

Discrepancies between Preoperative and Postoperative Histology following Robot Assisted Radical Cystectomy

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ABSTRACT

Introduction and Objective: We aimed to investigate the discrepancy between preoperative and postoperative histology in terms of the presence of variant histology (VH) following Robot-Assisted Radical Cystectomy (RARC) and its impact on oncologic outcomes.

Methods: A retrospective review of the multi-institutional prospectively maintained database, the International Robotic Cystectomy Consortium (IRCC), was performed. Preoperative histology was compared with the histology at RARC to determine discrepancies in terms of the presence of VH. Descriptive statistics were used to summarize the data. Multivariate analysis (MVA) was performed to identify variables associated with a discrepancy in histology. The Kaplan-Meier method was used to depict recurrence-free (RFS), disease-specific (DSS), and overall survival (OS).

Results: The mean age was 69 years and 20% of patients received neoadjuvant chemotherapy (NAC). 25% exhibited a discrepancy between preoperative and postoperative histology; 17% had pure urothelial (PU) preoperatively and were found to have VH at RARC, and 8% had VH preoperatively which was no longer evident at RARC. There was no significant difference between those who exhibited discrepancy versus those who did not in terms of pT, pN, surgical margins, or recurrences ($p > 0.05$ for all). There was a significant difference in RFS and DSS (log-rank 0.01 and < 0.01 , respectively). Patients with PU histology at RARC (pre/post-PU and pre-VH/post-PU) exhibited better OS compared to those with VH at RARC (pre/post-VH and pre-PU/post-VH) (log-rank $p < 0.01$). Patients with higher preoperative grade (OR: 4.19; 95% CI: 1.3-13.7; $p < 0.01$) and with preoperative nodal involvement (OR: 2.29, 95% CI: 1.2-4.3; $p = 0.01$) were more likely to have different histology postoperatively.

Conclusion: Discrepancies between preoperative and postoperative histology occurred in 25% of patients after RARC. Patients with preoperative variant histology that was no longer evident on postop histology exhibited similar survival to those with purely urothelial histology.

Keywords: Variant histology, bladder cancer, urothelial histology, robot-assisted, cystectomy, oncological, survival.

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INTRODUCTION

Variant histology (VH) in bladder cancer is less common but confers worse outcomes compared to urothelial carcinoma, with higher rates of advanced disease (T stage and lymph node involvement) and positive soft tissue surgical margins. VH has also been associated with lower recurrence-free (RFS), disease-specific (DSS), and overall survival (OS)^{1,2}. Each VH subtype may respond differently to systemic therapy or radiation, and therefore detection and quantification have important implications for management

and prognostication³.

Tumor heterogeneity has been noted as a major reason for the occurrence of VH, and the prevalence of VH largely depends on diagnostic pathologic criteria. A survey regarding the prevalence of the diagnosis of the

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micropapillary variant of bladder cancer (MPBC) was distributed to 632 members of the SUO, and 118 surveys were completed. 94% of respondents were urologists, 5% were medical oncologists, and 1% were pathologists. With 80% of respondents considering bladder cancer to be their main focus in practice, 78% responded that their institution had an affiliation with a dedicated genitourinary pathologist. Regarding pathologic criteria, 49% of those surveyed responded that their institutions use strict, standardized criteria for the diagnosis of MPBC. 51% of respondents answered that the diagnosis of MPBC is based on “variable” pathologic criteria⁴. In another study, a retrospective analysis of established histological diagnoses in cases of bladder cancer showed that a secondary review of such diagnoses by a genitourinary pathologist detected changes in tumor stage, grade, or presence of VH in almost 37% of bladder cancer cases⁵. Thus, variabilities in diagnostic criteria can pave the path for discrepancies in bladder cancer histology diagnoses.

