



# Assessing the Impact of Time to Cystectomy for Variant Histology of Urothelial Bladder Cancer

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<b>OBJECTIVE</b>	To determine if the timing of radical cystectomy for variant histology of urothelial carcinoma has an impact on survival. Variant histology has been associated with aberrant behavior compared to pure urothelial carcinoma, however the timing of surgery for these patients has not been studied.
<b>MATERIALS AND METHODS</b>	We identified 363 patients with cT2-T4N0M0 urothelial carcinoma who underwent radical cystectomy without perioperative intravesical and/or systemic therapy from 2003 to 2014. Clinicopathologic data were compared between pure urothelial carcinoma and variant histology. The time from diagnosis to radical cystectomy was analyzed as a continuous variable and dichotomized at 4-, 8-, and 12-weeks to determine impact on oncologic outcomes.
<b>RESULTS</b>	Patients with variant histology, when compared to those with pure urothelial carcinoma, were more likely to present with extravesical disease ( $P < .01$ ), be upstaged ( $P < .01$ ), have lymphovascular invasion ( $P < .01$ ) and have lymph node metastasis at radical cystectomy ( $P = .02$ ). The median days to radical cystectomy did not differ between pure urothelial and variant histology. On multivariable analysis controlling for age, comorbidities, tumor stage, lymph node status, lymphovascular invasion, and surgical margins, every month in delay was associated with a worse overall survival for variants (HR = 1.36, $P = .003$ ). At an 8-week delay or longer, those with variant histology had a statistically worse survival ( $P = .03$ ).
<b>CONCLUSION</b>	For patients with variant histology, delays in surgery were associated with an increased risk of death. UROLOGY 133: 157–163, 2019. © 2019 Elsevier Inc.

Bladder cancer is the most common malignancy of the urinary system in the United States with an estimated 81,000 new cases in 2018.<sup>1</sup> While the majority of tumors are diagnosed at an early stage, an estimated 30% of tumors will present as muscle-invasive bladder cancer (MIBC). Radical cystectomy (RC) with pelvic lymph node dissection and neoadjuvant chemotherapy is the gold standard therapy for MIBC, improving survival and decreasing risk of local recurrence.<sup>2-4</sup>

Urothelial carcinoma is known to be associated with a variety of histologic differentiations that occur in approximately 25% of cases.<sup>5</sup> These variants have gained attention for their initial presentation with advanced disease.<sup>5-7</sup> However, despite the aggressive presentation, the impact of variant histology (VH) on oncologic outcomes has demonstrated inconsistent findings.<sup>6,8</sup>

The timing of RC may have a significant impact on oncologic outcomes with some studies showing worse outcomes with delays to surgery of 40 days<sup>9</sup>, 12 weeks,<sup>10-13</sup> and 3 months<sup>14,15</sup> while other studies did not identify timing of surgery as a significant factor.<sup>16-18</sup> However, the timing of RC among patients with VH has not been explored. In this study, our objective was to analyze the impact of time to RC on oncologic outcomes for pure urothelial carcinoma (PUC) and VH.

## MATERIALS AND METHODS

### Study Population

We used our Institutional Review Board approved, prospectively maintained database to identify 1560 patients undergoing RC between January 2003 and December 2014. Patients were included if RC was performed with intent-to-cure ( $n = 1362$ ) for clinically muscle invasive disease (cT2-T4) ( $n = 869$ ). Patients with clinically metastatic disease (cN1 and/or cM1) were excluded ( $n = 89$ ). Furthermore, patients were excluded if they received intravesical immunotherapy or chemotherapy ( $n = 170$ ), systemic neoadjuvant chemotherapy ( $n = 132$ ), or postoperative chemotherapy and/or radiation ( $n = 99$ ). Patients with nonurothelial histology (eg, pure squamous cell carcinoma) ( $n = 5$ ) and

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those who did not receive urinary diversion ( $n = 2$ ) were also excluded. Finally, patients who received RC later than a year after diagnosis ( $n = 9$ ) were excluded to reach our final cohort of 363 patients.

