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Pathological and Survival Outcomes Associated with Variant Histology Bladder Cancers Managed by Cystectomy with or without Neoadjuvant Chemotherapy

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Abstract

Purpose: Although neoadjuvant chemotherapy is associated with a survival advantage in pure urothelial, muscle invasive bladder cancer, the role of neoadjuvant chemotherapy is less clear in variant histology or urothelial carcinoma with divergent differentiation. We compared chemotherapy response and survival outcomes of patients with nonpure urothelial carcinoma histology who were managed with neoadjuvant chemotherapy followed by cystectomy vs cystectomy alone.

Materials and Methods: We analyzed 768 patients with clinical muscle invasive bladder cancer (cT2–4N0M0) who were treated with cystectomy at a tertiary care center from 2007 to 2017. Patients were stratified by histology and treatment strategy. Adjusted logistic and Cox regression models were used to evaluate pathological downstaging, cancer specific survival and overall survival.

Results: The cohort consisted of 410 patients (53%) with pure urothelial carcinoma, 185 (24%) with urothelial carcinoma with divergent differentiation and 173 (23%) with variant histology. Overall, 314 patients (41%) received neoadjuvant chemotherapy prior to cystectomy. There were similar rates of complete (18% to 30%) and partial (37% to 46%) pathological downstaging with neoadjuvant chemotherapy across all histological subgroups ($p=0.30$ and $p=0.40$, respectively). However, while patients with pure urothelial carcinoma experienced an overall survival benefit (HR 0.71, 95% CI 0.51–0.98, $p=0.0013$) and those with variant histology experienced a cancer specific survival benefit (HR 0.55, 95% CI 0.30–0.99, $p=0.0495$) with neoadjuvant chemotherapy, patients with urothelial carcinoma with divergent differentiation did not experience overall or cancer specific survival benefits with the use of neoadjuvant chemotherapy prior to cystectomy.

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Conclusions: Among patients with muscle invasive bladder cancer those with nonpure urothelial carcinoma histology with variant histology achieved nearly equivalent response rates and survival benefits with the use of neoadjuvant chemotherapy as those with pure urothelial carcinoma, while patients with urothelial carcinoma with divergent differentiation experienced significantly worse survival outcomes regardless of the use of neoadjuvant chemotherapy prior to cystectomy.

Keywords

urinary bladder neoplasms; histology; carcinoma; transitional cell; neoadjuvant therapy

UP to a third of bladder cancers harbor aberrant, nonurothelial histological features.^{1–3} Recognition of histological variants in bladder cancer has increased recently due to advances in immunohistochemical techniques, and broadening awareness of their clinical behavior and prognostic implications.⁴ For example the presence of urothelial carcinoma with divergent differentiation (ie squamous or glandular differentiation) or variant histology (ie micropapillary, plasmacytoid, nested variant, sarcomatoid or neuroendocrine variant) is correlated with clinical up staging and poor cancer control.⁵ Due to their relative rarity and exclusion from large prospective clinical trials, treatment standards for nonpure urothelial histologies is lacking. Current management is leveraged by a collection of small retrospective studies with conflicting results regarding the benefit derived from perioperative radiotherapy or systemic chemotherapy.^{6,7}

While neoadjuvant chemotherapy is associated with a moderate survival advantage in the setting of muscle invasive pure urothelial carcinoma (cT2–T4), there is less certainty regarding the chemoresponsiveness of nonPUC bladder cancers.^{8–10} For example while some single center retrospective studies suggest certain patients with micropapillary bladder cancer experience down staging and survival benefits from NAC, a large meta-analysis of more than 3,000 micropapillary cases by Abufaraj et al concluded that the use of NAC did not improve recurrence-free, cancer specific or overall survival.^{11–13} The most recent clinical guidelines note that, aside from neuroendocrine, pure squamous cell and pure adenocarcinoma, the role of perioperative chemotherapy in other variant histology muscle invasive bladder cancer remains unclear.^{8,10,14}

In cases with heterogeneous histology comprised of both urothelial and nonurothelial components the limited availability of comparative data and conflicting results of existing studies pose an opportunity to better define the effectiveness of NAC and cystectomy.^{6,11,12,15–17} To address this clinical question, we compared chemotherapy response as measured by pathological down staging and survival outcomes among bladder cancers with nonPUC histology treated with either NAC followed by cystectomy or cystectomy alone.

