The role of neoadjuvant chemotherapy for patients with variant histology muscle invasive bladder cancer undergoing robotic cystectomy: Data from the International Robotic Cystectomy Consortium

Ian Cookea,#, Nassib Abou Heidara,#, Abdul Wasay Mahmooda, Ali Ahmada, Zhe Jinga, Michael St€ ockleb, Andrew A. Wagnerc, Morgan Roupretd, Eric Kime, Nikhil Vasdevf, Derya Balbayg, Koon Ho Rhah, Ahmed Aboumohamedi, Prokar Dasguptaj, Thomas J. Maatmank, Lee Richstonel, Peter Wiklundm, Franco Gaboardin, Qiang Lia, Ahmed A. Husseina, Khurshid Gurua,*

a Roswell Park Comprehensive Cancer Center, Buffalo, NY
b Saarland University Medical Center (UKS), Homburg, Germany
c Beth Israel Deaconess Medical Center, Boston, MA
d Pitie-Salpetriere Hospital, Paris, France
e Washington University St. Louis, St. Louis, MO
f Lister Hospital (ENHT NHS Trust), Stevenage, United Kingdom
g Ko ¸ c University Hospital, Zeytinburnu/ _ Istanbul, Turkey
h Yonsei Medical Health Care System, Sinchon-dong, Seodaemun District, South Korea
i Montefiore Medical Center, The Bronx, New York, NY
j Guy's Hospital, London, United Kingdom
k Metro Health Hospital, Cleveland, OH
l Arthur Smith Institute for Urology, Lake Success, NY
m Karolinska Institute, Solna, Sweden
n Luigi Sacco, Milano, Italy

Received 8 August 2023; received in revised form 14 December 2023; accepted 1 January 2024

Abstract

Objective: To assess the role of neoadjuvant chemotherapy (NAC) before robot-assisted radical cystectomy (RARC) for patients with variant histology (VH) muscle-invasive bladder cancer (MIBC).

Methods: Retrospective review of 988 patients who underwent RARC (2004–2023) for MIBC. Primary outcomes included the utilization of NAC among this cohort of patients, frequency of downstaging, and discordance between preoperative and final pathology in terms of the presence of VH. Secondary outcomes included disease-specific (DSS), recurrence-free (RFS), and overall survival (OS).

Results: A total of 349 (35%) had VH on transurethral resection or at RARC. The 4 most common VH subgroups were squamous (n = 94), adenocarcinoma (n = 64), micropapillary (n = 34), and sarcomatoid (n = 21). There was no difference in OS (log-rank: P = 0.43 for adenocarcinoma, P = 0.12 for micropapillary, P = 0.55 for sarcomatoid, P = 0.29 for squamous), RFS (log-rank: P = 0.25

for adenocarcinoma, P = 0.35 for micropapillary, P = 0.83 for sarcomatoid, P = 0.79 for squamous), or DSS (log-rank P = 0.91 for adenocarcinoma, P = 0.15 for micropapillary, 0.28 for sarcomatoid, P = 0.92 for squamous) among any of the VH based on receipt of NAC. Patients with squamous histology who received NAC were more likely to be downstaged on final pathology compared to those who did not (P < 0.01).

#Ian Cooke and Nassib Abou Heidar had equal contributions to the manuscript.
*Corresponding author. Tel.: +716-845-4155; fax: +716-845-3300.
E-mail address: Khurshid.Guru@roswellpark.org (K. Guru).

https://doi.org/10.1016/j.urolonc.2024.01.002
1078-1439/Ó 2024 Published by Elsevier Inc.
ARTICLE IN PRESS
Urologic Oncology: Seminars and Original Investigations 000 (2024) 1–9

Conclusion: Our data showed no significant difference in OS, RFS, or DSS for patients with VH MIBC cancer who received NAC before RARC. Patients with the squamous variant who received NAC had more pathologic downstaging compared to those who did not.
The role of NAC among patients with VH is yet to be defined. Results were limited by small number in each individual group and lack of exact proportion of VH. Ó 2024 Published by Elsevier Inc.