### Classification and Variables

Variables collected included basic demographics, Charlson-Comorbidity Index (CCI), clinical and pathologic stage, presence of hydronephrosis, extent of lymph node dissection defined as level 1 (proximally to the common iliac bifurcation), level 2 (presacral and proximally to the aortic bifurcation), and level 3 (superior to the aortic bifurcation), total removed and positive lymph nodes, type of urinary diversion performed, surgical margin status, and presence of lymphovascular invasion. Perioperative data included length of surgery in minutes, operative mortality defined as death within 30 days of surgery and/or during admission for RC, high grade ( $\geq$  grade III) Clavien-Dindo classification surgical complication, perioperative blood transfusion, and 90-day readmission. Urinary diversion was defined as either conduit (ileal or sigmoid conduit) or continent (right colon reservoir or orthotopic neobladder). Positive surgical margins included margins from soft tissue, ureters, or urethra.

All patients underwent a RC with pelvic lymph node dissection. We categorized variants into clinical variants (CV) identified during transurethral resection of bladder tumor (TURBT) and pathologic variants (PV) identified at cystectomy. Histopathology at cystectomy was determined by the institution's genitourinary pathologists. Presence of any amount of histologic variation within urothelial carcinoma was categorized as VH. VH was classified according to the World Health Organization/International Agency for Research on Cancer (WHO/IARC) 3rd edition definitions.<sup>19</sup> Cancer staging was based on the American Joint Committee on Cancer TNM cancer system, 5th edition.<sup>20</sup>

### Outcomes

The primary outcome was overall survival (OS) calculated from time of cystectomy to date of last follow-up or death. Patients who had recurrence were censored at the time of recurrence when analyzing recurrence-free survival (RFS).

We measured time from first diagnosis of muscle-invasive disease on biopsy to RC as a continuous variable and dichotomized at 3 time points: 4, 8, and 12 weeks. For each dichotomization, patients were categorized into "early" or "delayed" surgery to determine the impact of timing of surgery on outcomes. Patient clinical and demographic characteristics were first compared between PUC and VH with further analysis of outcomes in patients with VH based on time to RC.

### Statistical Analysis

Patient demographics and clinical characteristics were analyzed using Student's  $t$  test for continuous variables and Pearson's chi-squared test or Fisher's exact test when appropriate for categorical variables. Kaplan-Meier method and log-rank test were used to estimate OS and RFS. Univariate and multivariable Cox proportional hazards models were used to analyze the impact of time to RC on OS and RFS. All  $P$  values were 2-sided with  $P < .05$  considered statistically significant. Statistical analysis was performed using Stata 13 (StataCorp., College Station, TX).

## RESULTS

### Demographics

Of the 363 patients, 82 (22.6%) patients had CV and 68 (18.7%) had PV (Supplementary Table 1). Demographic results for pathologic and CV are shown in Table 1 and Supplementary Table 2, respectively. Median follow-up time was 42.4 months (IQR 11.8-73.8). PV were more likely to present with advanced local disease (cT3-T4) compared to PUC (16.2% vs 7.8%,  $P < .01$ ), but there was no difference in CCI: CV ( $P = .80$ ) and PV ( $P = .10$ ) or hydronephrosis: CV ( $P = .61$ ) and PV ( $P = .09$ ). Median days from diagnosis to RC did not differ between PUC 56 (IQR 38-75) and CV 50 (IQR 35-71),  $P = .22$  and PUC 55 (IQR 37-75) and PV 56 (IQR 36-73),  $P = .98$ . For PUC, time to RC ranged from 8 to 339 days with 238 patients (81.2%) undergoing surgery within 12 weeks. Similarly, for PV, time to RC ranged from 15 to 318 days with 57 patients (81.4%) undergoing surgery within 12 weeks. For CV, time to RC ranged from 10 to 159 days with 68 patients (82.9%) undergoing surgery within 12 weeks.

At cystectomy, 33.4% of PUC vs 2.9% of PV had tumor downstaging, while upstaging was seen in 31.2% of PUC vs 60.3% in PV ( $P < .01$ ). No differences in stage change were observed in CV,  $P = 0.43$ . Both PV (26.5%) and CV (19.5%) were more likely to have nodal metastases (pTanyN1) compared to PUC.