METHODS

A retrospective review of the multi-institutional, multinational prospectively maintained International Robotic Cystectomy Consortium (IRCC) database was performed (4139 patients from 33 institutions in 12 countries). Patients who exhibited a discrepancy in the presence of VH between preoperative and postoperative pathology were identified and compared in terms of perioperative, oncologic and survival outcomes. Data was reviewed for demographics (age, sex, race, body mass index (BMI), Charlson Comorbidity Index (CCI), and American Society of Anesthesiologists® (ASA) scores); preoperative characteristics (prior radiation therapy, hydronephrosis, previous abdominal surgery, clinical stage, grade, and the presence of VH); perioperative variables (transfusion, operative time, blood loss, and lymph node yield, diversion type, and approach); postoperative variables (inpatient and ICU stays, complications, and readmissions), pathologic outcomes (variant histology, positive surgical margins, tumor grade, pathologic TNM staging, and recurrences).

Pearson Chi-square and Fischer exact tests were used to describe categorical variables. Wilcoxon rank test was used to compare continuous variables. Multivariate Cox models were used to depict variables associated with discrepancies

between preoperative and postoperative histology. Kaplan Meier method was used to depict recurrence-free (RFS), disease-specific (DSS), and overall survival (OS). All tests were double-sided with statistical significance set at $p < 0.05$. All statistics were performed using SAS 9.4 software.

RESULTS

Patients with discrepant pathology had higher BMI (28 vs 27 kg/m², $p=0.40$), a higher ASA score more frequently (55% vs. 53%, $p=0.63$) and exhibited preoperative high grade more frequently (98% vs. 92%, $p<0.01$). There was no significant difference in pN+, positive margins, or local recurrence (Table 1). On the multivariate analysis, those with preoperative high grade (OR: 4.2; 95% CI: 1.3-13.7; $p<0.01$) and with preoperative lymph node involvement (OR: 2.3; 95% CI: 1.2-4.3; $p<0.01$) were more likely to have different histology postoperatively (Supplementary Table 1) Twenty-five percent of patients exhibited discrepancy between pathology at Transurethral Resection of Bladder Tumor (TURBT) and at RARC, 17% changed from pure urothelial to variant and 8% changed from variant to pure urothelial (Supplementary Table 2).

Kaplan Meier curves showed a difference in RFS between patients who had discrepancies and those who did not at 1, 3, and 5 years. (pre Urothelial, post Variant: 73%, 61%, 51%; pre Variant, post Urothelial: 77%, 66%, 63%; pre and post Urothelial: 83%, 68%, 64%; pre and post Variant: 75%, 63%, 60%; $p<0.01$) (Figure 1a). This was the same for DSS (pre Urothelial, post Variant: 83%, 70%, 65%; pre Variant, post Urothelial: 92%, 79%, 68%; pre and post Urothelial: 93%, 81%, 76%; pre and post Variant: 85%, 71%, 69%; $p<0.01$) at 1, 3 and 5 years, respectively (Figure 1b). A statistically significant difference was also observed in OS (pre Urothelial, post Variant: 74%, 54%, 41%; pre Variant, post Urothelial: 82%, 62%, 49%; pre and post Urothelial: 86%, 67%, 57%; pre and post Variant: 72%, 56%, 52%; $p<0.01$) (Figure 1c).

DISCUSSION

The presence of VH has been associated with higher disease stage and worse oncologic outcomes compared to urothelial carcinoma⁶⁻⁸. Hence, identifying the extent of cancer involvement and the presence of VH can significantly affect management, prognosis and patient counselling. An