MATERIALS AND METHODS

Data Source and Patient Selection

Using an institutional health informatics platform merged with a departmental cystectomy registry, we identified patients with clinical stage T2–T4 bladder cancer treated with radical

cystectomy at Moffitt Cancer Center between 2007 and 2017. The merged analytical data set included data elements consisting of patient demographics, clinical staging, treatment history (type of surgery, pathological results, receipt of chemotherapy) and survival outcomes. Patients with distant metastatic disease prior to surgery or missing data variables were excluded. Cancer staging was performed according to the AJCC TNM cancer system (5th edition) based on pathology from transurethral bladder tumor resection specimens, cross-sectional abdominopelvic and chest imaging, and physical examination,¹⁸ and histology was classified according to the World Health Organization classification system (3rd edition).¹⁹ Patients were categorized into one of 3 histology groups (PUC, UDD or VH) based on pathology. All pathology was reviewed by 3 expert genitourinary pathologists. Pathological classifications were based on review of original pathology reports and/or re-review of outside pathology, and histological classifications were based on review of transurethral resection specimens and/or cystectomy pathology reports.

All cases included in analysis consisted of UC with or without variant and/or differentiated components. Pure neuroendocrine, squamous cell and adenocarcinoma carcinoma cases were not included in the study. In cases of mixed tumors in which more than 1 variant histology was present the predominant histology was used for classification purposes. Percentages of variant and differentiated components were not included in the analysis due to lack of universal or standard reporting in all cases. VH cases included tumors with greater than 5% component of micropapillary, plasmacytoid, nested variant, sarcomatoid or neuroendocrine variant histology. UDD was defined according to the presence of any component of squamous and/or glandular differentiation. The study was approved and overseen by the Moffitt Cancer Center Scientific Review Committee and institutional review board (IRB protocol MCC#16525).

Study Measures and Outcomes

Cases were stratified by histology subgroup (PUC, UDD or VH) and the use of NAC. NAC regimens consisted of gemcitabine/cisplatin, dense dose methotrexate/vinblastine/doxorubicin/cisplatin, gemcitabine/carboplatin or cisplatin/etoposide. Other variables used for adjustment included demographic information, coexisting medical conditions, and pathological factors such as clinical and pathological stage, soft tissue surgical margin status, presence of lymphovascular or perineural invasion and presence of carcinoma in situ. Outcomes of interest included pathological down staging after cystectomy, and cancer specific and overall survival calculated from time of cystectomy to date of last followup or death.

Statistical Analysis

Patient characteristics were summarized and compared using the Kruskal-Wallis tests for continuous variables and the chi-square or Fisher exact tests for categorical variables. Logistic regression models were fit for the pathological response end points (complete response defined as pT0N0 and any down staging). Survival analyses were performed using the Kaplan-Meier method and adjusted Cox proportional hazard models for CSS and OS. Multivariable models were adjusted for age, clinical stage and comorbidities. Odds ratios and hazard ratios with corresponding 95% confidence intervals and p values were output

from models. For CSS deaths were only treated as events when cancer related cause of death was confirmed. All statistical analyses were performed with SAS 9.4 and R 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria). Statistical testing was performed at a 0.05 significance level.

RESULTS

Among 768 patients in the overall study cohort 592 (77%) were men and 176 (23%) were women. The median followup time was 21 months (range 1 to 130). Groups were similar across key demographic factors (table 1 and supplementary table 1, <https://www.jurology.com>). More than half of cases (410, 53%) were classified as PUC, while 185 (24%) were characterized by UDD and 173 (23%) contained VH. Within the VH group there were 76 (44%) micropapillary, 31 (18%) sarcomatoid, 27 (16%) neuroendocrine, 20 (12%) plasmacytoid and 19 (11%) nested variant cases. The distribution of NAC regimens and numbers of NAC cycles received were similar between the different histological subgroups. Of the 314 patients who received NAC the majority received a cisplatin based therapy (78%) and the median number of cycles received was 3 (range 1 to 19).