Keywords: Guidelines; Compliance; Multidisciplinary; Prostate Cancer

1. Introduction

Neoadjuvant cisplatin-based chemotherapy (NAC) has been shown to improve overall survival for patients with muscle-invasive urothelial bladder cancer (MIBC) [1]. However, there is a lack of evidence of the benefit of NAC for patients with variant histology (VH). A large recent retrospective study of patients in the National Cancer Database found that NAC was associated with improved overall survival (OS) for patients with sarcomatoid or neuroendocrine variants of urothelial carcinoma, but not for micropapillary, squamous, or adenocarcinoma subtypes [2]. Another retrospective analysis found that NAC was associated with lower odds of extravesical disease among patients with VH but only showed a survival benefit for patients with neuroendocrine tumors [3].

The International Robotic Cystectomy Consortium (IRCC) comprises 4,073 patients from 31 institutions across 11 countries. The IRCC has a robust pooled dataset as well as long-term follow-up for patients undergoing robot-assisted radical cystectomy (RARC) [4]. Our goal was to describe the utilization of NAC, report the frequency of pathologic downstaging, and survival outcomes among patients who underwent RARC for MIBC with VH using this multi-institutional dataset.

2. Methods

Our study was a multi-institutional retrospective study that examined patients who underwent RARC between the years 2004 and 2023. Patients who had MIBC (≥ cT2) and VH at transurethral resection (TUR) or at cystectomy were included. Patients with nonmuscle invasive bladder cancer at TUR were excluded as these patients would typically not be considered candidates for NAC. Also, those with cN positive disease and those who received suboptimal NAC (<3 cycles of Cisplatin-based combination chemotherapy, or non-Cisplatin -based regimens) were excluded. For some patients, VH found on TUR specimens was discordant with the final pathology seen at the time of cystectomy. We classified patients who had only a single variant subtype present either at the time or TUR or on final pathology according to that subtype. We classified those who had multiple or discordant VH as "multiple." We classified patients as pure urothelial if only urothelial carcinoma was seen on both TUR and final pathology with no variant subtype listed by the pathologist. Our dataset did not allow us to subdivide patients according to the proportion of pathologic specimens which represented VH, and thus we treated the presence of VH as a categorical variable without accounting for the percentage present as VH pure urothelial cancer.
Upstaging was defined as higher pT compared to cT, while downstaging was defined as lower pT compared to cT. Patients were classified into those who received NAC versus those who did not. Primary outcomes included the utilization of NAC among this cohort of patients, frequency of downstaging, and discordance between preoperative and final pathology in terms of the presence of VH. Secondary outcomes included disease-specific (DSS), recurrence-free (RFS), and overall survival (OS).
Descriptive statistics were used to summarize the data. The Wilcoxon Rank Sum test was used to compare continuous variables and Fisher's exact test was used for categorical variables. Kaplan Meier method was used to depict DSS, RFS, and OS. Multivariable analysis with forward model selection was used to identify the variables associated with DSS, RFS, and OS. All tests were double-sided, with a significance level of 0.05. Statistical analysis was performed with SAS 9.4.

3. Results

The final cohort comprised 349 patients with MIBC and VH, of who 80 (23%) received NAC. Median age was 70 (IQR 63–76), 263 (75%) were males, and 12% received neobladders. Eighty-two (23%) had 2 or more variants involved, 94 (27%) had squamous, 64 (18%) had adenocar-

cinoma, 34 (10%) had micropapillary, and 21 (6%) had sarcomatoid carcinoma. Median follow-up was 3.3 years (IQR 1.4, 8.1). Patients with pure urothelial histology were more likely to receive NAC when compared to patients with VH (29% vs. 23%, P = 0.04).

Patients who received neoadjuvant chemotherapy were younger (67 vs. 71, P < 0.001), had less median blood loss (200 ml vs. 300 ml, P = 0.001), and received intracorporeal urinary diversion (89% vs. 68%, P < 0.001). They had pT3 disease or higher less frequently on final pathology (45% vs. 61%, P = 0.014) (Table 1A–B). Patients with squamous VH who received NAC significantly downstaged at final pathology compared to those who did not receive NAC (29% vs. 15%, P < 0.01). This was not demonstrated for other VH subtypes (Table 2).

