



Overview of histologic variants of urothelial carcinoma: current trends and narrative review on treatment outcomes

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Background and Objective: The histologic variants of urothelial carcinoma (UC) are tumors arising from within the urothelium in which some component of the tumor morphology is other than urothelial. They are underdiagnosed, aggressive and have varying pathologic response rates to systemic chemotherapy. There are no consensus guidelines on the use of systemic chemotherapy in variant histology (VH) of UC. We performed a contemporary review on pathologic response rates to neoadjuvant systemic therapy and survival outcomes following radical cystectomy in order to provide a rationale for clinical practice recommendations on the management of UC with VH.

Methods: A PubMed literature search was conducted for all English articles from inception reporting either pathological response rates to neoadjuvant treatment or survival outcomes after radical cystectomy in non-metastatic VH of UC.

Key Content and Findings: Neoadjuvant chemotherapy (NAC) prior to radical cystectomy was shown to be a beneficial treatment strategy in UC with VH. The micropapillary, plasmacytoid, nested and sarcomatoid histologic variants were associated with worse survival outcomes compared to conventional UC and UC with squamous or glandular differentiation despite initial downstaging with chemotherapy. There is evidence of improved survival in patients with sarcomatoid differentiation receiving NAC compared to RC alone. The major prognostic factors that affect survival outcomes in VH of UC include histologic variant subtype, patient age, presence of lymphovascular invasion, hydronephrosis, nodal metastasis and advanced T stage at diagnosis. Recent studies demonstrate that VH of UC are heterogenous tumors and responsiveness to NAC may be a function of the molecular subtypes present.

Conclusions: Based on these findings, NAC to achieve pathologic downstaging prior to radical cystectomy is recommended for MIBC with VH. Biomarkers identified by molecular profiling with immunohistochemistry will need to be validated as predictors of response to NAC in future trials.

Keywords: Urothelial variants; squamous neoplasms; glandular neoplasms; radical cystectomy; neoadjuvant chemotherapy

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Introduction

Urothelial carcinoma (UC) is the most common malignancy of the urinary tract. The American cancer society estimates there are over 83,000 new cases and 17,100 deaths annually (1). UC accounts for over 90% of bladder cancers (2).

The histologic variants of UC include tumors arising from within the urothelium in which some component of the tumor morphology is other than urothelial. When present, these tumors can occur in mixed form or with a predominant histologic subtype. The histologic variants of urothelial carcinoma include micropapillary, microcystic, nested, lymphoepithelioma-like, plasmacytoid, sarcomatoid, giant cell, poorly differentiated, lipid rich, clear cell and urothelial carcinoma with divergent differentiation (including squamous, glandular, trophoblastic differentiation, among others) (2).

These histologic variants pose a diagnostic and treatment challenge for urologists, oncologists and pathologists alike. They are often underdiagnosed but not uncommon in clinical practice as the incidence of divergent differentiation, for instance, can be as high as 33% in cystectomy specimen and interobserver variability by reviewing pathologists could account for differences in incidence reporting (2). They are traditionally believed to be more aggressive, often diagnosed as locally advanced disease, and may have varying pathologic response rates to systemic chemotherapy (3).

In recent years, advances in genomics have led to a better understanding of the molecular drivers of carcinogenesis in urothelial carcinoma. However, the histologic variants of urothelial carcinoma have not been subjected to the same amount of scrutiny.

The purpose of this article is to review the histopathologic features, treatment modalities and prognostic factors in treatment of variant histology (VH) of urothelial carcinoma by providing a concise and detailed review of the pathologic response rates to treatment in non-metastatic disease and survival outcomes following radical cystectomy. We will also briefly discuss areas of ongoing research such as immunotherapy and the genomics of histologic variant subtypes of urothelial carcinoma. Neuroendocrine tumors, squamous cell carcinoma (SCC), primary adenocarcinoma, urachal adenocarcinoma, mesenchymal and other types of non-urothelial neoplasms are beyond the scope of this review. We present the following article in accordance with the Narrative Review reporting checklist (available at <https://tau.amegroups.com/article/view/10.21037/tau-22-43/rc>).

Methods

Search strategy

PubMed database was utilized to conduct a literature search. Our search strategy featured two combinations of regular keywords, separate combinations of a MeSH term with individual keywords “micropapillary variant”, “plasmacytoid variant”, “nested variant”, “sarcomatoid variant”, “lymphoepithelioma-like”, “clear cell variant”, “microcystic variant”, “squamous differentiation”, “glandular differentiation” and a combination of MeSH terms. *Table 1* is the search strategy summary. Details of the Search results from keyword and MeSH term combinations are in the *Table S1*. All articles published from inception, in English, were taken into consideration due to rarity of histologic variants of urothelial carcinoma in literature.

Inclusion and exclusion criteria

Studies within inclusion criteria were randomized clinical control trials (RCTs) and institutional observational studies reporting pathologic outcomes of histologic variant subtypes of UC in non-metastatic disease or survival outcomes after cystectomy with or without neoadjuvant chemotherapy (NAC). Studies that queried non institutional databases, review articles, case reports or series with a variant histology sample size <10 were excluded. The chosen studies were screened by two reviewers working independently.

Types of outcomes measured

- ❖ Pathologic outcomes, namely pathologic complete response (pCR) or pathologic downstaging after treatment at time of RC in non-metastatic disease.
- ❖ Survival outcomes following cystectomy regardless of treatment received. Survival outcomes of interest include disease recurrence, cancer specific survival (CSS), disease specific survival (DSS), overall survival (OS) and recurrence free survival (RFS).

Results

The composition of the 39 articles selected for final review included 1 clinical trial (4) and 38 observational studies. There were a total number n=24,775 patients in the studies chosen among whom n=5,553 (22.4%) were patients with VH of UC. *Figure 1* is a flow chart depicting the process of identifying relevant studies.

Table 1 The search strategy summary

Items	Specification
Date of search	10/3/2021
Databases and other sources searched	PubMed
Search terms used	<p>“variant histology bladder cancer” AND “radical cystectomy” AND “neoadjuvant chemotherapy” (“Urothelial carcinoma” OR “urothelial cancer” OR “bladder cancer” OR “bladder carcinoma”) AND (“variant” OR “differentiation” OR “VH”) AND (“multivariate OR multivariable”)</p> <p>“transitional cell, carcinoma” AND “micropapillary variant”</p> <p>“transitional cell, carcinoma” AND “plasmacytoid variant”</p> <p>“transitional cell, carcinoma” AND “nested variant”</p> <p>“transitional cell, carcinoma” AND “sarcomatoid variant”</p> <p>“transitional cell, carcinoma” AND “lymphoepithelioma-like”</p> <p>“transitional cell, carcinoma” AND “clear cell variant”</p> <p>“transitional cell, carcinoma” AND “microcystic variant”</p> <p>“transitional cell, carcinoma” AND “squamous differentiation”</p> <p>“transitional cell, carcinoma” AND “glandular differentiation”</p> <p>“Carcinoma, transitional cell/therapy” AND “neoadjuvant therapy/methods”</p>
Timeframe	From inception till 10/3/2022
Inclusion and exclusion criteria	<p>Inclusion criteria: Randomized clinical control trials (RCTs) and institutional observational studies reporting pathologic outcomes of histologic variant subtypes of urothelial carcinoma (UC) in non-metastatic disease or survival outcomes after cystectomy with or without neoadjuvant chemotherapy (NAC)</p> <p>Exclusion criteria: Studies that queried non institutional databases, review articles, case reports or series with a variant histology sample size <10</p>

Quality assessment

Quality assessment for the chosen studies was done using the Cochrane bias risk tool for clinical trials and the Newcastle-Ottawa scale tool for cohort studies.

Actual results

A total of twelve studies (4-15) meeting the inclusion criteria reported pathologic response to treatment. Ten discussed NAC, one (12) discussed trimodal bladder preserving therapy (TMT) whereas one (4) discussed neoadjuvant immunotherapy.

There were a total of 35 papers, 25 studies (5-7,9-11,14-32), then 10 studies (33-42) reporting survival outcomes after cystectomy. Five of these studies (18,21,24,38,40) reported survival after RC with adjuvant chemotherapy. One study (21) reported worse OS when adjuvant chemotherapy

was not administered in glandular differentiation.

Pathologic complete response was reported in ten studies (4-6,8,10-14,36) while pathologic downstaging was reported in nine studies (4,5,7,8,10,11,13-15).