Table 1: Patients with the same and different histology pre and postoperatively

Patient characteristics	No discrepancy in histology	Discrepancy in histology	All	p-value
Number of Patients	1114 (75)	370 (25)	1484	
Age, median (IQR), years	69 (61-75)	69 (62-76)	69 (61-75)	0.36
Sex: male, n (%)	852 (77)	286 (77)	1138 (77)	0.89
Body Mass Index, median (IQR), kg/m ²	27.3 (24.2-31.3)	27.8 (24.4-31.6)	27.4 (24.3-31.4)	0.40
Black Race, n (%)	38 (3.4)	9 (2.4)	47 (3.2)	0.39
High ASA score, n (%)	551 (53)	198 (55)	749 (54)	0.63
Neoadjuvant Chemotherapy exposure, n (%)	212 (19)	76 (21)	288 (20)	0.55
Charlson Comorbidity Index before NAC, median (IQR)	5 (4-7)	5 (4-7)	5 (4-7)	0.13
Prior radiation treatment, n (%)	60 (6)	16 (4)	76 (6)	0.35
Prior abdominal surgery, n (%)	504 (51)	176 (50)	680 (51)	0.76
Preoperative cT3/cT4, n (%)	87 (8)	34 (10)	121 (9)	0.32
Preoperative N+, n (%)	60 (6)	37 (12)	97 (8)	<0.01
Preoperative Hydronephrosis, n (%)	188 (19.2)	78 (22.3)	266 (20)	0.21
Preoperative high tumor grade	572 (92)	184 (98)	756 (94)	<0.01
History of renal insufficiency, n (%)	97 (10)	45 (12)	142 (10)	0.13
ICU admission after NAC, n (%)	421 (41)	151 (41)	572 (41)	0.95
ICU stay duration, median (IQR), days	1 (1-2)	1 (1-2)	1 (1-2)	0.72
Inpatient stay duration, median (IQR), days	8 (6-13)	8 (6-13)	8 (6-13)	0.65
History of blood transfusion, n (%)	97 (10)	25 (7)	122 (9)	0.19
Number of lymph node yield	18 (13-26)	18 (13-27)	18 (13-26)	1.0
Intracorporeal Urinary Diversion approach, n (%)	754 (71)	243 (68)	997 (70)	0.29
Neobladder Urinary Diversion, n (%)	186 (17)	48 (13)	234 (16)	0.08
Estimated blood loss, mL	300 (150-500)	300 (150-500)	300 (150-500)	0.56
Operative time, median (IQR), hours	6 (5-8)	6 (5-8)	6.3 (5.1-7.5)	0.91
Positive tumor margin, n (%)	130 (12)	40 (11)	170 (12)	0.71
Return to OR within 30 days, n (%)	67 (6)	30 (8)	97 (7)	0.18
Return to OR within 48 hours, n (%)	8 (0.7)	4 (1.1)	12 (0.8)	0.51
RARC yearly volume, mean (SD)	25.22 ± 13.93	26.89 ± 13.39	25.64 ± 13.81	0.01
Cystectomy Era: before 2010, n (%)	296 (27)	92 (25)	388 (26)	0.84
Cystectomy Era: 2011-2014, n (%)	288 (26)	103 (28)	391 (26)	
Cystectomy Era: 2019 and after, n (%)	199 (18)	68 (18)	267 (18)	
Any complications, n (%)	765 (71)	279 (75)	1044 (72)	0.08
Complications: 0-30 days, n (%)	531 (49)	190 (51)	721 (50)	0.44
Complications: 30-90 days, n (%)	638 (59)	227 (61)	865 (60)	0.43
High grade complications, n (%)	362 (33)	136 (37)	498 (34)	0.25
High grade complications: 0-30 days, n (%)	170 (16)	65 (18)	235 (16)	0.41
High grade complications: 0-90 days, n (%)	229 (21)	90 (24)	319 (22)	0.22
Any recurrence, n (%)	301 (27)	118 (32)	419 (28)	0.07
Any distal recurrence, n (%)	235 (21)	97 (26)	332 (22)	0.04
Any local recurrence, n (%)	145 (13)	56 (15)	201 (14)	0.29
Number of deaths, n (%)	382 (36)	152 (42)	534 (38)	0.04