### Time Analysis for Variant Histology

The impact of time to RC was first analyzed as a continuous variable in months for PV and CV in Table 2 and Supplementary Table 3, respectively. On univariate Cox regression analysis, for the entire cohort, time was associated with worse OS (HR = 1.14 [95% CI 1.02-1.27;  $P = .03$ ]). When stratified by histology, every month in delay was associated with a worse OS for PV (HR = 1.43 [95% CI 1.21-1.70;  $P < .0001$ ]) but not for CV ( $P = .15$ ). Adjusting for age, CCI, pathologic tumor stage, lymph node status, lymphovascular invasion, and surgical margin status on multivariable Cox regression analysis, every month in delay continued to be associated with a worse OS for PV (HR = 1.36 [95% CI 1.11-1.65;  $P = .003$ ]). Time to RC was not associated with RFS in our study.

Subsequently, we dichotomized time to RC as "early" or "delayed" surgery, performing exploratory analysis at each 4-week interval up to 12-weeks postbiopsy, for PV and CV as shown in Table 3 and Supplementary Table 4, respectively. On univariate analysis, for PV delays in surgery of 8 weeks or longer were associated with a worse OS (HR = 2.14 [95% CI 1.09-4.21;  $P = .03$ ]) and for CV, delays greater than 12 weeks were associated with a worse OS (HR = 2.15 [95% CI 1.02-4.55;  $P = .04$ ]). Adjusting for the same prior covariables on multivariable analysis, a delay in RC  $>12$  weeks was associated with a worse OS for PV (HR = 3.45 [95% CI 1.55-7.89;  $P = .003$ ]), CV (HR = 2.39 [95% CI 1.04-5.51;  $P = .04$ ]), and PUC (HR = 1.56 [95% CI 1.02-2.38;  $P = .04$ ]). No differences in RFS were identified comparing early or delayed surgery at a 12-week cutoff.

Patient demographics and clinical features of PV compared at an 8-week cutoff and CV compared at a 12-week cutoff are presented in Supplementary Table 5. Perioperative outcomes are presented in Supplementary Table 6. Median OS for patients who underwent surgery  $\leq 8$  weeks from diagnosis was 84 and 23 months, respectively for PV. For CV, the median OS survival was 84 and 5 months for surgery  $\leq 12$  and  $>12$  weeks, respectively. Among patients with PV, the 5-year OS estimate was 64% for cystectomy  $\leq 8$  weeks and 35% for  $>8$  weeks from diagnosis, log-rank test  $P = .02$  (Fig. 1). For