Survival benefit with NAC in VH of UC was demonstrated in two studies (5,14), and specifically with sarcomatoid differentiation (11) and squamous differentiation (6,9).

Nineteen studies (5,6,8-10,13,16,17,19,21,23,24,27,29-31,33,41,42) analyzed independent factors other than VH affecting either response to treatment or survival outcomes. Age, lymphovascular invasion, hydronephrosis, nodal metastasis and pathological/clinical stage were the most commonly reported factors. At least one of these factors was reported as having an impact of survival after RC in ten studies (10,17,21,23,24,26,30,31,41,42).

Other independent prognostic factors mentioned in the literature reviewed include circulating tumor cells in

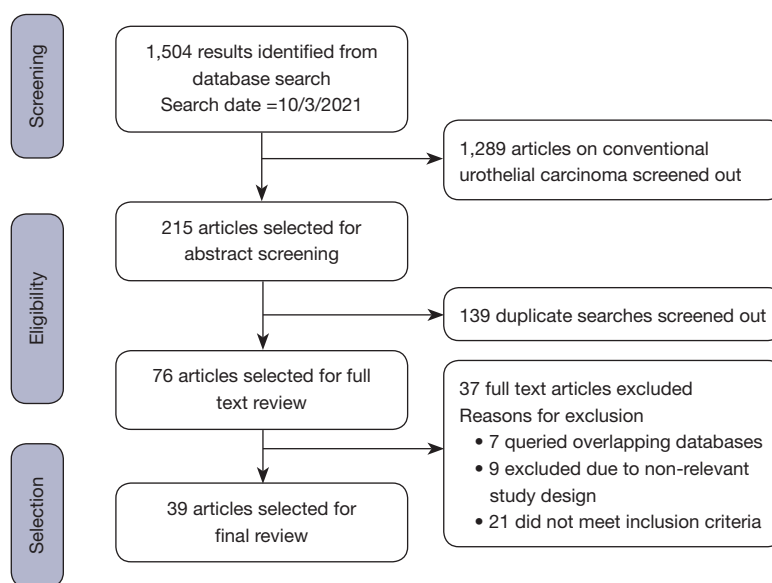


Figure 1 Selection of relevant studies.

preoperatively collected blood samples prior to radical cystectomy (19) and neutrophil-lymphocyte ratio in squamous differentiation (9).

Tables 2-11 is a concise summary of the reviewed studies categorized by variant histology and type of treatment reported.

Discussion

This review provides a concise summary of the 2016 WHO classification of urothelial tumors and presents the data on pathologic response with neoadjuvant systemic therapy including immunotherapy and survival outcomes in histologic variants of UC after RC regardless of treatment received. There are no consensus guidelines on the use of systemic chemotherapy in VH of UC. There are few randomized clinical trials involving VH of UC. This review provides an executive summary of most the studies that report either pathologic response in non-metastatic disease or survival outcome after RC. The histopathologic features of individual histologic variants included in this review are summarized in *Figure 2* and are discussed briefly.

Histologic variants of urothelial carcinoma

Micropapillary

Micropapillary urothelial carcinoma has been described,

morphologically, as tumor cells arranged in multiple small nests without fibrovascular cores aggregating within lacunae (43). The presence of multiple small nests within the same lacunar space is characteristic. Overexpression or amplification of ERBB2 at a molecular level has been reported in up to 42% of these tumors (44-46). The management of this variant has been disputed to date with conflicting reports of responsiveness to NAC and survival outcomes after RC. Some studies (15,47) have recommended expeditious RC. The earliest recommendation for expeditious RC over NAC in muscle-invasive bladder cancer (MIBC), was made by Kamat *et al.* in a series involving 55 patients at MD Anderson cancer center (15). This recommendation was made after a higher percentage of patients receiving NAC had \geq pT3 disease than those who didn't (69% vs. 35%, $P=0.0016$) at time of cystectomy (15). A more recent series by Meeks *et al.* with 44 patients showed that 45% of patients with micropapillary UC treated with NAC achieved downstaging prior to RC compared to 13% who did not ($P=0.049$) (10). The rate of \geq pT3 disease was observed to be only 39% leading to the suggestion that this observed difference between studies may be indicative of improved pre-RC clinical staging and that NAC should be considered in these patients. Another study showed that despite presenting as a more locally advanced disease, patients with micropapillary UC had similar pathologic response rates to NAC compared to conventional UC (48).

Table 2 Studies on micropapillary UC reporting outcomes with either neoadjuvant chemotherapy or upfront radical cystectomy

Author (year)	Pathologic complete response	Pathologic downstaging	Median follow up after cystectomy	Survival outcomes after cystectomy	Major independent factor(s) other than histologic phenotype affecting response/outcomes analyzed	Comments
Meeks (10) (2013), n=44 (VH n=44)	Comparing those who received NAC with those who did not, pCR occurred in 45% vs. 13% (P=0.049)	Comparing those who received NAC with those who did not, pathologic downstaging was achieved in 35% vs. 47% (P=0.4)	24 months	Patients with p T0 disease had improved survival outcomes after cystectomy at 24 months follow up. Higher survival rates (25 vs. 92%) with a longer mean time to death [72 (95% CI: 55–90) vs. 29 (95% CI: 22–37) months, P=0.004] and lower rates of disease recurrence (21 vs. 79%) with longer time to recurrence [73 (95% CI: 56–90) vs. 26 (95% CI: 17–35) months, P=0.03]	Pathologic T stage was associated with worse survival outcomes	
Mitra (17) (2019), n=1,497 (VH n=151)			10.7 years for conventional UC group, 7.8 years for micropapillary VH	Inferior 5-year RFS (70% vs. 44%; P<0.01) and OS (61% vs. 38%; P<0.01) compared to conventional UC. No association with risk of micropapillary recurrence or mortality on multivariable analysis	Pathologic T stage, tumor grade and lymphovascular invasion were associated with worse survival outcomes	
Kamat (15) (2007), n=100 (VH n=100)		14 of 23 patients (61%) achieved pathologic downstaging with NAC		Patients alive at 5 yrs follow up were 32% for NAC group and 71% among those treated with initial cystectomy. Median OS was 43.2 for the 23 patients in NAC group. The median survival had not been reached at time of last follow up for the 32 patients treated with initial cystectomy		In this study, 55 patients underwent RC for surgically resectable disease=≤c T4A. In this subgroup, 23 received NAC and 32 had initial cystectomy.
Fairey (22) (2014), n=1,380 (VH n=33)			10 years	Comparing patients with conventional UC and micropapillary UC, predicted five-year OS (61% vs. 67%, log rank P=0.96) and RFS (69% vs. 58%, log rank P=0.33). Micropapillary histologic subtype was not independently associated with OS on multivariable analysis (HR 0.91, 95% CI: 0.55–1.49, P=0.70) or RFS (HR 0.97, 95% CI: 0.55–1.73, P=0.92)		Controlling for clinical and pathologic factors, survival outcomes of micropapillary histologic subtype were similar to conventional UC after radical cystectomy

Table 2 (continued)

Table 2 (continued)

Author (year)	Pathologic complete response	Pathologic downstaging	Median follow up after cystectomy	Survival outcomes after cystectomy	Major independent factor(s) other than histologic phenotype affecting response/outcomes analyzed	Comments
Comp�erat (23) (2010), n=72 (VH n=72) 57 patients were treated with RC stratified into three groups based on % histologic variant on TURB 1. <10% 2. 10–50% 3. >50%				Comparison of groups stratified based on % of micropapillary variant, mean survival was 18 months, 16.8 months and 12.1 months for <10%, 10–50% and >50% groups respectively.	Percentage of histologic variant was analyzed. Tumors with a higher percentage of histologic variant had higher likelihood of disease recurrence and death (P=0.04 and P=0.009). Pathological T stage was predictive of disease specific survival both in univariate and multivariate analysis (P=0.01 and P=0.04, respectively)	The presence of micropapillary histologic subtype in any amount including CIS had impact on clinical outcomes
Wang (27) (2012), n=821 (VH n=73)			9.6 years	Comparing UC with micropapillary VH with conventional UC, 10-year cancer specific survival was 31% vs. 53%; P=0.001. No significant difference was noted between groups after being stage matched for 10-year RFS (62% vs. 69%; P=0.87) or CSS (31% vs. 40%; P=0.41)	Percentage of histologic variant had no correlation with worse survival outcomes	When matched to persons with micropapillary VH was observed not to have increased rates of local/distant disease recurrence or inferior CSS after RC

UC, urothelial carcinoma; VH, variant histology; NAC, neoadjuvant chemotherapy; pCR, pathologic complete response; RFS, recurrence free survival; RC, radical cystectomy; CSS, cancer specific survival; OS, overall survival; CIS, carcinoma-in-situ; TURB, transurethral resection of bladder tumor.