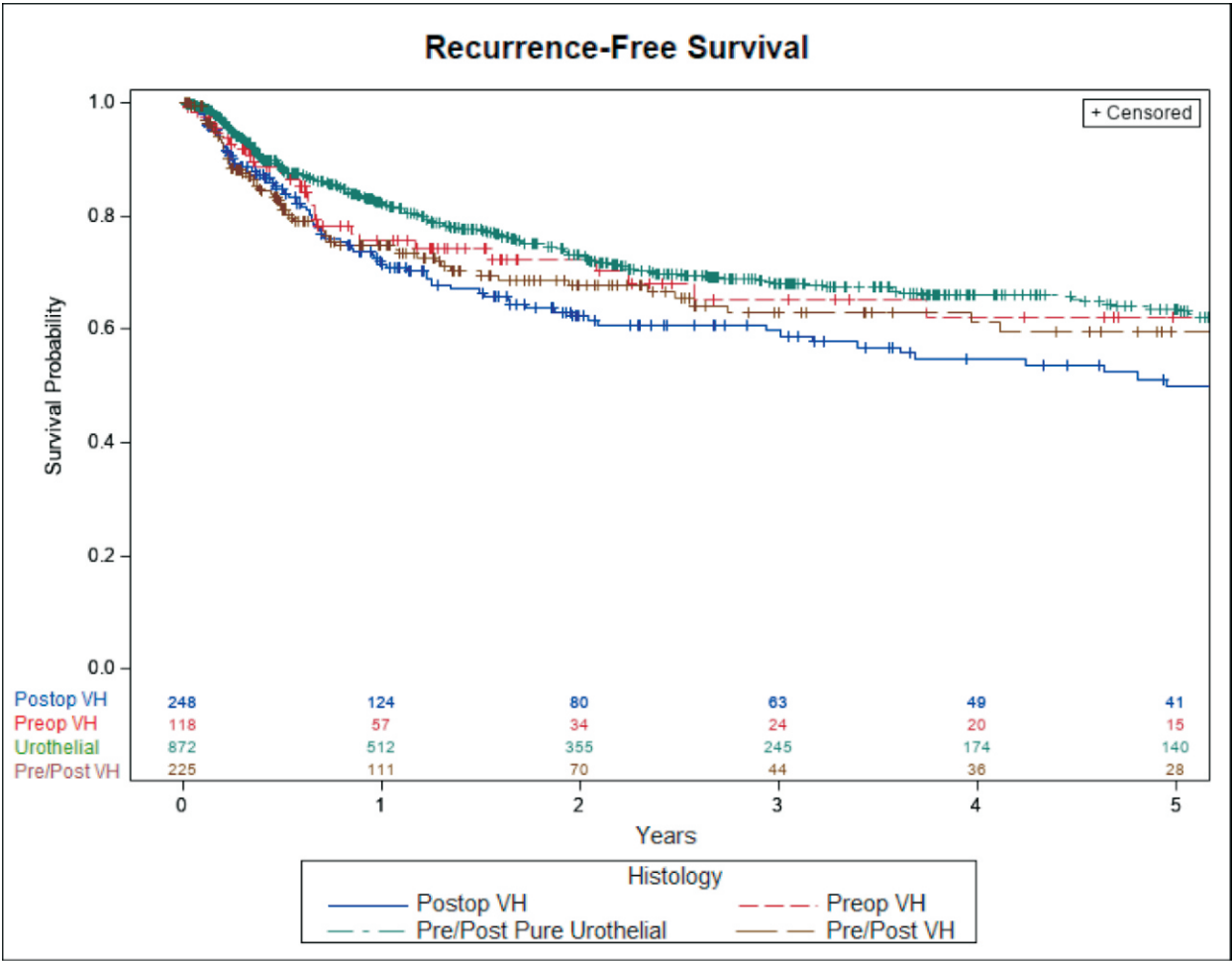
Supplementary Table 1: Multivariate Analysis of tumor grade association with different postoperative histology

Variable	Odds Ratio	95% Confidence Interval	p-value
Preoperative high grade	4.2	1.3-13.7	<0.02
Preoperative lymph nodal involvement	2.3	1.2-4.3	<0.01

Supplementary Table 2: Discrepancy between preoperative and final pathology after RARC