Table 1A
Demographics and perioperative outcomes of patients with MIBC who underwent RARC (bold refers to statistically significant variables).

Variable	MIBC without NAC	MIBC with NAC	All	P-value
N of patients, N (%)	269 (77)	80 (23)	349	-
Age, median (IQR)	71 (64,78)	67 (58,72)	70 (63,76)	< 0.001
Male, N (%)	198 (74)	65 (81)	263 (75)	0.185
BMI, median (IQR)	27.1 (23.9,30.1)	28.5 (26.1,31.1)	27.4 (24.2,30.5)	0.023
ASA ≥ 3, N (%)	134 (52)	47 (59)	181 (54)	0.302
Charlson Comorbidity Index, Median (IQR)	5 (4,6)	5 (4,5)	5 (4,6)	< 0.001
Preoperative radiation, N (%)	21 (8)	3 (4)	24 (7)	0.315
Preoperative abdominal surgery, N (%)	136 (52)	28 (35)	164 (48)	0.010
cT3 or higher, N (%)	38 (14)	11 (14)	49 (14)	1.000
- cT2, N (%)	231 (86)	69 (86)	300 (86)	0.27
- cT3, N (%)	21 (8)	9 (11)	30 (9)	
- cT4, N (%)	17 (6)	2 (3)	19 (5)	
Preoperative GFR, median (IQR)	72.0 (55.3,85.6)	72.3 (54.8,91.9)	72.0 (55.1,86.7)	0.329
Preoperative hydronephrosis, N (%)	63 (24)	20 (25)	83 (24)	0.882
Lymph node yield, median (IQR)	19 (14,28)	23 (18,31)	20 (15,28)	0.005
Estimated blood loss (ml), median (IQR)	300 (150,500)	200 (100,300)	250 (150,400)	0.001
Blood transfusion, N (%)	13 (5)	9 (12)	22 (6)	0.062
Intracorporeal diversion approach, N (%)	177 (68)	68 (89)	245 (73)	< 0.001
Neo-bladder urinary diversion, N (%)	28 (10)	14 (18)	42 (12)	0.115
Operative time (hours), median (IQR)	6.3 (5.2,7.7)	6.2 (5.2,7.4)	6.2 (5.2,7.6)	0.645
Postoperative ICU admission, N (%)	119 (44)	40 (50)	159 (46)	0.374
Days of ICU stay if admitted, median (IQR)	1 (1,2)	2 (1,2)	1 (1,2)	0.299
In-hospital stay (days), median (IQR)	8 (6,13)	7 (5.5,10.5)	8 (6,12)	0.013
Return to OR within 30 Days, N (%)	20 (7)	9 (11)	29 (8)	0.354
Cystectomy era 2004–2010, N (%)	73 (27)	5 (6)	78 (22)	< 0.001

Cystectomy era 2011–2014, N (%) 50 (19) 19 (24) 69 (20)
Cystectomy era 2015–2018, N (%) 87 (32) 22 (27.5) 109 (31)
Cystectomy era 2019–2023, N (%) 59 (22) 34 (42.5) 93 (27)
Table 1B
Pathological outcomes of patients with MIBC who underwent RARC (bold refers to statistically significant variables).
Variable MIBC without NAC MIBC with NAC All P-value
Single variant histology involved, N (%) 209 (78) 58 (73) 267 (77) 0.368
2 or more variant histology involved, N (%) 60 (22) 22 (27) 82 (23)
Adenocarcinoma, N (%) 60 (22.3) 4 (5.0) 64 (18.3) 0.001
Clear cell, N (%) 0 (0) 1 (1.3) 1 (0.3)
Giant cell, N (%) 4 (1.5) 0 (0) 4 (1.2)
Lymphoepithelial, N (%) 4 (1.5) 4 (5.0) 8 (2.3)
Micropapillary, N (%) 21 (7.8) 13 (16.3) 34 (9.7)
Nested, N (%) 6 (2.2) 3 (3.8) 9 (2.6)
Neuroendocrine, N (%) 1 (0.4) 1 (1.3) 2 (0.6)
Plasmacytoid, N (%) 2 (0.7) 4 (5.0) 6 (1.7)
Sarcomatoid, N (%) 17 (6.3) 4 (5.0) 21 (6.0)
Small cell, N (%) 8 (3.0) 2 (2.5) 10 (2.9)
Squamous, N (%) 73 (27.1) 21 (26.3) 94 (26.9)
Other, N (%) 13 (4.8) 1 (1.3) 14 (4.0)
Multiple (≥ 2 types), N (%) 60 (22.3) 22 (27.5) 82 (23.5)
pT3 or higher, N (%) 164 (61) 36 (45) 200 (57) 0.014
-pT0, N (%) 12 (4) 20 (25) 32 (9) < 0.001
-pT1, N (%) 9 (3) 2 (2) 11 (3)
-pT2, N (%) 69 (26) 16 (20) 85 (25)
-pT3, N (%) 115 (43) 28 (35) 143 (41)
-pT4, N (%) 49 (18) 8 (10) 57 (16)
-pTa/CIS, N (%) 15 (6) 6 (8) 21 (6)
pN+, N (%) 70 (26) 20 (25) 90 (26) 1.000
Positive surgical margin, N (%) 32 (14) 7 (9) 39 (13) 0.326