Table 3 Studies on plasmacytoid UC reporting outcomes with either neoadjuvant chemotherapy or upfront radical cystectomy

Author (year)	Pathologic complete response	Pathologic downstaging	Median follow up after cystectomy	Survival outcomes after cystectomy	Major independent factor(s) other than histologic phenotype affecting response/outcomes analyzed	Comments
Li (7) (2019), n=1,410 (VH n=98) (45 patients with plasmacytoid variant received, NAC and 41 patients did not)		Regardless of receipt of NAC, 22% (95% CI: 14–32%) of patients who had a clinical stage ≥ cT2 were down staged to pT1 on RC	5 years for plasmacytoid group. 7.6 years for conventional UC group	Median OS for plasmacytoid histology vs. conventional UC was 3.8 and 8 yr respectively. Plasmacytoid histology was associated with increased overall mortality on univariable analysis (HR=1.34, 95% CI: 1.02–1.78; P=0.039) but not on multivariable analysis		17.6% of patients developed peritoneal carcinomatosis on median follow up of 4.6 years
Kaimakliotis (28) (2014), n=308 (VH n=30)			30 months	UC with plasmacytoid VH had significantly inferior OS outcomes. Median OS for plasmacytoid VH patients was 19 months, median OS for conventional UC patients had not been reached at 68 months		Plasmacytoid VH at cystectomy was associated with increased adjusted risk of mortality (HR 2.1; 95% CI: 1.2–3.8; P=0.016)

UC, urothelial carcinoma; VH, variant histology; NAC, neoadjuvant chemotherapy; RC, radical cystectomy; CSS, cancer specific survival; OS, overall survival.

Table 4 Studies on nested UC reporting outcomes with either neoadjuvant chemotherapy or upfront radical cystectomy

Author (year)	Pathologic complete response	Pathologic downstaging	Median follow up after cystectomy	Survival outcomes after cystectomy	Major independent factor(s) other than histologic phenotype affecting response/outcomes analyzed	Comments
Linder (36) (2013), n=52 (VH n=52)	None of the patients had achieved pCR with NAC	–	10.8 years	When matched with a cohort of patients with conventional UC, there was no significant difference in 10-year local RFS (83% vs. 80%; P=0.46) or 10-year CSS (41% vs. 46%; P=0.75)	–	–

UC, urothelial carcinoma; VH, variant histology; NAC, neoadjuvant chemotherapy; pCR, pathologic complete response; RFS, recurrence free survival; CSS, cancer specific survival.

Table 5 Studies on sarcomatoid differentiation reporting outcomes with either neoadjuvant chemotherapy or upfront radical cystectomy

Author (year)	Pathologic complete response	Pathologic downstaging	Median follow up after cystectomy	Survival outcomes after cystectomy	Major independent factor(s) other than histologic phenotype affecting response/outcomes analyzed	Comments
Almassi (11) (2021), n=1,853 (VH n=259)	Comparing UC with sarcomatoid differentiation with conventional UC, pCR rate 20% vs. 24% (P=0.6)	Pathologic downstaging to <T2 rate 24% vs. 31% (P=0.6), comparing between UC with sarcomatoid differentiation and conventional UC	5.8 years	Sarcomatoid differentiation was associated with inferior survival outcomes compared to conventional UC: five-year RFS of 45% vs. 71%, CSS estimate at five years of 51% vs. 75%, OS estimate at five years of 45% vs. 63%. In the sarcomatoid differentiation group, comparing patients who received NAC vs. those who did not, five-year RFS after RC was 55% vs. 40% (P=0.1)	–	Pathologic response rates to NAC between UC with sarcomatoid differentiation and conventional UC was similar. UC with sarcomatoid differentiation was associated with inferior survival outcomes but greater survival among patients receiving NAC

UC, urothelial carcinoma; VH, variant histology; NAC, neoadjuvant chemotherapy; pCR, pathologic complete response; RFS, recurrence free survival; CSS, cancer specific survival; OS, overall survival.

A retrospective review of a single institutional bladder cancer database at Cleveland Clinic with 38 bladder cancer patients having the micropapillary UC concludes by recommending neoadjuvant chemotherapy alongside RC as an ideal treatment strategy (20). In this study, 26 (93%) in a group of 28 patients with localized disease, clinical stage \leq T2N0 who did not receive NAC demonstrated pathologic upstaging at cystectomy. This study also reports poor outcomes in patients with stage cTa-T1 treated initially with bladder preservation approach using BCG as these patients all had pathologically advanced disease at cystectomy. All patients treated with perioperative chemotherapy died of metastatic disease (20).

To determine the impact of micropapillary UC on survival outcomes after RC, two studies (22,27) reported that controlling for clinical and pathologic factors, survival outcomes of micropapillary UC were similar to conventional UC after radical cystectomy. However, Mitra *et al.* (17) observed that micropapillary UC was associated with inferior 5-year RFS (70% vs. 44%; $P < 0.01$) and OS (61% vs. 38%; $P < 0.01$) compared to conventional UC but

this association was lost on multivariable analysis. Masson-Lecomte *et al.* (24) studied patients who received adjuvant chemotherapy after RC and observed that micropapillary histologic subtype was associated with higher disease recurrence rates after RC and platinum-based adjuvant chemotherapy compared to conventional UC. It has been observed that micropapillary UC has a preponderance to metastasize to abdomen and lungs after RC (26).

Most of the data about treatment outcomes in micropapillary UC are from single-center retrospective studies or population-based registries. A cumulative summary of patient characteristics and outcomes was made by Abufaraj *et al.* in a systematic review (49). It included studies comprising of a total of 863,459 participants with urothelial carcinoma among whom 3,154 (0.4%) had the micropapillary UC. There was a notable male predominance (84%) and a higher prevalence of muscle-invasive disease at diagnosis (41%). Pooled results in that review showed that the use of neoadjuvant chemotherapy resulted in pathological downstaging and pathological complete response in 55% and 37% of patients respectively,

Table 6 Studies on glandular/squamous differentiation reporting outcomes with either neoadjuvant chemotherapy or upfront radical cystectomy

Author (Year)	Pathologic complete response	Pathologic downstaging	Median follow up after cystectomy	Survival outcomes after cystectomy	Major independent factor(s) other than histologic phenotype affecting response/outcomes analyzed	Comments
Speir (6) (2021), n=71 (VH n=71) MIBC patients having Squamous differentiation who had Radical Cystectomy	NAC resulted in 12.4 times higher likelihood to achieve pCR, more than seen in patients who did not receive NAC [60% vs. 10.8%; odds ratio (OR), 12.4; 95% confidence interval (CI), 3.15–48.7; P<0.001]		38.2 months	Comparing patients who received NAC and those who did not, there was improved OS, DSS and RFS in patients receiving NAC	% squamous differentiation was used to group patients into two categories (<50% vs. ≥50%), probability of pCR was higher in patients with % squamous differentiation <50% (26.7 vs. 8.7) and benefit in OS and RFS with NAC was lost when % SV was ≥50	
Buisan (9) (2017), n=50 (VH n=50) MIBC patients having squamous differentiation. 19 patients were treated with NAC			29 months		Neutrophil-to-lymphocyte (NLR) ratio in squamous differentiation was predictive of positive response to NAC. (NLR) ratio on treatment NAC was of significant benefit in patients with NLR<5. CSS was 91.2 months vs. 38.1 months for those treated with upfront RC (P=0.009). There was no statistically significant difference in survival for patients with NLR ≥5	Aim of this study was to determine impact of neutrophil-to-lymphocyte (NLR) ratio on treatment outcomes. Patients were stratified into two groups, 1. NLR <5; 2. NLR ≥5
Zargar-Shoshtari (13) (2016), n=126 (VH n=20)	Comparing two patient groups receiving NAC - UC with divergent glandular or squamous differentiation vs. conventional UC, pCR were similar between the groups (25% vs. 21%; P=0.07)	Comparing two patient groups receiving NAC - UC with divergent differentiation vs. conventional UC, rates of pathological downstaging were significantly higher in divergent glandular or squamous differentiation vs. subgroup receiving NAC (60 vs. 32%; P=0.02)			Only clinical stage was predictive of pathologic response to NAC	Divergent glandular or squamous differentiation were independent predictors of pathologic downstaging [odds ratio (OR), 4.01; 95% confidence interval (CI), 1.16-13.9] and clinical stage (OR, 2.91; 95% CI, 1.06-7.94) in a multivariable logistics regression model