Use of cisplatin based NAC was similar across histology groups: 33% for PUC, 30% for UDD and 32% for VH ($p=0.84$). UDD and VH cases were associated with more aggressive disease as indicated by higher pathological stage ($p<0.01$), lymphovascular invasion ($p<0.001$) and positive surgical margins ($p<0.004$). However, among those who received NAC complete pathological response was achieved in 23% of PUC cases, 18% of UDD cases and 30% of VH cases. Partial response (down staging) was achieved in 46% of PUC cases, 37% of UDD cases and 41% of VH cases. When comparing all 3 groups, there were no statistical differences in the rates of complete or partial response ($p=0.30$ and $p=0.40$, respectively). Although UDD and VH groups had similar odds of pathological down staging with NAC compared to patients with PUC in adjusted analyses, pathological down staging outcomes after radical cystectomy alone were inferior for all groups ($p<0.05$, table 2).

Among patients who received NAC the OS was improved in PUC cases (HR 0.71, 95% CI 0.51–0.98; fig. 1 and table 3). In the VH group patients who received NAC had improved CSS compared to those who were treated with cystectomy alone (HR 0.55, 95% CI 0.30–0.99; fig. 2). In contrast, OS and CSS were not significantly different in patients with UDD who received NAC and were treated with cystectomy alone (HR 0.92, 95% CI 0.58–1.46 and HR 1.06, 95% CI 0.63–1.79, respectively). Overall and cancer specific survival were worse in UDD cases compared to PUC cases (OS HR 1.63, 95% CI 1.07–2.48; CSS HR 1.59, 95% CI 1.01–2.51). These outcomes were not significantly different between VH and PUC groups. Notably cancer specific survival was similar between PUC and VH groups treated with NAC (HR 1.02, 95% CI 0.61–1.73, $p=0.93$). Patients managed by radical cystectomy alone experienced inferior OS across all histology groups vs the reference standard group of PUC treated with NAC. Detailed hazard ratios and corresponding 95% confidence intervals are shown in table 3. Response rates and Kaplan-Meier analyses of OS of each individual histological subtype are shown in supplementary table 2 (<https://www.jurology.com>) and the supplementary figure (<https://www.jurology.com>).

DISCUSSION

The role of NAC in managing nonPUC histology bladder cancer is not clearly defined. Similar to prior studies, we found that UDD and VH were associated with aggressive pathological features (higher pathological stage, lymphovascular invasion and positive surgical margins). Despite comparable rates of complete and partial response to NAC in all 3 histological subgroups, patients with UDD did not achieve improved overall or cancer specific survival with NAC. In contrast, patients in the VH group experienced similar rates of down staging and survival benefits compared to those with PUC who received NAC prior to radical cystectomy.

Squamous differentiation is the most commonly reported histological variant with an estimated incidence of 20% to 40%, while glandular differentiation is found in up to 18% of patients with invasive bladder cancer.^{20,21} In the absence of prospective trial data it is not unreasonable to presume that cases characterized by some degree of divergent differentiation (ie squamous or glandular) exhibit comparable responses to NAC as cases of PUC.⁴ However, our data showed that patients with UDD had worse overall and cancer specific survival compared to those with PUC. In fact, there was no survival difference between UDD cases receiving NAC and those managed by cystectomy alone.

In accordance with our findings Minato et al reported that patients with squamous differentiation had significantly worse survival outcomes than those with PUC in a small series of 38 patients with clinical cT3–4aN0M0 disease who received 2 to 3 cycles of cisplatin based NAC.²² However, in contrast to our findings, the authors reported a reduced incidence of pathological down staging in squamous differentiation cases compared to PUC cases (11.1% vs 51.7%, $p=0.031$).²² A secondary analysis of a landmark prospective randomized trial directed by the Southwestern Oncology Group (S8710) found that patients with squamous/glandular differentiation (61) experienced a survival benefit from NAC (HR 0.46, 95% CI 0.25–0.87, $p=0.02$) with marginal evidence that this benefit was greater than it was for patients with PUC (interaction $p=0.09$).²³

These inconsistent findings can partially be attributed to the small case numbers included in these retrospective and secondary studies. A strength of our analysis is that it includes a greater number of cases than most previous reports and it adds to the existing data suggesting that patients with invasive UDD may not benefit from standard cisplatin based NAC.