There was no significant difference among patients who received NAC versus those who did not among various VH subtypes for RFS (adenocarcinoma: log-rank P = 0.25, micropapillary: log-rank P = 0.35, and sarcomatoid: log-rank P = 0.83 and squamous: log-rank P = 0.79); DSS (adenocarcinoma: log-rank P = 0.90, micropapillary: log-rank P = 0.15, sarcomatoid: log-rank P = 0.28 and squamous: log-rank P = 0.92) or OS (adenocarcinoma: log-rank P = 0.43, micropapillary: log-rank P = 0.12, sarcomatoid: log-rank P = 0.55 and squamous: log-rank P = 0.29) (Figs. 1–4).

On multivariable analyses, age (HR 1.04, 95% CI 1.02–1.06, P < 0.001), blood transfusion (HR 2.40, 95% CI 1.30–4.43, P = 0.005), preoperative hydronephrosis (HR 1.65, 95% CI 1.10–2.47, P = 0.015), pN+ (HR 2.38, 95%

CI 1.59–3.57, P < 0.001), pT3 or higher (HR 4.62, 95% CI 2.74–7.77, P < 0.001), were associated with RFS. Positive surgical margin (HR 1.99, 95% CI 1.10–3.60, P = 0.022), age (HR 1.04, 95% CI 1.01–1.07, P = 0.007), pN+ (HR 2.09, 95% CI 1.23–3.56, P = 0.007), and pT3 or higher (HR 6.93, 95% CI 3.10–15.53, P < 0.001), were associated with DSS. Age (HR 1.04, 95% CI 1.02–1.06, P < 0.001), ICU admission (HR 1.59, 95% CI 1.09–2.30, P = 0.015), positive margin status (HR 1.91, 95% CI 1.24–2.96, P = 0.004), pN+ (HR 2.04, 95% CI 1.39–3.01, P < 0.001) and pT3 or higher on final pathology (HR 4.12, 95% CI 2.55–6.65, P < 0.001) were associated with OS (Table 3A–C). There was no statistical difference between NAC and no NAC in RFS, DSS, or OS for all the VH subtypes (Table 4A–C).

4. Discussion

Approximately 25% of bladder cancer comprise histological variants of urothelial cancer [5]. More recently, VH has been increasingly recognized as an important factor that can significantly affect prognosis and treatment strategies. [6] As VH might confer a poorer prognosis and a higher stage at diagnosis, this might warrant treatment intensification with NAC. On the other hand, futile NAC for VH might increase the risk of disease progression. The role of NAC is well established for patients with pure urothelial histology MIBC, with approximately 16% reduction in the risk of mortality and a 6% improvement in survival at 10 years [7,8]. However, the role of NAC in patients with VH is unclear, with most of the data being retrospective. Some retrospective studies have found an association between NAC and improved survival in patients with neuroendocrine or sarcomatoid variants, but this pattern has not been consistent across other studies [2,3]. Neoadjuvant chemotherapy does not seem to offer a survival benefit for patients with squamous cell carcinoma of the bladder—but this may not be the case for urothelial carcinoma with squamous differentiation [9]. On the other hand, plasmacytoid VH is known to be sensitive to chemotherapy but does confer a more aggressive form of bladder cancer biology [10,11]. Previous studies showed conflicting results regarding the benefit of NAC for VH. Multiple studies showed no survival benefit for NAC for squamous variant [9,12–14]. Similarly, Kamat et al. and Meeks et al. found no benefit for NAC for the micropapillary variant [15,16]. On the other hand, Lynch et al. reported improved survival among the squamous variant [14], and Vetterlein et al. and