Table 6 (continued)

Table 6 (continued)

Author (year)	Pathologic complete response	Pathologic downstaging	Median follow up after cystectomy	Survival outcomes after cystectomy	Major independent factor(s) other than histologic phenotype affecting response/outcomes analyzed	Comments
Kim (29) (2012), n=1,023 (VH n=186)			11.4 years	Comparing survival outcomes between UC with divergent squamous or glandular differentiation with conventional UC; 10-year CSS did not differ significantly between the two groups (52% vs. 51%; P=0.71)	Pathological stage, lymph node status and lymphovascular invasion were associated with an increased risk of mortality	UC with divergent squamous or glandular differentiation was not significantly associated with risk of death from bladder cancer after adjusting for clinicopathologic features (HR 0.79, P=0.10)
Antunes (30) (2007), n=133 (VH n=25)			24 months	Comparing patients with tumors having squamous differentiation to those who did not, disease recurrence occurred in 64% vs. 34% (P=0.001), and death occurred in 40% vs. 16% of patients (P=0.002)	Univariate analysis revealed that pathological T stage, tumor size and lymph node involvement were predictors of CSS. Only tumor size was an independent predictor of outcome on multivariable analysis	
Ehdie (31) (2012), n=145 (VH n=67)			44 months	There was no statistically significant difference in survival outcomes between SCC and UC with squamous differentiation in terms of CSS and OS	Patients with squamous differentiation with lymph node involvement had worse OS and CSS	The aim of the study was to compare outcomes and determine predictors of CSS and OS between SCC cases and UC with squamous differentiation cases after RC
Minato (33) (2018), n=101 (VH n=20)			31 months	Comparing UC with squamous differentiation and conventional UC, five-year OS and RFS rates were 41.1% vs. 69.7% (P=0.002) and 51.8% vs. 59.5% (P=0.027) respectively	Percentage/extent of squamous differentiation had no effect on survival outcomes	Squamous differentiation was a significant independent predictor of OS on multivariate analysis (HR: 4.22; 95% CI: 1.20–14.8; P=0.024)

UC, urothelial carcinoma; VH, variant histology; NAC, neoadjuvant chemotherapy; MIBC, muscle invasive bladder cancer; pCR, pathologic complete response; RFS, recurrence free survival; CSS, cancer specific survival; OS, overall survival; DSS, disease specific survival; NLR, neutrophil-lymphocyte ratio; OR, odds ratio; SCC, squamous cell carcinoma.

Table 7 Studies on multiple variant histologies reporting outcomes with either neoadjuvant chemotherapy or upfront radical cystectomy

Author (year)	Pathologic complete response	Pathologic downstaging	Median follow up after cystectomy	Survival outcomes after cystectomy	Major independent factor(s) other than histologic phenotype affecting response/outcomes analyzed	Comments
Kaimakliotis (5) (2016), n=919 (VH n=181) Patients received either MVAC or GC as NAC regimen	Patients who received either regimen had higher incidence of pCR (29% vs. 8%, P=0.002) compared to those who did not. The pCR to NAC in squamous and glandular differentiation was similar to conventional UC (pCR 29 vs. 22%; P=0.443)	There was higher incidence of pathologic downstaging (52% vs. 14%; P<0.001), comparing those who received either regimen as NAC versus those who did not. Pathological downstaging to NAC in squamous and glandular differentiation was similar to conventional UC (52% vs. 43%; P=0.370)	77 months	VH was not associated with an increased risk of mortality. Use of either MVAC or GC as NAC was associated with decreased the risk of mortality in the cox proportional hazards regression model	Regimen used had no impact on pathologic response as both MVAC and GC resulted in improved pathologic response rates. Comparing MVAC to GC, either resulted in decreased mortality in VH subgroup studied. Only MVAC reached statistical significance	–
Shen (8) (2015), n=90 (VH n=90)	pCR reported as 23.9% vs. 4.5% comparing recipients of NAC vs. recipients of upfront RC	Rate of downstaging to < pT2 was 32.6% vs. 9%. Comparing recipients of NAC vs. recipients of upfront RC			Notable changes both in percent variant differentiation and mitotic rate occurred with NAC use from Bx/TUR to RC but not in non-NAC treated tumors. Neither change was predictive of response to NAC	The aim of this study was to describe changes in bladder tumors during NAC use and to identify features at Bx/TUR that may predict response
Hajiran (14) (2021), n=768 (VH n=358) NAC Treatment response stratified into three groups 1. Conventional UC 2. UC with VH 3. UC with divergent glandular or squamous differentiation	pCR was achieved in 23% of conventional UC cases, 30% of UC with VH cases and 18% of UC with divergent squamous or glandular differentiation cases (P=0.30)	Partial response was achieved in 46% of conventional UC cases, 41% of UC with VH cases and 37% of UC with divergent squamous or glandular differentiation cases (P=0.40)	21 months	Conventional UC cases had OS benefit (HR 0.71, 95% CI: 0.51–0.98, P=0.0013) with NAC. UC with VH cases has CSS benefit (HR 0.55, 95% CI: 0.30–0.99, P=0.0495) with NAC. UC with divergent glandular or squamous differentiation cases did not experience any survival benefit with NAC prior to RC		Rates of complete and partial pathologic response were similar between the three groups
Soave (19) (2017), n=188 (VH n=47) Patients with UC treated with RC without NAC			25 months	UC with VH had worse survival outcomes compared to UC with divergent squamous differentiation. UC with VH and presence of circulating tumor cells (CTC) were associated with reduced RFS and CSS (P≤0.016)	In multivariable analysis, presence of CTC, not variant histology, was an independent predictor for recurrence of disease (HR 3.45; P≤0.001) and CSS (HR 2.62; P=0.002)	The primary aim of this study was to determine the effect of circulating tumor cells (CTC) on survival outcomes of in patients with VH after RC
Soave (16) (2015), n=485 (VH n=96)			45 months	VH was associated with inferior CSS (P≤0.02) and disease recurrence (P=0.002).	Comparing survival outcomes based on extent of VH i.e., ≥70% or <70%, there was no statically significant difference between the two groups. Age, advanced tumor stage, lymph node involvement and a positive soft tissue margin were all associated with worse survival outcomes	
Moschini (25) (2017), n=338 (VH n=338) Patients with non-metastatic UC treated with RC were stratified in three groups: 1. UC with mixed VH cases 2. UC with a predominant VH (micropapillary or small cell) cases 3. Conventional UC cases			6.5 years	On multivariable analysis, patients with a predominant VH had inferior survival outcomes compared to conventional UC (P<0.01). On multivariable cox regression analysis predicting recurrence, cancer specific mortality and overall mortality, there were no difference between mixed variant and conventional UC (all P>0.1)		Only the presence of a predominant VH was associated with inferior survival outcomes after RC compared the conventional UC. Same was not true for UC with mixed VH cases which had similar survival outcomes with conventional UC cases
Martini (26) (2021), n=2,422 (VH=528)				Relative to conventional UC, patients with VH had higher rates of recurrence with RFS 30% vs. 51%; P<0.001 and shorter median time to disease recurrence (88 vs. 123 months; P<0.01)		The study concluded by Study recommending longer oncologic surveillance time for VH UC
Sefik (32) (2018), n=146 (VH n=23)				No significant difference in survival was observed between VH and conventional UC		
Xylinas (34) (2013), n=1,983 (VH n=488)			55 months	In univariable analysis, patients with conventional UC and squamous differentiation had similar risk for disease recurrence and cancer-specific mortality. UC with VH had significantly higher risk for disease recurrence and cancer specific mortality on univariable but not multivariable analysis		

Table 7 (continued)

Table 7 (continued)

Author (year)	Pathologic complete response	Pathologic downstaging	Median follow up after cystectomy	Survival outcomes after cystectomy	Major independent factor(s) other than histologic phenotype affecting response/outcomes analyzed	Comments
Takemoto (35) (2020), n=102 (VH n=26)			39.5 months	VH of UC was associated with significantly worse survival compared to conventional UC in RFS (P=0.018) and CSS (P=0.036)		
Naspro (37) (2021), n=525 (VH n=131)			31 months	Presence of VH was an independent risk factor for cancer-specific mortality (P=0.001) with significantly higher risk for recurrence, cancer-specific mortality and overall mortality (all P ≤0.001)		
Stroman (39), n=403 (VH n=73)			45 months	VH, specifically squamous differentiation was associated with worse survival outcomes		
Komina (41) (2021), n=185 (VH n=58)			28.9 months		On multivariable analysis, positive soft tissue margin and lymphovascular invasion were associated with worse RFS and OS	
Marks (42) (2019), n=138 (VH n=96)			45 months		Although VH was not associated with increased incidence of lymph node involvement, patients with positive lymph nodes or extra nodal extension undergoing RC had worse survival outcomes	

UC, urothelial carcinoma; VH, variant histology; NAC, neoadjuvant chemotherapy; pCR, pathologic complete response; RC, radical cystectomy; CSS, cancer specific survival; OS, overall survival; RFS, recurrence free survival; MVAC, methotrexate-vinblastine-doxorubicin-cisplatin chemotherapy; GC, gemcitabine-cisplatin chemotherapy; Bx/TUR, biopsy/transurethral resection; CTC, circulating tumor cells.