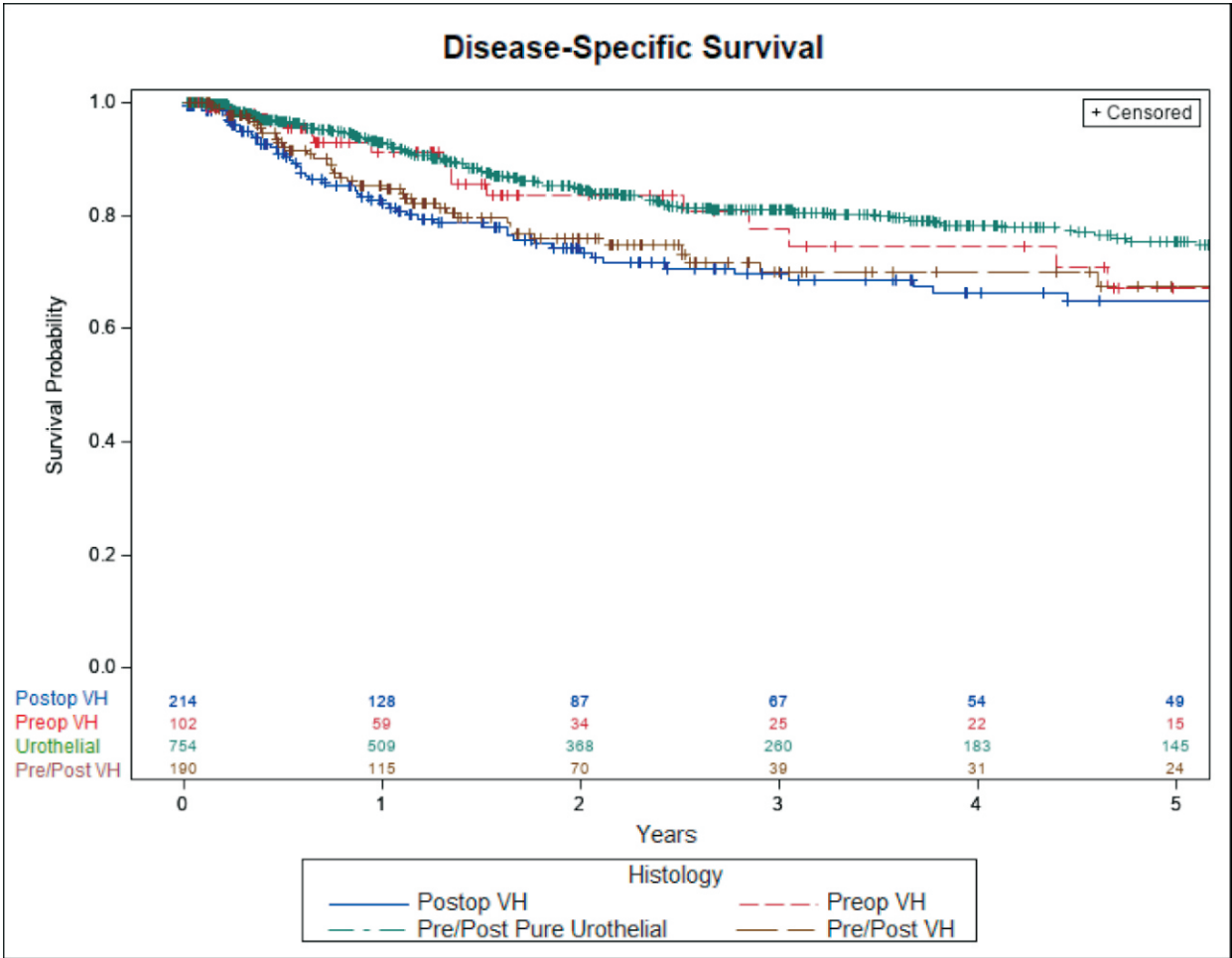
Histology	Patients (%)	p-value
No discrepancy, n (%)	1114 (75)	< 0.01
Preop and postop pure Urothelial, n (%)	884 (60)	
Preop and postop Variant, n (%)	230 (15)	
Discrepancy, n (%)	370 (25)	
Preop Urothelial; postop Variant, n (%)	250 (17)	
Preop Variant; postop pure Urothelial, n (%)	120 (8)	

Fig. 1a: Kaplan Meier curves depicting recurrence-free survival (Log rank p=0.01)