The reason for the unfavorable survival outcomes in the UDD group is not fully understood. Previous studies have suggested that squamous and glandular differentiation are associated with features of biologically aggressive disease and are independent predictors of CSS.²⁴ Molecular subtyping of bladder cancers has shown that basal MIBCs, which have a tendency toward early invasion and metastases and seem to have more aggressive behavior than luminal subtypes, are enriched with squamous features.²⁵ However, the role of molecular subtyping in histologically heterogeneous bladder cancer (ie UDD) is currently unclear, as Hovelson et al demonstrated, through pairing of urothelial and squamous components of the same tumor using DNA and RNA sequencing, that the same tumor may have identical

driving genomic alterations but markedly different transcriptional profiles.²⁶ These authors concluded that continued work in understanding the impact of histological heterogeneity on expression profiles and patient outcome in the presence and absence of NAC is urgently needed to guide appropriate use of expression based subtyping analyses.

Notably we found that patients in the VH group who received NAC prior to radical cystectomy exhibited comparable rates of pathological down staging and survival compared to patients with PUC. Micropapillary bladder cancer was the most common subtype in our cohort, comprising 44% of the VH group. Past studies on micropapillary bladder cancer have recognized that this variant is associated with high risk features and that those with nonMIBC may experience a survival benefit when managed by early radical cystectomy compared to intravesical therapies.^{7,12} In the setting of MIBC, however, reports and opinions conflict regarding the benefit of NAC.^{6,11,12,15–17} In a review of 2,018 patients with nonPUC histology from the National Cancer Database Vetterlein et al found that although NAC decreased the frequency of nonorgan confined disease at the time of cystectomy in micropapillary bladder cancer cases, this did not translate into a survival benefit.¹⁵ However, in a series of 82 patients from Memorial Sloan Kettering Cancer Center down staging to pT0 occurred in 45% of patients who received NAC compared to 13% who did not, and patients with pT0 disease had higher OS rates (92% vs 25%) and lower rates of recurrence (21% vs 79%) at 24-month followup.¹¹ Our findings provide further support regarding the effectiveness of NAC in micropapillary MIBC.

There is clearer evidence supporting NAC in some variant subgroups, such as pure neuroendocrine tumors, where prior observational studies have shown that neuroendocrine variants are responsive to chemotherapy.^{27,28} Plasmacytoid, nested variant and sarcomatoid histologies represent a smaller proportion of patients in our VH group, which is also in line with previous reports; however, given the rarity of these individual subtypes, it is difficult to discern the potential benefits of NAC from limited retrospective series.^{15,29} Recent genomic characterization studies have provided meaningful insights into the molecular biology of bladder cancer and have revealed different molecular subtypes. For example micropapillary, plasmacytoid, and small cell histologies show distinct mutational patterns and expression signatures, which determine their aggressive features and may represent novel therapeutic targets.³⁰ The genomic classification of MIBC will likely ultimately drive precision treatment strategies in the future.

Several limitations should be considered in interpreting our results. The study design is retrospective and nonrandomized, which increases the risk of selection bias. Previous bladder cancer literature has shown that NAC is generally underused, the quality of chemotherapy regimens is often inconsistent with guideline recommendations and candidates for NAC are carefully selected. These factors are important when interpreting retrospective data and extrapolating survival outcomes. We attempted to account for potential selection bias by using adjusted multivariable models to balance differences in clinical and demographic variables; however, the findings of this study should still be interpreted as hypothesis generating given the aforementioned potential confounding variables. In addition, the proportions of VH within a tumor sample were not consistently reported and so were not included in our final analyses. Furthermore, we were unable to

perform meaningful subanalyses on individual histological variant groups due to the relatively small numbers of patients within variant groups. This is a known challenge with studying rare cancers. Earlier recognition of nonPUC histology in patients with MIBC, inclusion of nonPUC histology cases in prospective clinical trials, identification of reliable biomarkers, and further delineation of specific molecular alterations will lead to better understanding and treatment of this group of bladder cancers.