Table 8 Studies reporting outcomes with perioperative chemotherapy

Author (year)	Pathologic complete response	Pathologic downstaging	Median follow up after cystectomy	Survival outcomes after cystectomy	Major independent factor(s) other than histologic phenotype affecting response/outcomes analyzed	Comments
Ghoneim (20) (2011), – n=38 (VH n=38) Patients with micropapillary UC treated with perioperative chemotherapy	–	–	17 months	Median survival of the patients who had and had not received perioperative cisplatin-based chemotherapy was 23 months (95% CI: 9–32) and 46 months (95% CI: 12–69), respectively. All patients who received perioperative cisplatin-based chemotherapy died of metastatic disease. 5-year OS rate was 40% (95% CI: 16–64)	–	–

VH, variant histology; UC, urothelial carcinoma; OS, overall survival.

but this did not translate into better survival outcomes (49).

Plasmacytoid

Plasmacytoid UC, a rare neoplasm, is one of the more aggressive variants that often presents as a locally advanced disease at the time of diagnosis (2). These tumors are comprised of discohesive cells with eccentric nuclei and abundant eosinophilic cytoplasm. Some of the tumor cells may have cytoplasmic vacuoles giving them a signet ring appearance. Of note, the 2016 WHO update classification describes signet ring cell carcinoma as belonging in same category as plasmacytoid UC (2). Loss of E-cadherin, which is encoded by CDH1 gene, has been described in a large cohort of patients with plasmacytoid urothelial carcinoma. Truncating mutations in CDH1 have been described in 87% of plasmacytoid UC, whereas no CDH1 mutations have been reported in conventional urothelial carcinoma. Loss of E-cadherin protein expression by immunohistochemistry has been reported in up to 70% of plasmacytoid carcinomas as opposed to 11% of conventional urothelial carcinomas (50–52). The loss of E-cadherin is thought to confer enhanced migratory capacity in tumor cells and may explain why this variant is frequently associated with peritoneal carcinomatosis (53). Like the micropapillary histologic variant, there are also conflicting findings in the literature regarding its responsiveness to NAC (53).

Regarding survival outcomes after RC, Kaimakliotis *et al.* (28) observed that plasmacytoid UC at cystectomy was associated with increased adjusted risk of mortality (HR

2.1; 95% CI: 1.2–3.8; P=0.016). Keck *et al.* observed these outcomes were worse when compared to micropapillary UC (38). The study by Li *et al.* (7) represents the largest single institutional series on plasmacytoid UC (n=98). In this study, median OS for plasmacytoid UC *vs.* conventional UC was 3.8 years and 8 years respectively. Plasmacytoid histology was associated with increased overall mortality on univariable analysis (HR 1.34, 95% CI: 1.02–1.78; P=0.039) but not on multivariable analysis and almost one out of every five patients with plasmacytoid UC developed peritoneal carcinomatosis at median follow up of 4.6 years (7).

Nested

Nested urothelial carcinoma is less commonly reported in the literature. Histologically it has been described as innocuous appearing and invading lamina propria either as discrete or small confluent nests/tubules of cells (2). It may resemble other benign proliferations such as von Brunn's nests but foci of cytologically malignant cells are present in every case (54). A "large-nested" histologic variant has also been described in the literature (55). Nested UC is associated with advanced stage at time of diagnosis and its innocuous histologic appearance may delay definitive treatment. Linder *et al.* (36) studied 52 MIBC patients with nested UC and observed that when matched with a cohort of patients with conventional UC, there was no significant difference in 10-year local RFS (83% *vs.* 80%; P=0.46) or 10-year CSS (41% *vs.* 46%; P=0.75) at median follow up of 10.8 years.

Table 9 Studies reporting outcomes with radical cystectomy + adjuvant chemotherapy (survival outcomes only)

Author (year)	Pathologic complete response	Pathologic downstaging	Median follow up after cystectomy	Survival outcomes after cystectomy	Major independent factor(s) other than histologic phenotype affecting response/ outcomes analyzed	Comments
Monn (18) (2015), n=411 (VH n=411)			38 months	UC with VH cases at RC had 1.69-times increased risk of disease-specific mortality (P=0.030) and 1.57-times increased adjusted risk of all-cause mortality (P=0.027) compared to UC with divergent squamous differentiation		UC with VH was associated with worse survival outcomes regardless of pathologic stage, NAC or adjuvant chemotherapy compared to UC with divergent squamous differentiation
Mitra (21) (2014), n=1,762 (VH n=259)			15.2 years for cases, 11.0 years for controls, 12.2 for independent cohort	No differences in survival outcomes between cases and controls were observed Pathologic stage was predictive of outcome in cases with differentiation	Higher pathologic T stage, age and hydronephrosis were associated with increased mortality risk In glandular differentiation, non-administration of adjuvant chemotherapy was associated with worse OS	Patients with squamous or glandular or both differentiation had survival outcomes similar to conventional UC after cystectomy. they however presented with a higher pathologic stage
<p>This was a case-control analysis, cases were stratified into three groups: 1. Squamous differentiation 2. Glandular differentiation 3. Squamous + glandular differentiation</p> <p>Controls were conventional UC patients matched 1:1 to cases and an independent cohort of 1,244 conventional UC</p>						
Masson-Lecomte (24) (2015), n=266 (VH n=31)				Comparing patients with micropapillary VH with conventional UC, median survival was 29 vs. 31 months. Five-year RFS (15% vs. 42%; P=0.007), five-year CSS (24% vs. 47%; P=0.058)	Positive tissue margin and high ASA score was associated with worse RFS in univariate and multivariate analysis. Age, lymph node positivity and a positive soft tissue margin were associated with CSS in univariate and multivariate analysis	Micropapillary histologic subtype was associated with higher disease recurrence rates after RC and platinum-based adjuvant chemotherapy compared to conventional UC

Table 9 (continued)

Table 9 (continued)

Author (year)	Pathologic complete response	Pathologic downstaging	Median follow up after cystectomy	Survival outcomes after cystectomy	Major independent factor(s) other than histologic phenotype affecting response/outcomes analyzed	Comments
Keck (38) (2013), n=205 (VH n=27)				Plasmacytoid UC had significantly worse outcomes compared to micropapillary and conventional UC after RC and adjuvant cisplatin-based chemotherapy with a median OS of 27.4 months		
Zamboni (40) (2021), n=3,963 (VH n=906)			32 months	Adjuvant chemotherapy failed to improve survival outcomes in any of histologic variants (P>0.05)		
723 patients received RC and adjuvant chemotherapy						

VH, variant histology; UC, urothelial carcinoma; NAC, neoadjuvant chemotherapy; RC, radical cystectomy; MIBC, muscle invasive bladder cancer; OS, overall survival; ASA, American Society of Anesthesiologists; RFS, recurrence free survival; CSS, cancer specific survival.

Table 10 Studies reporting outcomes with trimodal bladder preserving therapy (TMT)

Author (year)	Pathologic complete response	Pathologic downstaging	Median follow up after cystectomy	Survival outcomes after cystectomy	Major independent factor(s) other than histologic phenotype affecting response/outcomes analyzed	Comments
Nagumo (12) (2020), n=148 (VH n=11) 11 patients having VH MIBC were treated with TMT	pCR was achieved in 9 out of 11 (82%) patients treated with TMT	-	-	-	-	6 out of 7 patients with squamous or glandular differentiation achieved pCR with TMT.