Hajiran et al. found a survival benefit for NAC in mixed VH [3,17] (Table 5).

We found that NAC was associated with a higher likelihood of pT0 on final pathology in patients with squamous differentiation (29% vs. 4%, P < 0.01), adenocarcinoma (25% vs. 3%, P = 0.18), micropapillary (15% vs. 5%, P = 0.74) and sarcomatoid (25% vs. 12%, P = 0.23); however, adenocarcinoma, micropapillary and sarcomatoid were not statistically significant and did not translate to a survival benefit. It is unknown whether this is related to the proportion of variant histology in comparison with the urothelial carcinoma component. Our findings contrast with those of the S8710 trial for MIBC, which showed improved survival with NAC in a subset of patients with squamous or glandular differentiation. [18] Our data showed improved downstaging, which could potentially have oncological benefits. Some data has shown that the largest survival advantage for those with pure urothelial cancer receiving NAC is among the patients that are downstaged to pT0 at the time of cystectomy [19,20]. Less is known about the

Table 2
Up and downstaging on final pathology among patients with adenocarcinoma, micropapillary, squamous, and sarcomatoid VH, and MIBC (bold refers to statistically significant variables).

Type	Adenocarcinoma		Micropapillary		Squamous		Sarcomatoid	
Group	NAC	No NAC	NAC	No NAC	NAC	No NAC	NAC	No NAC
pT0 (%)	1 (25)	2 (3)	2 (15)	1 (5)	6 (29)	3 (4)	1 (25)	2 (12)
Down (%)	1 (25)	9 (15)	1 (8)	2 (9)	0 (0)	8 (11)	1 (25)	1 (6)
Same (%)	1 (25)	19 (32)	6 (46)	8 (38)	4 (19)	24 (33)	1 (25)	3 (17)
Up (%)	1 (25)	30 (50)	4 (31)	10 (48)	11 (52)	38 (52)	1 (25)	11 (65)
Total	4 (100)	60 (100)	13 (100)	21 (100)	21 (100)	73 (100)	4 (100)	17 (100)
P-value	0.18	0.74	<0.01	0.23				

impact of downstaging on the survival of patients with VH. Catarino, et al. found that patients with VH were less likely to be downstaged after NAC than patients with only urothelial cancer [21]. Zargar-Shoshtari et al. found that among patients with squamous or glandular differentiation, NAC was associated with improved rates of pathologic downstaging but no changes in OS [22]. Similarly, we observed improvements in the rates of downstaging for the VH without associated significant changes in OS, RFS, or DSS. As VH urothelial carcinoma cases are usually diagnosed at a more advanced stage, [21] clinical and pathological downstaging might confer an oncological benefit.

Figure 1. A–C. Kaplan Meier curves depicting RFS, DSS, and OS for

patients with MIBC and adenocarcinoma variant histology who received NAC before RARC versus those who did not.
Figure 2. A–C. Kaplan Meier curves depicting RFS, DSS, and OS for patients with MIBC and micropapillary variant histology who received NAC before RARC versus those who did not.