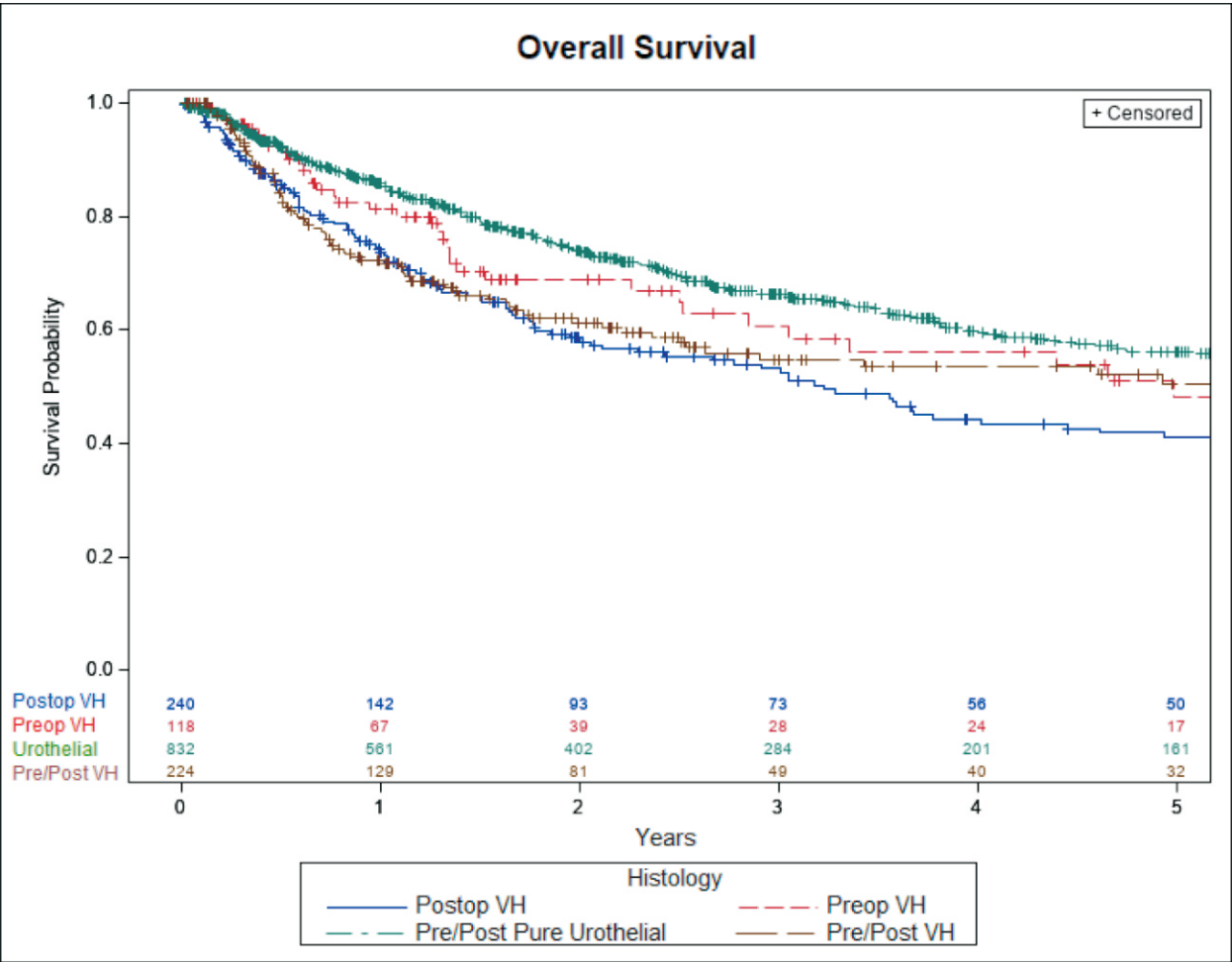
Survival Rate					
Group	Years				
	1	2	3	4	5
Postoperative VH	0.73	0.64	0.61	0.56	0.51
Preoperative VH	0.77	0.74	0.66	0.63	0.63
Pre/Post Pure Urothelial	0.83	0.73	0.68	0.67	0.64
Pre/Post VH	0.75	0.68	0.63	0.62	0.60

Fig. 1b: Kaplan Meier curves depicting disease-specific survival (log rank p-value<0.01)



Survival Rate					
Group	Years				
	1	2	3	4	5
Postoperative VH	0.83	0.75	0.70	0.67	0.65
Preoperative VH	0.92	0.84	0.79	0.75	0.68
Pre/Post Pure Urothelial	0.93	0.85	0.81	0.79	0.76
Pre/Post VH	0.85	0.77	0.71	0.71	0.69