VH, variant histology; MIBC, muscle invasive bladder cancer; TMT, trimodal bladder preserving therapy; pCR, pathologic complete response.

Sarcomatoid

Sarcomatoid UC has a biphasic nature with features of epithelial and mesenchymal differentiation (both morphologically and on immunohistochemical staining). The epithelial component consists of urothelial carcinoma in most cases (56). Occurrence is associated with prior pelvic irradiation and intravesical cyclophosphamide therapy (57). Almassi *et al.* (11) assessed pathologic response to NAC and survival outcomes after RC in this histologic

variant. Pathologic response rates to NAC were similar for sarcomatoid and conventional UC. Regarding survival outcomes after RC, sarcomatoid UC was independently associated with inferior survival outcomes, but greater survival was observed among patients receiving NAC.

Lymphoepithelioma-like carcinoma (LELC)

LELC, is so named due to its resemblance to lymphoepithelial carcinoma of the nasopharynx but unlike

Table 11 Studies reporting outcomes with neoadjuvant immunotherapy (Pembrolizumab)

Author (year)	Pathologic complete response	Pathologic downstaging	Median follow up after cystectomy	Survival outcomes after cystectomy	Major independent factor(s) other than histologic phenotype affecting response/outcomes analyzed	Comments
Neechi (4) (2020), n=114 (VH n=34) VH patients were stratified into two groups	pCR to neoadjuvant pembrolizumab compared between predominant VH, non-predominant VH and conventional UC was 16%, 53% and 39% respectively	Pathologic downstaging to pT ≤ 1N0 was 42%, 67% and 56% in predominant VH, non-predominant VH and conventional UC patients respectively	–	–	A high tumor mutational burden and combined positive score for PD-L1 expression was found to correlate with response to therapy FGFR3 mutations had no correlation with response	The efficacy of neoadjuvant pembrolizumab was significantly lower in patients with predominant VH. However, a subgroup analysis showed the response to be greatest among patients with the squamous differentiation and lymphoepithelioma-like VH

VH, variant histology; pCR, pathologic complete response; UC, urothelial carcinoma; PD-L1, programmed death ligand 1; FGFR3, fibroblast growth factor receptor 3.

LELC in other organ systems, it is not associated with Epstein-Barr virus infection (58). It commonly presents as painless hematuria in older males (59). Microscopically, tumor cells have a syncytial pattern with prominent lymphoid infiltration which may be mistaken for chronic cystitis (58). A study by Monn *et al.* (18) showed that the lymphoepithelioma-like variant shares similar worse outcomes alongside other UC histologic variants when compared to conventional urothelial carcinoma, after adjusting for systemic chemotherapy and pathological stage. It is thought that this shared prognosis occurs when mixed with other variants. In its pure form, LELC has a low metastatic potential and has shown to be responsive to platinum-based chemotherapy (59).

Clear cell variant

The clear cell (glycogen-rich) variant of UC has been very rarely reported in literature. The tumor cells have clear (glycogen-rich) cytoplasm and can closely resemble clear cell adenocarcinoma of the bladder or female genital tract (2). Immunohistochemistry is revealing for CK7, GATA3, p40 and S100P staining, with some cases being positive for desmoglein 3 as well (60). They are aggressive tumors and can rapidly progress to muscle invasive and metastatic disease (61). The single largest series on this histologic variant did not specifically report pathologic response to treatment, however, there was an observed rapid progression to T3 disease in a majority and death in up to

half of patients at 20 months of follow up (62).

Microcystic

Microcystic UC has a deceptively benign histologic appearance, with microcysts, macrocysts or tubular structures lined by transitional cells. The cysts and tubular structures may be empty or contain necrotic debris or mucin. It may mimic other benign growths such as cystitis cystica (and glandularis) or nephrogenic metaplasia. Focal high-grade conventional UC may also be identified in about 40% of cases. Microcystic urothelial carcinoma has been associated with asymptomatic colon cancer (63). There are no large series that describe pathologic response rate for this rare histologic variant. Aggressiveness is reportedly related to advanced stage at diagnosis (61).

Urothelial carcinoma with divergent differentiation

Squamous cell differentiation

Urothelial carcinoma with squamous differentiation is the most reported variant (21% of urothelial carcinomas) and is defined by the presence of squamous features such as intercellular bridges or keratinization (2). Strictly speaking, squamous cell carcinoma (SCC), which makes up about 3% of all bladder cancers, should be differentiated from UC with squamous differentiation. UC with squamous differentiation can be distinguished from SCC by the presence of associated urothelial carcinoma in the former

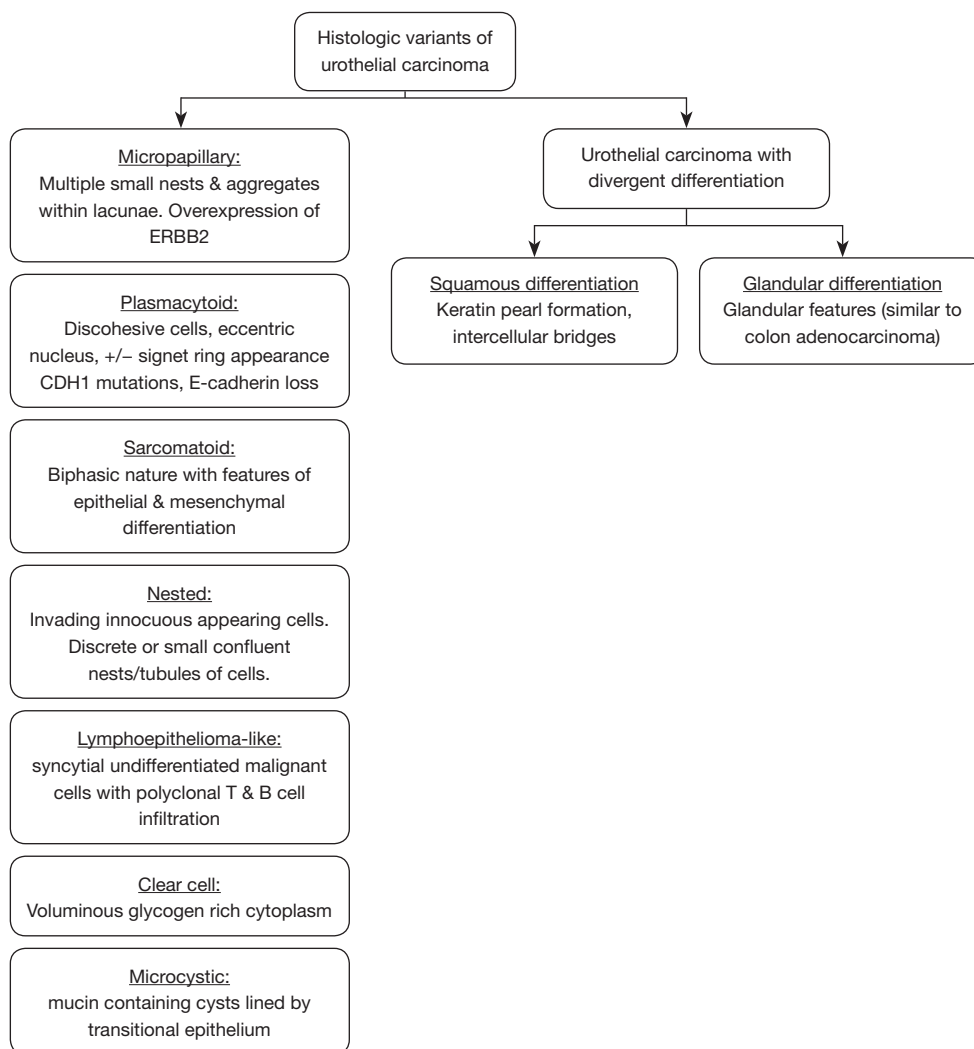


Figure 2 Histopathologic features of histologic variants of urothelial carcinoma.

entity. We discuss studies that report outcomes in divergent squamous differentiation to the exclusion of SCC. NAC resulted in higher likelihood to achieve pCR, more than seen in patients who did not receive pCR (5,6) and higher incidence of downstaging (5). Three studies (5,13,14) reported that in comparison, the pathologic complete response rates to NAC were similar in conventional UC and UC with squamous differentiation while rates of pathologic downstaging was higher in UC with squamous differentiation (5,13). A single institutional study showed excellent rates of pathologic complete response with trimodal bladder preserving therapy as well (12). Regarding survival outcomes after RC, statistically, patients who had NAC had better OS and RFS outcomes at median follow up

of 38.2 months (6), and similar survival outcomes compared to conventional UC (20,29,31,34).