**Table 1.** Patient demographics and clinical features of pathologic variants

	Pure Urothelial Carcinoma	Pathologic Variant Histology	P
No. patients	295 (81.3)	68 (18.7)	-
Median age (IQR)	73 (64-79)	74 (68-79)	.41
Gender, n (%)			.17
Male	231 (78.3)	48 (70.6)	
Female	64 (21.7)	20 (29.4)	
Race, n (%)			.71
Caucasian	268 (91.2)	61 (89.7)	
Non-Caucasian	26 (8.8)	7 (10.3)	
Charlson Comorbidity, n (%)			.10
0	122 (41.4)	30 (44.1)	
1	83 (28.1)	11 (16.2)	
≥2	90 (30.5)	27 (39.7)	
Clinical stage, n (%)			<.01
T2	272 (92.2)	57 (83.8)	
T3	14 (4.7)	11 (16.2)	
T4	9 (3.1)	0 (0)	
Hydronephrosis, n (%)			.09
No	225 (76.3)	44 (64.7)	
Yes	63 (21.3)	23 (33.8)	
Unknown	7 (2.4)	1 (1.5)	
Median time to cystectomy, days (IQR)	55 (37-75)	56 (36-73)	.98
Change in staging at cystectomy, n (%)			<.01
No change	105 (35.6)	25 (36.8)	
Downstage	98 (33.2)	2 (2.9)	
Upstage	92 (31.2)	41 (60.3)	
Pathologic stage, n (%)			<.01
T0	35 (11.8)	0 (0)	
T1/Ta/Tis	61 (20.7)	2 (2.9)	
T2	90 (30.5)	17 (25.0)	
T3	89 (30.2)	40 (58.8)	
T4	20 (6.8)	9 (13.2)	
Pathologic node status, n (%)			.02
N0	249 (84.4)	48 (70.6)	
N1	44 (14.9)	18 (26.5)	
Nx	2 (0.7)	2 (2.9)	
Extent of lymph node dissection, n (%)			.28
Level 1	34 (11.5)	8 (11.8)	
Level 2	42 (14.2)	6 (8.8)	
Level 3	217 (73.6)	52 (76.5)	
Unknown	2 (0.7)	2 (2.9)	
Mean nodes removed (SD)	56.7 (28.2)	63.4 (37.8)	.10
Mean nodes positive (SD)	1.2 (6.8)	1.8 (4.6)	.50
Urinary diversion, n (%)			.03
Conduit	97 (32.9)	32 (47.1)	
Continent	198 (67.1)	36 (52.9)	
Surgical margins, n (%)			.96
Negative	286 (97.0)	66 (97.1)	
Positive	9 (3.0)	2 (2.9)	
Lymphovascular invasion, n (%)			<.01
Present	85 (28.8)	28 (41.2)	
Absent	118 (40.0)	34 (50.0)	
Indeterminate	92 (31.2)	6 (8.8)	

**Table 2.** Impact of time (in months) to cystectomy on overall survival

	Univariate Analysis		Multivariable Analysis	
	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P
Overall cohort (N = 363)	1.14 [1.02-1.27]	.03	1.01 [0.90-1.13]	.88
Pure urothelial carcinoma (N = 295)	1.04 [0.90-1.21]	.56	0.93 [0.81-1.07]	.32
Pathologic variant histology (N = 68)	1.43 [1.21-1.70]	<.01	1.36 [1.11-1.65]	.003

Multivariable controlling for age, CCI, tumor stage, node status, LVI, surgical margins.

**Table 3.** Univariate and multivariable Cox regression of overall survival for pure urothelial carcinoma and pathologic variant histology

	Univariate Analysis			Multivariable Analysis		
	HR	95% CI	P	HR	95% CI	P
>4 wk						
PUC	0.79	0.49-1.28	.35	0.72	0.44-1.17	.18
VH	1.48	0.57-3.85	.42	0.92	0.32-2.59	.87
>8 wk						
PUC	0.92	0.65-1.31	.64	0.84	0.59-1.20	.33
VH	2.14	1.09-4.21	.03	1.50	0.68-3.29	.32
>12 wk						
PUC	1.54	1.01-2.33	.04	1.39	0.91-2.12	.13
VH	3.96	1.90-8.24	<.01	3.45	1.51-7.86	.003

Multivariable regression controlling for age, CCI, LVI, surgical margins, pathologic tumor and lymph node stage.

CV, the 5-year OS estimate was 61% and 36%, log-rank test  $P = .04$  for cystectomy  $\leq 12$  weeks and  $>12$  weeks from diagnosis (Supplementary Figure 1).