Fig. 1c: Kaplan Meier curves depicting overall survival (log rank p-value<.01)



Survival Rate					
Group	Years				
	1	2	3	4	5
Postoperative VH	0.74	0.59	0.54	0.45	0.41
Preoperative VH	0.82	0.69	0.62	0.57	0.49
Pre/Post Pure Urothelial	0.86	0.74	0.67	0.60	0.57
Pre/Post VH	0.72	0.62	0.56	0.54	0.52

established reason for the existence of variant histology is tumor heterogeneity, which refers to the clonal expansion of individual mutations. In effect, cellular differentiation occurs with the occurrence of each cell division in cancer tissue and can lead to tumor evolution^{9,10}. The phenomenon of tumor heterogeneity alters the histologic makeup of tissue, and in turn, the resulting histological variants necessitate unique modes of management. Whereas the established primary management for urothelial bladder cancer is radical cystectomy, management for certain variant cases differs, with muscle-invasive variants such as Small Cell, Sarcomatoid, Plasmacytoid, and Micropapillary that respond positively to Neoadjuvant Chemotherapy (NAC), and pure Squamous and Adenocarcinoma variants that respond positively to perioperative radiation therapy (XRT)¹¹. Furthermore, not all variants respond to alternative treatments such as NAC¹². Patients with variant cases that are unresponsive to NAC to whom NAC is administered, run the risk of experiencing drug-related complications with no benefit of improved cancer status. The unnecessary administration of NAC leads to delays in surgical treatment, unnecessarily prolonging the duration of cancer in patients¹³.

Knowing that variant histology cases require unique modes of management makes the identification of variant cases all the more important. Not only is it important to identify cases of discrepancy to guide better methods of management; it is just as important to understand the reasons behind their occurrence. Discrepancies between preoperative and postoperative histology in bladder cancer can be explained by tissue sampling methods. Histological preoperative and postoperative records depend heavily on the accuracy of these tissue sampling methods. Since variant histology cases are naturally known to be more aggressive than urothelial, a lack of complete tumor staging may also result in a lack of variant histology identification. A study detailing the process of bladder cancer staging at the Cleveland Clinic in Ohio reported that bladder specimens require the presence of the lamina propria layer to ensure appropriate pT1 staging. The presence of cautery artefacts in specimens also makes it difficult to determine the exact tumor depth. A lack of complete staging may thus lead to a lack of complete histological identification¹⁴. Philip et al., in their paper, describe how the amount of adipose tissue in the

wall of the urinary bladder can affect management. When a TUR is done in such cases, the presence of adipose tissue in the lamina propria can be mistaken as perivesical soft tissue involvement of cancer, which would cause a pT3 misdiagnosis¹⁵. Since VH cases are known to be more aggressive, the lack of correct tumor staging may translate to a lack of VH recognition, and this ultimately may lead to cancer mismanagement¹⁶. Finally, the relationship between the higher bladder cancer stage and the presence of VH can be exemplified by the particularly increased prevalence of micropapillary and clear cell variants in cases of bladder cancer with lymph node metastasis¹⁷.

Finally, a few reasons underlie the conflicts in staging according to the type of the variant. Nested variants are known to have a morphology that mimics von Brunn nests. The morphology of microcystic variants has been noted to resemble cases of cystitis cystica. If nested and microcystic variant cases are deemed as having non-cancerous characteristics, this may prevent adequate variant histology recognition. Appropriate management is thereby limited in these cases. In our study, of the 75% of patients who had no discrepancy in histology, 60% had urothelial throughout, and 15% had the variant. Of the 25% of patients with discrepancies, 17% had preoperative urothelial and postoperative variants, while 8% had preoperative variant and postoperative urothelial (Supplementary Table 2). Our patients with postoperative urothelial histology, irrespective of the type of preoperative variant or urothelial histology, had improved OS (82%, 62%, 49% and 86%, 67%, 57%) as compared to that of patients with postoperative VH, irrespective of having variant or urothelial preoperative histology (74%, 54%, 41% and 72%, 56%, 52%), each at 1, 3 and 5 years, respectively (all $p=0.01$). On multivariate analysis, patients with higher preoperative tumor grade and preoperative lymph nodal involvement were more likely to have different postoperative histology (Table 1).