Glandular differentiation

Urothelial carcinoma with glandular differentiation is the second most reported histologic variant (about 6% of urothelial carcinoma) and is defined by the presence of glandular features (i.e., true glandular spaces) within the tumor (64). A tumor with mixed glandular and urothelial differentiation is classified as urothelial carcinoma with glandular differentiation, and the percentage of the glandular component should be reported. The presence of glandular differentiation if present, even focally, in association with urothelial carcinoma, portends poor

prognosis. The diagnosis of adenocarcinoma is reserved for pure tumors (lacking an associated urothelial component). Primary bladder adenocarcinomas account for 0.5–2% of malignant bladder tumors. The 2016 WHO classification of bladder tumors divides adenocarcinomas into the following categories: enteric (colonic) type, mucinous type, mixed type and adenocarcinoma, not otherwise specified (NOS). These tumors can be impossible to distinguish from colonic adenocarcinoma based on microscopic and immunophenotypic features alone, and clinical and radiologic correlation is often necessary to determine the site of origin (2). A study in our review reports that it shares similar responsiveness to NAC as UC with squamous differentiation and conventional urothelial carcinoma (5). Two studies (20,29) highlight that survival outcomes after RC in conventional UC and UC with divergent squamous or glandular differentiation are similar with one (20) showing survival benefit with adjuvant chemotherapy after RC.

In summary, the data regarding response to systemic chemotherapy from single/multicenter observational studies is not robust and often conflicting. Other published literature such as a retrospective cohort of non-metastatic cases from the National Cancer Database (NCDB) show that use of NAC correlates with higher likelihood to achieve pathologic complete response or downstaging prior to RC, whereas patients who did not receive NAC had very low rates of pCR (<6%) and downstaging (<10%) for all histologic variants (65).

Prognostic factors that impact response to NAC or survival outcomes in histologic variants of urothelial carcinoma after RC

Certain histologic variants have been associated with worse survival outcomes after RC. Micropapillary, plasmacytoid, nested and sarcomatoid UC have been associated with worse survival outcomes compared to conventional UC and UC with squamous or glandular differentiation (16,18,19,35,37,38). Among these four histologic variants, survival benefit with NAC was demonstrated in sarcomatoid differentiation when controlling for other prognostic factors (11). It can be hypothesized that in mixed histology, the presence of urothelial histologic variants might be a driver for poorer outcomes. Moshcini *et al.* (25) demonstrated that only the presence of pure histologic variants of UC was associated with inferior survival outcomes after RC compared the conventional UC. The same was not true for comparisons between mixed variant

histology with conventional UC. It is worth noting that some studies that reported no significant difference in survival outcomes between conventional UC and VH of UC had predominantly squamous and/glandular differentiation such as was reported in Sefik *et al.* (32). Hajiran *et al.* (14) was the only study to compare the survival benefit of NAC between the three groups of conventional UC, UC with VH and UC with variant differentiation (squamous or glandular); here survival benefit with NAC was only achieved in conventional UC and UC with VH. A possible explanation for this apparent lack of survival benefit for NAC in variant differentiation was offered by Chakiryan *et al.* (65). It was suggested that these patients may appear not benefit from NAC, despite significant pathological downstaging, because of generally more favorable outcomes.

The impact of the extent or percentage of variant subtype pattern is controversial. Shen *et al.* (8) investigated the change in variant differentiation during NAC in VH of UC between TUR and RC. An interesting finding was that the percent differentiation at TUR did not affect responsiveness to NAC. However, Speir *et al.* (6) demonstrated an inverse correlation between the percent of histologic variant involvement and likelihood to achieve a complete pathologic response with NAC prior to radical cystectomy in patients with squamous differentiation. The study also suggests that the survival benefit of NAC is lost in the subgroup of patients with variant differentiation $\geq 50\%$. Soave *et al.* (16) noted that the presence of variant histology particularly non-squamous cell differentiation and the extent were associated with cancer-specific mortality in univariable but not in multivariable analyses. In micropapillary UC for instance, one study (23), demonstrated that tumors with a higher percentage of micropapillary UC at TURBT, had a higher likelihood of death from disease on univariate ($P=0.01$) but not on multivariate analysis and the presence of CIS was predictive of recurrence on univariate and multivariate analysis ($P=0.03$ and $P=0.003$) while another study (27), found no association between variant percentage and survival outcomes. In summary, although the studies present differing views regarding the impact of the extent or percentage of variant histology, its presence and percentage should be reported because of potential impact on survival outcomes.

Molecular subtypes of urothelial carcinoma

There are several overlapping molecular subtyping nomenclatures that have been developed for MIBC. The

Table 12 Molecular subtypes in variant histology of urothelial carcinoma

Variant subtype	Molecular subtype
Micropapillary	Luminal
Plasmacytoid/signet ring	Luminal
Microcystic	Luminal/Basal
Nested	Luminal/Basal
Clear cell	Luminal/Basal
Lymphoepithelioma-like	Basal
Sarcomatoid	Basal

Lund university approach, for instance, is based on mRNA profiling. It includes the following subtypes: urothelial-like, genomically unstable, SCC-like, mesenchymal-like and neuroendocrine-like (66).

The molecular subtypes of bladder tumors can be broadly classified into the following two groups:

- (I) Luminal subtype—demonstrates markers of urothelial differentiation
- (II) Basal-squamous subtype—demonstrates markers of basal cell or squamous differentiation.

The Cancer Genome Atlas (TCGA) bladder cancer group analysis further expanded the luminal subtype into luminal-papillary (enriched with FGFR3 overexpression) and luminal-infiltrated (distinguished by lymphocyte infiltration) (67).

The consensus molecular classification for MIBC, identified a set of six molecular classes namely- luminal papillary, luminal non-specified, luminal unstable, stroma-rich, basal/squamous and neuroendocrine-like (68).

Micropapillary and plasmacytoid UC express luminal biomarkers. The luminal papillary subtypes have better survival outcomes. Their high rates of FGFR3 mutations make them potentially susceptible to FGFR inhibitors; however, more study is needed (69).

LELC and sarcomatoid UC express basal biomarkers. The basal type appears more aggressive but is chemo sensitive and has improved outcomes with NAC (70).

Table 12 summarizes the molecular subtypes of VH of UC.

Warrick *et al.* (70) studied the molecular subtypes of the histologic variants using the immunohistochemistry method developed at Lund University. This was performed on a consecutive retrospective series of cystectomy cases (n=83). 39% of these tumors with multiple VH of UC exhibited molecular heterogeneity. This heterogeneity was

highest among basal-squamous tumors with almost 80% co-occurring with either urothelial-like or genomically unstable molecular subtypes. The following observations were made in this study:

- (I) Despite exhibiting molecular heterogeneity, these tumors had common markers of cell cycle regulation such as loss of P16 or RB1 expression. This suggests that CDK4/6 inhibitors are a potential effective treatment strategy since P16 or RB1 expression loss is an early occurrence in carcinogenesis shared by these tumors (70).
- (II) Tumors treated with NAC had a substantially lower basal-squamous cancer burden compared to tumors that were only treated with cystectomy (P=0.02). This gives credence to a prior study which suggested that platinum-based NAC would be most effective in patients with basal tumors (71).

The significance of these findings is that it presents pathologic response to neoadjuvant therapy as a function of the molecular subtypes of the variants rather than their histologic phenotypes. However, any future attempts at risk-stratifying tumors based on molecular subtypes will have to consider the molecular heterogeneity within any given tumor before being applicable in a clinical setting.

Neoadjuvant immunotherapy, predictors of response and directions for future research

Immune checkpoint inhibitors (ICIs) could potentially change the treatment outlook for VH of UC. Currently, there are five FDA approved immune checkpoint inhibitors for UC, namely atezolizumab, avelumab, durvalumab, nivolumab and pembrolizumab. In urothelial carcinoma, ICIs have only been approved for use after progression on platinum-based chemotherapy and in cisplatin ineligible patients with PDL1 positive tumors.

In VH of UC there are ongoing trials evaluating the efficacy of combination immunotherapy in VH patients with advanced disease (72,73), however, data on efficacy of immunotherapy in the neoadjuvant setting is lacking.