Our data did not show any evidence of oncological benefits in terms of survival or downstaging of the micropapillary variant. Prior published data concerning micropapillary variants are mostly retrospective. Previously published series did not show survival benefits, but some cohorts showed reduced extravesical extension [3] and improved downstaging to pT0 [16].
The study of NAC in VH is further complicated by the fact that many patients may have multiple variants. In our data, 23.5% of the VH patients had multiple VH simultaneously. In patients with predominantly pure urothelial carcinoma, it is conceivable that the histologic percentage of VH present would impact the response to therapy and have prognostic implications, but given the relatively small sample sizes, it
Figure 3. A–C. Kaplan Meier curves depicting RFS, DSS, and OS for patients with MIBC and squamous variant histology who received NAC before RARC versus those who did not.
Figure 4. A–C. Kaplan Meier curves depicting RFS, DSS, and OS for patients with MIBC and sarcomatoid variant histology who received NAC before RARC versus those who did not.

is difficult to study VH patients with this level of granularity. We treated the presence of VH categorically, in part because of the multi-institutional nature of our study and the lack of standardization of reporting among pathologists. Another issue that has rarely been addressed is that suboptimal chemotherapy regimens in retrospective studies are prevalent in databases, and this has been previously shown to confer suboptimal survival benefits to MIBC patients. [23]
The small-cell variant of urothelial carcinoma is another variant that rarely presents as localized. In those cases, management is directed mainly toward a chemotherapy regimen borrowed from small cell lung cancer, which is highly chemosensitive. In these cases, cisplatin/etoposide is a preferable regimen over the traditional cisplatin-based systemic treatment for urothelial carcinoma. [14,24] Although guidelines still do not widely advocate for the use of NAC for patients with VH (except for small cell carcinoma) MIBC,

it is still frequently utilized. In our dataset, 80 of 349 patients (23%) with VH received NAC despite a dearth of prospective data showing its efficacy. Given that NAC increases the time to surgery and has associated adverse effects without clear survival benefits, clinicians should utilize NAC thoughtfully in the VH population.

To our knowledge, the current study represents 1 of the largest for NAC and VH. However, some of the less common variants still had relatively few patients. Because of the limitations of our multi-institutional dataset, we were only able to represent histological data categorically, without the ability to differentiate between patients with respect to the proportions of the variant histology. Moreover, there was no dedicated central pathology review, which introduces the possibility of missing variant histology as well as interobserver variability between different pathologists. Another potential limitation of the current study is the lack of a standardized NAC regimen among the patients, as different regimens can yield potentially different clinical efficacy. In addition, owing to the retrospective and

Table 3A
Multivariate analysis for predictors of RFS (bold refers to statistically significant variables).

Variable	Hazard ratio	Confidence interval	P
Age	1.04	1.02–1.06	<.001
Blood transfusion	2.40	1.30–4.43	0.005
Preoperative hydronephrosis	1.65	1.10–2.47	0.015
pN+	2.38	1.59–3.57	<.001
pT3 or higher	4.62	2.74–7.77	<.001

Table 3B
Multivariate analysis for predictors of DSS (bold refers to statistically significant variables).

Variable	Hazard ratio	Confidence interval	P
Positive surgical margin	1.99	1.10–3.60	0.022
Age	1.04	1.01–1.07	0.007
pN+	2.09	1.23–3.56	0.007
pT3 or higher	6.93	3.10–15.53	<.001

Table 3C
Multivariate analysis for predictors of OS (bold refers to statistically significant variables).

Variable	Hazard ratio	Confidence interval	P
Age	1.04	1.02–1.06	<.001
ICU admission	1.59	1.09–2.30	0.015
Positive margin status	1.91	1.24–2.96	0.004
pN+	2.04	1.39–3.01	<.001
pT3 or higher	4.12	2.55–6.65	<.001

*Table 3A–3C: Age, gender, BMI, Caucasian Race, ASA ≥ 3, Charlson

Comorbidity Index, Previous Radiation, Previous Abdominal Surgery, Preop Hydronephrosis, Neoadjuvant Chemotherapy, ICU Admission, Hospital Stay, Blood Transfusion, Lymph Node Yield, Intracorporeal Diversion, Neobladder Type, Estimated Blood Loss, Operative Time, Pathological Grade 3, pN+, pT3/pT4, Positive Surgical Margin, RARC Yearly Volume, Pathological Additional Variant Histology were included in the univariate analysis.

Table 4A
RFS Hazard ratio of NAC exposure on different variant histology types.

Histology that treated with NAC	Hazard ratio	Confidence interval	P
Adenocarcinoma	–	–	0.993
Micropapillary	0.56	(0.16, 1.93)	0.355
Sarcomatoid	1.19	(0.25, 5.73)	0.830
Squamous	1.11	(0.52, 2.37)	0.795

Table 4B
DSS hazard ratio of NAC exposure on different variant histology types.