The current study is not without limitations. The retrospective has its known biases and limitations. IRCC has multiple institutions with varying diagnostic protocols. A centralized pathology review was not performed and may have further influenced our results. The presence of VH without differentiating pure variants from mixed variants, and the proportion of VH may have also affected outcomes.

CONCLUSION

Twenty-five percent of patients had differences in preoperative versus postoperative histology. Patients with preoperative variant histology that disappeared on postop histology exhibited similar overall survival as patients with purely urothelial histology.

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Written informed consent: Taken

REFERENCES

1. Stroman, L., et al., *The impact of non-urothelial variant histology on oncological outcomes following radical cystectomy*. BJU Int, 2019. **124**(3): p. 418-423.
2. Sefik, E., et al., *Effect of variant histology presence and squamous differentiation on oncological results and patient's survival after radical cystectomy*. Arch Ital Urol Androl, 2018. **90**(3): p. 172-175.
3. Black, P.C., G.A. Brown, and C.P. Dinney. *The impact of variant histology on the outcome of bladder cancer treated with curative intent*. in *Urologic Oncology: Seminars and Original Investigations*. 2009. Elsevier.
4. Willis, D.L., et al. *Micropapillary bladder cancer: current treatment patterns and review of the literature*. in *Urologic Oncology: Seminars and Original Investigations*. 2014. Elsevier.
5. Gordetsky, J., et al., *Second Opinion Expert Pathology Review in Bladder Cancer: Implications for Patient Care*. Int J Surg Pathol, 2018. **26**(1): p. 12-17.
6. Lobo, N., et al., *What Is the Significance of Variant Histology in Urothelial Carcinoma?* Eur Urol Focus, 2020. **6**(4): p. 653-663.
7. Kaimakliotis, H.Z., et al., *Plasmacytoid bladder cancer: variant histology with aggressive behavior and a new mode of invasion along fascial planes*. Urology, 2014. **83**(5): p. 1112-1116.
8. Warrick, J.I., *Clinical significance of histologic variants of bladder cancer*. Journal of the National Comprehensive Cancer Network, 2017. **15**(10): p. 1268-1274.
9. Gerlinger, M., et al., *Intratumor heterogeneity and branched evolution revealed by multiregion sequencing*. N Engl J Med, 2012. **366**: p. 883-892.
10. Meeks, J.J., et al., *Genomic heterogeneity in bladder cancer: challenges and possible solutions to improve outcomes*. Nature Reviews Urology, 2020. **17**(5): p. 259-270.
11. Black, P., *Should Variant Histology Change Management of Bladder Cancer*. Grand Rounds in Urology, 2018.
12. Daneshmand, S. and A. Nazemi, *Neoadjuvant chemotherapy in variant histology bladder cancer: current evidence*. European Urology Focus, 2020. **6**(4): p. 639-641.
13. da Costa, J.B., et al. *Molecular tumor heterogeneity in muscle invasive bladder cancer: biomarkers, subtypes, and implications for therapy*. in *Urologic Oncology: Seminars and Original Investigations*. 2018. Elsevier.
14. Abd el-Latif, A., et al., *The sensitivity of initial transurethral resection or biopsy of bladder tumor (s) for detecting bladder cancer variants on radical cystectomy*. The Journal of urology, 2013. **189**(4): p. 1263-1267.
15. Philip, A.T., et al., *Intravesical adipose tissue: a quantitative study of its presence and location with implications for therapy and prognosis*. Am J Surg Pathol, 2000. **24**(9): p. 1286-90.
16. Hansel, D.E., et al., *A contemporary update on pathology standards for bladder cancer: transurethral resection and radical cystectomy specimens*. European urology, 2013. **63**(2): p. 321-332.
17. Moschini, M., et al., *Characteristics and clinical significance of histological variants of bladder cancer*. Nature Reviews Urology, 2017. **14**(11): p. 651-668.