Majority of the clinical trials that have investigated pathologic response rates of UC to ICIs such as the KEYNOTE-057 (74) or ABACUS (75) trials, have the major limitation of excluding patients with a predominant VH. Therefore, the study of the efficacy of neoadjuvant immunotherapy in VH of UC constitutes an area of unmet medical need.

An attempt to address this need was made by the

amended PURE-01 study (4). It is the largest clinical trial of a neoadjuvant checkpoint inhibitor in MIBC till date. The updated results (details in *Table 11*) allowed for the inclusion of patients with a predominant VH and was more representative of the heterogeneous MIBC population. Future clinical trials will need to include more patients with VH of UC to better reflect the real-world population of UC.

The biomarkers that have been studied that may predict response to immunotherapy in VH of UC include PD1 and PDL1 expression, tumor inflammatory microenvironment and tumor mutational burden (TMB). Li *et al.* (76) stratified these biomarkers by histologic and molecular subtypes in an attempt to predict response to immunotherapy. The biomarkers (PD1, CD3, CD8, CD68 in tumor infiltrating immune cells and PDL1 expression in tumor microenvironment) were evaluated by immunohistochemistry and semi-quantitatively assigned a score (0-3). The major conclusion in this study was that the immunogenicity and thus likelihood to respond to immunotherapy correlates with tumor invasive status, histologic phenotype and molecular subtype. Regarding tumor invasive status, the highest and lowest scores were assigned to MIBC and non-invasive papillary UC, respectively. Therefore, CIS and NMIBC may require additional therapy to augment a predicted low response to immunotherapy. Invasive sarcomatoid differentiation had a significantly higher PD-L1 score while plasmacytoid, sarcomatoid and squamous histologies tended to have greater intra-tumoral lymphocyte infiltration. Based on the scoring system, these histologic phenotypes were considered as being “immunogenic”. Likewise, regarding molecular subtypes, the genomically unstable subtype was observed to be enriched with a high immune cluster (76).

The only caveat is due to intra-tumoral heterogeneity; hence caution is needed when attempting to extrapolate results from a limited tissue sample.

These findings seem to be supported by the results of the PURE-01 study wherein it was observed that responsiveness to pembrolizumab was dependent on tumor biomarkers (4).

Regardless of how promising these findings are, any proposed biomarkers to predict response to immunotherapy

will also need to be validated in large prospective trials before being applicable in clinical decision making.

Limitations

The limitations of this review include the absence of detailed demographic data in some studies. Several studies do not specify the type and regimen (dosage and number of cycles) of chemotherapeutic agents used, thus comparisons between regimen could not be made. Some less commonly reported variants were categorized together under sub-heading ‘others’, thus limiting data that can be attributable to the rare variant histologies. In addition, most of the outcomes pertain to only MIBC with VH.

Clinical practice recommendations

Based on the available evidence, a decision-making aid summarizing our findings pertaining to treatment options in non-metastatic MIBC with VH is presented in *Figure 3* and VH specific recommendations are given in *Table 13*.

Conclusion

VH of UC presents a diagnostic and treatment dilemma due to their rarity and aggressive nature. Despite somewhat conflicting reports in the literature, we present a comprehensive review of the available data on pathologic response rates to neoadjuvant systemic therapy and survival outcomes after radical cystectomy. NAC prior to radical cystectomy has been shown to be a beneficial treatment strategy with the responsiveness of urothelial carcinoma with squamous and glandular differentiation being comparable to conventional UC among studies reviewed. The micropapillary, plasmacytoid, nested and sarcomatoid histologic variants have been associated with worse survival outcomes compared to conventional UC and UC with squamous or glandular differentiation despite initial downstaging with chemotherapy. There is evidence of improved survival in patients with sarcomatoid differentiation receiving NAC compared to RC alone.

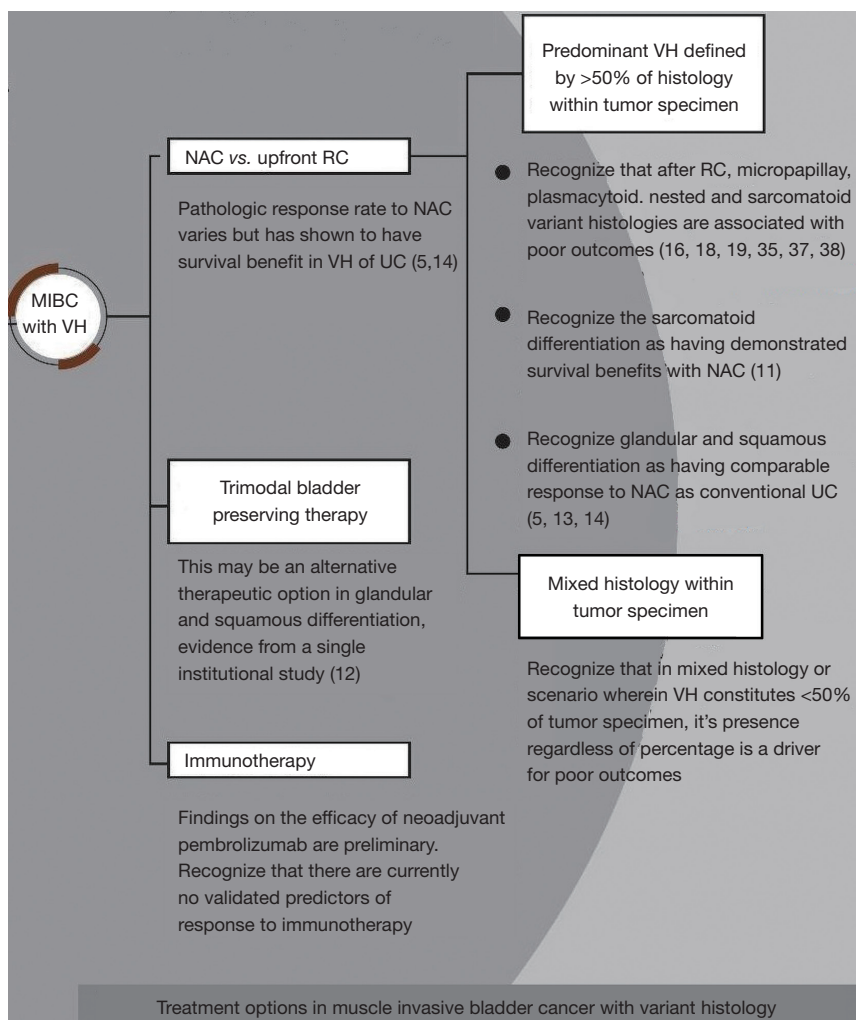


Figure 3 Treatment options in muscle invasive bladder cancer with variant histology. MIBC, muscle invasive bladder cancer; VH, variant histology; NAC, neoadjuvant chemotherapy; RC, radical cystectomy; UC, urothelial carcinoma.

The major prognostic factors that affect survival outcomes in VH of UC include histologic variant, patient age, presence of lymphovascular invasion, hydronephrosis, nodal metastasis and advanced T stage at diagnosis. Recent studies

demonstrate that VH of UC are heterogenous tumors and responsiveness to NAC may be a function of the molecular subtypes present. Biomarkers identified by molecular profiling with immunohistochemistry will need to be

Table 13 Variant histology specific recommendations

Variant histology	Recommendation
Micropapillary, plasmacytoid, nested, clear cell and microcystic UC	In MIBC with VH, we recommend NAC to achieve pathologic downstaging prior to RC as a higher pathologic T stage at RC is associated with worse survival outcomes and there is evidence of survival benefit A longer period of surveillance after RC is also warranted
Sarcomatoid differentiation	We recommend NAC in MIBC due to evidence of survival benefit
Lymphoepithelioma-like UC	Where LELC constitutes the predominant histology in MIBC, we recommend NAC due to chemosensitivity and evidence of survival benefit in other variants
Squamous/glandular divergent differentiation	NAC is warranted in these tumors. Despite having similar pathologic response to NAC compared to conventional UC, they are more likely to present at a higher pathologic stage. Adjuvant chemotherapy should be considered as a therapeutic option due to evidence of worse OS in glandular differentiation when not administered

UC, urothelial carcinoma; MIBC, muscle invasive bladder cancer; VH, variant histology; NAC, neoadjuvant chemotherapy; RC, radical cystectomy; LELC, lymphoepithelioma-like carcinoma; OS, overall survival.

validated as predictors of response to NAC in future trials.

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