Histology that treated with NAC	Hazard ratio	Confidence interval	P
Adenocarcinoma	0.88	(0.12, 6.73)	0.905
Micropapillary	0.29	(0.05, 1.7)	0.171
Sarcomatoid	0.33	(0.04, 2.77)	0.305
Squamous	0.95	(0.34, 2.64)	0.921

Table 4C
OS hazard ratio of NAC exposure on different variant histology types.

Histology that treated with NAC	Hazard ratio	Confidence interval	P
Adenocarcinoma	0.46	(0.06, 3.38)	0.444
Micropapillary	0.34	(0.08, 1.39)	0.132
Sarcomatoid	0.63	(0.13, 2.98)	0.556
Squamous	0.68	(0.33, 1.40)	0.291

nonrandomized nature of our study design, there is a high likelihood of bias in the selection process of patients who were deemed to be candidates for NAC.

5. Conclusion

Our study found that there were significantly higher rates of pathologic downstaging in patients with the squamous variant who received NAC. There were no significant differences in OS, RFS, or DSS among patients with VH based on the receipt of NAC. This study highlights the need for specialized genitourinary pathologists who can best define patients' pathology at the time of TURBT so that the

presence of VH can be appropriately identified, and the most informed treatment decisions can be made regarding the care of MIBC patients. Future research and prospective, randomized data are needed to better define the role of NAC in patients with VH bladder cancer.

Table 5
Summary of literature discussing NAC in VH MIBC.

Author	Year	No. of patients	Histology	Chemotherapy	Benefit for NAC?
Current	2023	349 (80 NAC)	Squamous = 27% Micropapillary = 10% Adenocarcinoma = 18% Sarcomatoid = 6% Small cell = 3%	NA	No
Fu et al. [25]	2021	5,335 total 419 VH	15% Squamous 7% glandular 17% micropapillary 45% small cell 15% sarcomatoid	NA	NA
Stensland et al. [12]	2020	828 (53 NAC)	Squamous	NA	No
Hajiran et al. [17]	2020	410 pure UC 173 VH	NA	NA	Yes
Dotson et al. [9]	2019	671 (48 NAC)	Squamous	NA	No
Matulay et al. [13]	2019	260 (75 NAC)	Squamous	NA	No
Vetterlein et al. [3]	2017	2018 (369 NAC)	Micropapillary = 8% Sarcomatoid = 15% Squamous = 40% Adenocarcinoma= 18% Neuroendocrine= 13% Other = 6%	MVAC or GC	Yes (most benefit for Neuroendocrine tumors)
Pokuri et al. [26]	2016	50	Mixed	Cisplatin-based = 96% non-cisplatin based = 4%	No
Sui et al. [27]	2016	4,397,188 total 3,083 NAC 31 Micropapillary	Micropapillary (31 patients)	NA	No
Lin et al. [28]	2013	195 (37 NAC)	Mixed	MVAC = 42% GC = 25% Gemcitabine +carboplatin = 33%	No

Lynch et al. [14] 2013 172 (48 NAC) Squamous ifosfamide+doxorubicine
+etoposide +cisplatin = 54%
etoposide +cisplatin = 15%
MVAC = 10% paclitaxel
+methotrexate +cisplatin = 6%
cisplatin+gemcitabine
+ifosfamide = 4% etoposide
+doxorubicin +cisplatin = 4%
ifosfamide +doxorubicine = 2%
gemcitabine
+cyclophosphamide = 2%
gemcitabine+doxorubicin
+paclitaxel = 2%
Yes
Meeks et al. [16] 2013 44 (29 NAC) Micropapillary GC = 21
GC+sunitinib=2 gemcitabine
+carboplatin=2
paclitaxel+GC= 3
MVAC=1
No
Siefker-Radtke et al. [24] 2009 65 (43%VH) Mixed MVAC NA
Kamat et al. [15] 2007 100 (23 NAC) Micropapillary NA No

Declaration of competing interest
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.
Acknowledgments
Roswell Park Alliance Foundation.
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