CONCLUSIONS

Patients with VH MIBC achieved nearly equivalent response rates and survival benefits when treated with NAC followed by cystectomy vs those with PUC managed by the same treatment strategy. Conversely patients with UDD MIBC exhibited worse survival outcomes regardless of the use of NAC. These findings add to limited existing data regarding treatment outcomes for nonPUC bladder cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Abbreviations and Acronyms

AJCC	American Joint Committee on Cancer
CSS	cancer specific survival
MIBC	muscle invasive bladder cancer
NAC	neoadjuvant chemotherapy
OS	overall survival
PUC	pure urothelial carcinoma
UC	urothelial carcinoma
UDD	urothelial carcinoma with divergent differentiation
VH	variant histology

REFERENCES

1. Cai T, Tiscione D, Verze P et al.: Concordance and clinical significance of uncommon variants of bladder urothelial carcinoma in transurethral resection and radical cystectomy specimens. *Urology* 2014; 84: 1141. [PubMed: 25239253]
2. Xylinas E, Rink M, Robinson BD et al.: Impact of histological variants on oncological outcomes of patients with urothelial carcinoma of the bladder treated with radical cystectomy. *Eur J Cancer* 2013; 49: 1889. [PubMed: 23466126]
3. Moschini M, Dell'Oglio P, Luciano R et al.: Incidence and effect of variant histology on oncological outcomes in patients with bladder cancer treated with radical cystectomy. *Urol Oncol* 2017; 35: 335. [PubMed: 28087131]
4. Chalasani V, Chin JL and Izawa JI: Histologic variants of urothelial bladder cancer and nonurothelial histology in bladder cancer. *Can Urol Assoc J* 2009; 3: S193.

5. Kim SP, Frank I, Cheville JC et al.: The impact of squamous and glandular differentiation on survival after radical cystectomy for urothelial carcinoma. *J Urol* 2012; 188: 405. [PubMed: 22704101]
6. Kamat AM, Dinney CP, Gee JR et al.: Micropapillary bladder cancer: a review of the University of Texas M. D. Anderson Cancer Center experience with 100 consecutive patients. *Cancer* 2007; 110: 62. [PubMed: 17542024]
7. Willis DL, Fernandez MI, Dickstein RJ et al.: Clinical outcomes of cT1 micropapillary bladder cancer. *J Urol* 2015; 193: 1129. [PubMed: 25254936]
8. National Comprehensive Cancer Network: Bladder Cancer, version 5.2020. Plymouth Meeting, Pennsylvania: National Comprehensive Cancer Network 2020.
9. Advanced Bladder Cancer (ABC) Meta-analysis Collaboration: Neoadjuvant chemotherapy in invasive bladder cancer: update of a systematic review and meta-analysis of individual patient data advanced bladder cancer (ABC) meta-analysis collaboration. *Eur Urol* 2005; 48: 202. [PubMed: 15939524]
10. Chang SS, Bochner BH, Chou R et al.: Treatment of non-metastatic muscle-invasive bladder cancer: AUA/ASCO/ASTRO/SUO guideline. *J Urol* 2017; 198: 552. [PubMed: 28456635]
11. Meeks JJ, Taylor JM, Matsushita K et al.: Pathological response to neoadjuvant chemotherapy for muscle-invasive micropapillary bladder cancer. *BJU Int* 2013; 111: E325.
12. Ghoneim IA, Miocinovic R, Stephenson AJ et al.: Neoadjuvant systemic therapy or early cystectomy? Single-center analysis of outcomes after therapy for patients with clinically localized micropapillary urothelial carcinoma of the bladder. *Urology* 2011; 77: 867. [PubMed: 21296399]
13. Abufaraj M, Foerster B, Schernhammer E et al.: Micropapillary urothelial carcinoma of the bladder: a systematic review and meta-analysis of disease characteristics and treatment outcomes. *Eur Urol* 2019; 75: 649. [PubMed: 30553613]
14. Horwich A, Babjuk M, Bellmunt J et al.: EAU-ESMO consensus statements on the management of advanced and variant bladder cancer-an international collaborative multi-stakeholder effort: under the auspices of the EAU and ESMO Guidelines Committees. *Ann Oncol* 2019; 30: 1697. [PubMed: 31740927]
15. Vetterlein MW, Wankowicz SAM, Seisen T et al.: Neoadjuvant chemotherapy prior to radical cystectomy for muscle-invasive bladder cancer with variant histology. *Cancer* 2017; 123: 4346. [PubMed: 28743155]
16. Bandini M, Pederzoli F, Madison R et al.: Unfavorable cancer-specific survival after neoadjuvant chemotherapy and radical cystectomy in patients with bladder cancer and squamous cell variant: a multi-institutional study. *Clin Genitourin Cancer* 2020; 18: e543.
17. Willis DL, Porten SP and Kamat AM: Should histologic variants alter definitive treatment of bladder cancer? *Curr Opin Urol* 2013; 23: 435. [PubMed: 23880739]
18. Sobin LH and Fleming ID: TNM Classification of Malignant Tumors, 5th edition. Union Internationale Contre le Cancer and the American Joint Committee on Cancer. *Cancer* 1997; 80: 1803. [PubMed: 9351551]
19. Eble J, Sauter G, Epstein J et al.: Pathology and Genetics of Tumours of the Urinary System and Male Genital Organs. Lyon, France: IARC Press 2004.
20. Black PC, Brown GA and Dinney CP: The impact of variant histology on the outcome of bladder cancer treated with curative intent. *Urol Oncol* 2009; 27: 3. [PubMed: 18367107]
21. Matulay JT, Narayan VM and Kamat AM: Clinical and genomic considerations for variant histology in bladder cancer. *Curr Oncol Rep* 2019; 21: 23. [PubMed: 30806832]
22. Minato A, Fujimoto N and Kubo T: Squamous differentiation predicts poor response to cisplatin-based chemotherapy and unfavorable prognosis in urothelial carcinoma of the urinary bladder. *Clin Genitourin Cancer* 2017; 15: e1063.
23. Scosyrev E, Ely BW, Messing EM et al.: Do mixed histological features affect survival benefit from neoadjuvant platinum-based combination chemotherapy in patients with locally advanced bladder cancer? A secondary analysis of Southwest Oncology Group-Directed Intergroup Study (S8710). *BJU Int* 2011; 108: 693. [PubMed: 21105991]
24. Lee YJ, Moon KC, Jeong CW et al.: Impact of squamous and glandular differentiation on oncologic outcomes in upper and lower tract urothelial carcinoma. *PLoS One* 2014; 9: e107027.

