89 (1.91-3.01), respectively.

A recent meta-analysis, which include 20544 patients of 39 studies, has concluded that patients with VH have worse OS (pooled HR 1.44; 95% CI 1.26-1.65; significant heterogeneity), DSS (pooled HR 1.37; 95% CI 1.24-1.50; no significant heterogeneity) and RFS (pooled HR 1.32; 95% CI 1.20-1.45; no significant heterogeneity).

Furthermore, the subgroup analyses showed that the variants with worst OS were small cell (pooled HR 3.32; 95% CI 1.98-5.59; no significant heterogeneity), plasmacytoid (pooled HR 2.03; 95% CI 1,17-3,52; significant heterogeneity) and micropapillary VH (pooled HR 1.20; 95% CI 1.02-1.41; no significant heterogeneity) (15).

The 2020 *European Urology Association Guidelines* strongly recommends to offer neoadjuvant cisplatin-based combination therapy to patients with muscle-invasive BC prior to RC, based in a 8% improve on 5-year OS (16).

However, this survival benefit of NAC was mostly seen in patients with UC histology. At the best of our knowledge, the available evidence regarding the added benefit of NAC for patients with VH is limited due to the lack of RCT. In a retrospective study, *Vetterlein et al.* evaluated the benefit of NAC in patients with muscle-invasive VH and concluded that NAC lowered the rates of non-organ-confined disease at the time of RC in patients with neuroendocrine, micropapillary, sarcomatoid and adenocarcinoma differentiation tumours. However, that pathological benefit only translates in better OS for neuroendocrine patients (HR 0.49; 95% CI 0.33-0.74; p = 0.01) (17).

In our study, patients of both groups had better OS, DSS and RFS in univariate analyses when stratified for NAC, although no statistical difference was seen.

Furthermore, the potential negative effect of delayed cystectomy due to NAC was not seen in multivariate Cox analyses, as time to cystectomy was not a predictor of worst survival outcomes.

There are several limitations that worth mention. First and foremost, it was a retrospective single-center study and our findings should be interpreted in this context. Second, RC specimens weren't re-review and so pathological findings are unified in two dedicated genitourinary pathologists. Third, the small proportions of VH limited the subanalyses and conclusions in this regard.

Fourth, there were more RC specimens with pT0 and pTa-T1-cis in the PUC group (51.4%) comparing with VH group (11.5%). For this, probably contributes the higher rate of PUC patients submitted to NAC prior to cystectomy and although it was accounted for multivariate Cox analyses, this may contribute to worse survival outcomes for VH patients.

## Conclusions

Our study evidenced the high incidence of bladder cancers with variants histologies. Although clearly associated with features of more aggressive behavior, there was not any significant impact in survival expectancies when all cofounders are adjusted in multivariate analyses. More than large prospective studies assessing outcomes of different morphology variants, we believed that the future directions are in treatment modalities targeting molecular subtypes of bladder cancer.

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