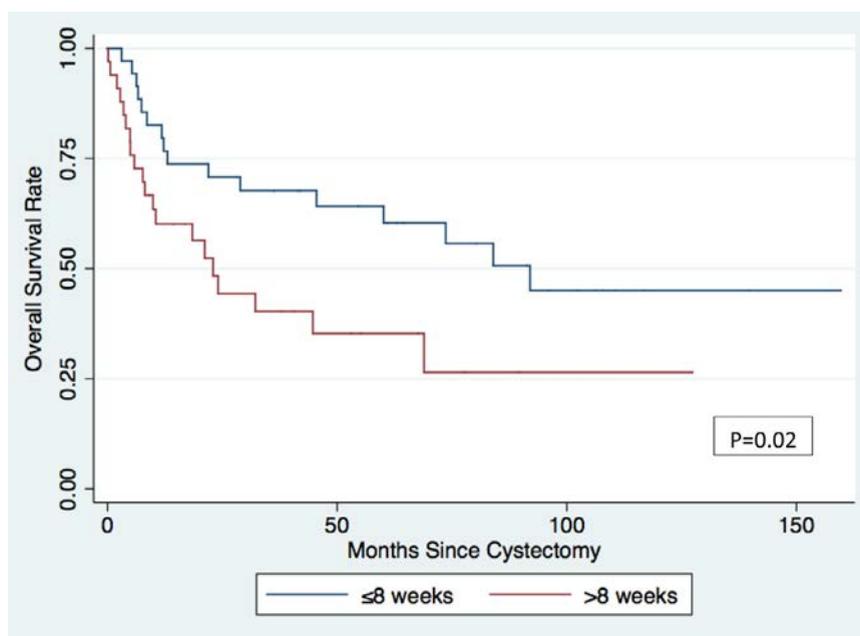
## DISCUSSION

In our study, we found time to RC to be a significant driver of OS for patients with VH. For PV, when time was analyzed as a continuous variable, every month in delay was associated with a worse survival. Furthermore, when analyzing time as a dichotomous variable, we identified worse OS for patients experiencing a delay to cystectomy despite the fact that there were no observed differences in perioperative outcomes and tumor or lymph node stage. We also confirmed findings in the existing literature that patients with VH tend to present with locally advanced disease and nodal metastases at RC.<sup>5-7,21,22</sup>

PV had a propensity to present with more advanced disease compared to PUC. This aggressive growth pattern may

explain why patients with VH are more susceptible to delay-related adverse outcomes compared to PUC. Previous studies have shown that patients with extravesical disease have worse OS compared to patients with organ confined tumors.<sup>2,3</sup> Although not statistically significant, patients who had surgery beyond 8 weeks had higher rates of extravesical disease (78.8% vs 65.7%), specifically pT4 disease (18.2% vs 8.6%). However, there was no significant difference in rates of upstaging for patients with delay greater than 8 weeks. This discrepancy may imply that certain features of VH which increase its propensity for metastasis are not fully captured by pathologic staging.

Interestingly, for PV, we did not observe an increased rate in lymph node metastasis with a delay in surgery (29.4% vs 27.8%). Even in the setting of a negative histologic examination following a thorough pelvic lymph node dissection, occult disease sites or micrometastases may be present, which have been shown to be an independent predictor of disease recurrence, cancer-specific,



**Figure 1.** Kaplan-Meier curves using log-rank test for postcystectomy OS in patients with pathologic variant histology stratified by  $\leq 8$  weeks or  $>8$  weeks from diagnosis. (Color version available online.)

and overall mortality.<sup>23,24</sup> It is perhaps the combination of advanced stage, presence of undetected micrometastases, and hematologic spread of disease that explains why patients with a delay in surgery have a worse outcome. However, we acknowledge the possibility of confounding factors, as patients who received RC >8 weeks were older and had higher rates of comorbidities.

Our study excluded patients who received intravesical therapy or perioperative chemotherapy because the objective of the study was to describe the impact of unnecessary delays from diagnosis of MIBC to RC and to analyze timing of surgery while excluding other potential contributing factors influencing outcome. Although a delay in cystectomy as a result of administration of neoadjuvant chemotherapy does not appear to impact survival,<sup>25</sup> the rate of response to neoadjuvant chemotherapy varies among the histologic variants<sup>26</sup> and further studies are needed to determine the efficacy of NAC in patients with VH.

We assessed variants identified both clinically at TURBT and pathologically at RC. PV showed worse outcomes with delays in RC when time was analyzed as a continuous variable while CV did not. When we dichotomized the time to RC, CV had a higher risk of overall death (HR = 2.39) than PUC (HR = 1.56) at a 12-week cutoff.