25. Sjobahl G, Lauss M, Lovgren K et al.: A molecular taxonomy for urothelial carcinoma. Clin Cancer Res 2012; 18: 3377. [PubMed: 22553347]
26. Hovelson DH, Udager AM, McDaniel AS et al.: Targeted DNA and RNA sequencing of paired urothelial and squamous bladder cancers reveals discordant genomic and transcriptomic events and unique therapeutic implications. Eur Urol 2018; 74: 741. [PubMed: 30033047]
27. Siefker-Radtke AO, Kamat AM, Grossman HB et al.: Phase II clinical trial of neoadjuvant alternating doublet chemotherapy with ifosfamide/doxorubicin and etoposide/cisplatin in small-cell urothelial cancer. J Clin Oncol 2009; 27: 2592. [PubMed: 19414678]
28. Kaushik D, Frank I, Boorjian SA et al.: Long-term results of radical cystectomy and role of adjuvant chemotherapy for small cell carcinoma of the bladder. Int J Urol 2015; 22: 549. [PubMed: 25761779]
29. Dayyani F, Czerniak BA, Sircar K et al.: Plasmacytoid urothelial carcinoma, a chemosensitive cancer with poor prognosis, and peritoneal carcinomatosis. J Urol 2013; 189: 1656. [PubMed: 23159581]
30. Guo CC and Czerniak B: Bladder cancer in the genomic era. Arch Pathol Lab Med 2019; 143: 695. [PubMed: 30672335]

Figure 1.

Kaplan-Meier curves show overall survival of patients with muscle invasive bladder cancer stratified by histology and receipt of neoadjuvant chemotherapy prior to radical cystectomy. A, PUC with NAC, and UDD with vs without NAC. B, PUC with NAC, and VH with vs without NAC.

Figure 2.

Kaplan-Meier curves illustrate cancer specific survival of patients with muscle invasive bladder cancer stratified by histology and receipt of neoadjuvant chemotherapy prior to radical cystectomy. *A*, PUC with NAC, and UDD with vs without NAC. *B*, PUC with NAC, and VH with vs without NAC.