One explanation for the discrepancy in results between CV and PV is the under- and misdetection of variants on TURBT. Previous studies have shown that TUR specimens have less than a 40% sensitivity for predicting VH at cystectomy.<sup>27,28</sup> Furthermore, Shah et al reported that upon pathologic re-review of specimens at their large referral hospital, 44% of variants were not reported by community pathologists.<sup>29</sup> American Urological Association/American Society of Clinical Oncology/American Society for Radiation Oncology/Society of Urologic Oncology 2017 guidelines for treatment of nonmetastatic MIBC recommends that an experienced genitourinary pathologist review pathology when VH is suspected.<sup>30</sup> Regardless of when histologic variants were identified, PV and CV appear to have worse delay-associated outcomes compared to PUC.

There are several limitations to our study. As a retrospective analysis, the results are prone to the risk of selection bias. The discrepancy between finding a worse OS with delays in surgery and no significant differences in recurrence-free survival is likely due to patient bias in cystectomy offering and timing. Like Chang et al<sup>15</sup> who did not use 90 days as a cutoff to measure a safe period before disease progression, we are not advocating that an 8-week cutoff be used as a way to measure safety and quality of cystectomy for VH. The decision of when to perform cystectomy is a complex decision, incorporating both patient and physician factors. Nevertheless, among patients with VH, we demonstrated that increased time from diagnosis of MIBC to RC was associated with worse OS. While all cystectomy specimens were read by experienced genitourinary pathologists at our tertiary referral center, not all TURBT samples were re-read at our institution. Due to the rarity of VH, we were limited in our sample size and treated all variants as a single group. Future prospective

studies will require multi-institutional collaboration to power a sample large enough to individually assess outcomes for each variant histologic type.

## CONCLUSION

VH has a propensity to be upstaged and present with lymph node metastasis. VH identified at both TURBT or cystectomy appear to portend delay-related adverse OS. Greater recognition and detection of VH should be considered.

## SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at <https://doi.org/10.1016/j.urology.2019.07.034>.

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In this study, the authors performed a retrospective review of 363 patients who underwent radical cystectomy at their institution for cT2-T4 bladder cancer between 2003 and 2014. Notably, they excluded patients who received intravesical immunotherapy or chemotherapy, systemic chemotherapy (either neoadjuvant or adjuvant), or postoperative radiation. Their main objective was to determine whether time from diagnosis to radical cystectomy impacted oncologic outcomes. Consistent with previous studies, the authors found that patients with variant histology were more likely to have nonorgan confined disease, upstaging, and lymphovascular invasion. On univariate analysis, patients with histologic variants who experienced a delay in surgery for 8 weeks or longer had a worse overall survival but not recurrence-free survival compared with patients with conventional urothelial carcinoma who experienced the same delay. A delay of 12 weeks or longer was associated with worse overall survival for both histologic variant and conventional urothelial carcinoma groups. Interestingly, there was no differences seen in recurrence-free survival.

The literature regarding the effect of delaying cystectomy on oncologic outcome has been mixed, since the definition of delay is variable, and delay can be due to a number of reasons including but not limited to risk stratification by the treatment team, medical optimization for borderline surgical candidates, recovery from the adverse effects of neoadjuvant chemotherapy, and seeking multiple opinions.<sup>6-10</sup> These reasons can confound any relationship between cystectomy timing and oncologic outcome. Nonetheless, the present study suggests that those with histologic variants should be prioritized so that no delay occurs. Additionally, the authors did not evaluate the effect of neoadjuvant chemotherapy on the study population. Although cisplatin-based chemotherapy appears to be effective against certain histologic variants (eg, small cell carcinoma), its role needs to be clarified with other variants. Whether or not radical cystectomy should be delayed for neoadjuvant chemotherapy or other novel therapies will require further investigation.

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## EDITORIAL COMMENT



Most bladder cancers present as classic urothelial carcinoma, but up to 30% of invasive urothelial carcinomas will contain at least 1 histologic variant. There are over 15 histologic variants recognized by the World Health Organization Classification, which demonstrates the vast potential of the urothelium for divergent differentiation during carcinogenesis.<sup>1</sup> These variants can be present at varying percentages, and they are associated with higher rates of locally advanced and metastatic disease at radical cystectomy.<sup>2-5</sup>

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