Table 1.
Clinicopathological features of patients with muscle invasive bladder cancer stratified by histology

	PUC	UDD	VH	p Value*
No. pts	410	185	173	
Median yrs age (IQR)	67 (61–74)	69 (60–75)	69 (61–76)	0.77
No. gender (%):				0.59
Female	88 (21)	46 (25)	42 (24)	
Male	322 (79)	139 (75)	131 (76)	
No. race/ethnicity (%):				0.29
White	393 (96)	169 (91)	167 (97)	
Nonwhite	17 (4)	16 (9)	11 (3)	
Median Elixhauser comorbidity (IQR)	4 (2–6)	3 (2–5)	4 (2–6)	0.64
No. AJCC clinical T stage (%):				0.02
cT2	325 (79)	127 (69)	143 (83)	
cT3	55 (13)	37 (20)	21 (12)	
cT4	30 (7)	21 (11)	9 (5)	
No. neoadjuvant chemotherapy (%)	158 (38)	78 (42)	78 (45)	0.31
No. chemotherapy regimen (%):				
Cisplatin based [†]	134 (33)	56 (30)	55 (32)	0.84
Noncisplatin based	24 (6)	23 (12)	23 (13)	0.01
None	252 (61)	95 (58)	95 (55)	0.31
Median No. chemotherapy cycles (%):				0.34
Less than 3	24 (15)	11 (14)	10 (13)	
3	83 (53)	40 (51)	32 (41)	
4 or More	51 (32)	27 (35)	36 (46)	
No. AJCC pathological stage (%):				<0.01
0 (pT0N0M0)	67 (16)	22 (12)	29 (17)	
I (pT1/pTa/pTisN0M0)	69 (17)	18 (10)	21 (12)	
II (pT2N0M0)	74 (18)	18 (10)	19 (11)	
III (pT3-T4aN0M0, pT1-T4aN1–3M0)	80 (20)	68 (37)	35 (20)	
IV (pT4bN0–3M0, pT0–4N0–3M1)	119 (30)	56 (31)	68 (40)	

	PUC		UDD		VH		p Value*
No. complete down staging after NAC (%)	37	(23)	14	(18)	23	(30)	0.30
No. any down staging after NAC (%)	73	(46)	29	(37)	32	(41)	0.40
No. lymphovascular invasion (%)	132	(32)	74	(40)	85	(49)	<0.001
No. pos surgical margins (%)	43	(10)	34	(18)	34	(20)	0.004
No. adjuvant chemotherapy (%)	52	(13)	18	(10)	26	(15)	0.31

* Comparison between all 3 histological groups. Association between categorical variables and 3 end points were evaluated using chi-square or Fisher exact tests when expected frequencies were less than 5.

[†] Gemcitabine/cisplatin or dense dose methotrexate/vinblastine/doxorubicin/cisplatin.

Table 2.

Multivariable logistic regression model for degree of bladder cancer down staging among patients with muscle invasive bladder cancer

	Complete Down Staging			Any Down Staging		
	OR (95% CI) *	p Value		OR (95% CI) *	p Value	
PUC:		0.0013			0.0132	
Without NAC	1.0 (referent)			1.0 (referent)		
With NAC	2.46 (1.43, 4.28)			1.69 (1.12, 2.57)		
UDD:		0.0199			0.0047	
Without NAC	1.0 (referent)			1.0 (referent)		
With NAC	3.15 (1.22, 8.61)			2.79 (1.38, 5.78)		
VH:		0.0002			0.0158	
Without NAC	1.0 (referent)			1.0 (referent)		
With NAC	6.69 (2.62, 19.69)			2.35 (1.18, 4.76)		

Cases are stratified by histology and administration of neoadjuvant chemotherapy before radical cystectomy.

* Odds of down staging.

Table 3.

Multivariable Cox proportional hazard regression model for overall survival and cancer specific survival

	Overall Survival		Cancer Specific Survival	
	HR (95% CI) *	p Value	HR (95% CI) *	p Value
PUC:		0.0346		0.2560
Without NAC	1.0 (referent)		1.0 (referent)	
With NAC	0.71 (0.51, 0.98)		0.81 (0.56, 1.17)	
UDD:		0.7332		0.8162
Without NAC	1.0 (referent)		1.0 (referent)	
With NAC	0.92 (0.58, 1.46)		1.06 (0.63, 1.79)	
VH:		0.0825		0.0495
Without NAC	1.0 (referent)		1.0 (referent)	
With NAC	0.63 (0.38, 1.06)		0.55 (0.30, 0.99)	

Cases are stratified by histology and administration of neoadjuvant chemotherapy before radical cystectomy.

* Odds of death.