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The Impact of Plasmacytoid Variant Histology on the Survival of Patients with Urothelial Carcinoma of Bladder after Radical Cystectomy

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Abstract

Background: The clinical significance of the plasmacytoid variant (PCV) in urothelial carcinoma (UC) is currently lacking.

Objective: To compare clinical outcomes of patients with any PCV with that of patients with pure UC treated with radical cystectomy (RC).

Design, setting, and participants: We identified 98 patients who had pathologically confirmed PCV UC and 1312 patients with pure UC and no variant history who underwent RC at our institution between 1995 and 2014.

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The presence of plasmacytoid variant of the bladder is rare and associated with higher disease burden at radical cystectomy compared with pure urothelial carcinoma. However, plasmacytoid variant was not an independent predictor of overall survival on multivariable analysis.

Outcome measurements and statistical analysis: Univariable and multivariable Cox regression and Cox proportional hazards regression to determine if PCV was associated with overall survival (OS).

Results and limitations: Patients with PCV UC were more likely to have advanced tumor stage ($p = 0.001$), positive lymph nodes ($p = 0.038$), and receive neoadjuvant chemotherapy than those with pure UC (46% vs 22%, $p < 0.0001$). The rate of positive soft tissue surgical margins was over five times greater in the PCV UC group compared with the pure UC group (21% vs 4.1%, respectively, $p < 0.0001$). Median OS for the pure UC versus the PCV patients were 8 yr and 3.8 yr, respectively. On univariable analysis, PCV was associated with an increased risk of overall mortality (hazard ratio = 1.34, 95% confidence interval: 1.02–1.78, $p = 0.039$). However, on multivariable analysis adjusted for age, sex, neoadjuvant chemotherapy received, lymph node status, pathologic stage, and soft margin status, the association between PCV and OS was no longer significant (hazard ratio = 1.06, 95% confidence interval: 0.78, 1.43, $p = 0.7$). This retrospective study is limited by the lack of pathological reanalysis, and the impact of other concurrent mixed histology cannot be determined in this study.

Conclusions: Patients with PCV features have a higher disease burden at RC compared with those with pure UC. However, PCV was not an independent predictor of survival after RC on multivariable analysis, suggesting that PCV histology should not be used as an independent prognostic factor.

Patient summary: Plasmacytoid urothelial carcinoma is a rare and aggressive form of bladder cancer. Patients with plasmacytoid urothelial carcinoma had worse adverse pathologic features, but this was not associated with worse overall mortality when compared with patients with pure urothelial carcinoma.

Keywords

Neoadjuvant chemotherapy; Overall survival; Plasmacytoid variant; Radical cystectomy; Urothelial carcinoma of bladder

1. Introduction

Urothelial carcinoma of the bladder (UCB) is well known for its numerous histologic morphologies [1]. Approximately 80% of UCB is pure or conventional urothelial carcinoma (UC), while the remaining 20% is represented by variant histologic architectures, also known as divergent differentiation. Variant histology has recently become a topic of increasing interest as some variants may be significant drivers of disease and may necessitate different therapeutic approaches [2–5]. Plasmacytoid variant (PCV) UC was first described as tumor cells with “a striking plasmacytoid appearance” by Sahin et al [6] in a patient presenting with bone metastases from primary bladder cancer. Emerging evidence suggests that PCV is associated with advanced stage at cystectomy, rate of lymph node metastasis, sensitivity to chemotherapy, and poor prognosis [2,7,8]. Information on outcomes for patients with PCV histology is limited due to the rarity of the disease, and we seek to investigate whether patients with PCV UC have worse overall survival (OS) than those with pure UC after radical cystectomy (RC).

2. Materials and methods

Between 1995 and 2014, 3173 patients were treated with RC urinary diversion at Memorial Sloan Kettering Cancer Center. Following institutional review board approval, we identified 98 patients with pathologically confirmed UCB and plasmacytoid features on the official pathology reports of transurethral resection of the bladder (TURB) or RC specimens. Clinical and pathologic information was retrospectively obtained from patient charts and electronic medical records. The clinicopathological demographics of these patients were compared to those of 1312 patients with pure UC and no variant history. Patients with primary urachal or urethral adenocarcinoma with signal features were excluded from the study. Among these patients, 33 had plasmacytoid features only on the TURB specimen and 34 had other mixed histologies with concurrent PCV (glandular, squamous, nested, micropapillary, neuroendocrine, osteoclast variant). Positive soft tissue margin was defined as the presence of tumor at inked areas of soft tissue on the RC specimen [9]. Positive urothelial margin was defined as the presence of carcinoma in situ, noninvasive carcinoma, or invasive carcinoma at the ureteral or urethral margin [10]. Of the 45 (46%) PCV patients receiving neoadjuvant chemotherapy (NACT), two had methotrexate, vinblastine, adriamycin, and cisplatin, 33 had gemcitabine/cisplatin with or without third regimen, five had gemcitabine/carboplatin with or without third regimen, and five had others.

Differences in patient characteristics between PCV and pure UC were tested for using the Wilcoxon rank sum (continuous variables) and Fisher's exact tests (categorical variables). We visualized OS by histology using Kaplan-Meier curves. Univariable Cox proportional hazards regression was used to determine if PCV histology was associated with OS. We also tested whether this association held after adjusting for other factors including age (continuous), sex, receipt of NACT, lymph node status, pathologic stage (pT1 vs pT2 and pT1 vs pT3/pT4) and soft tissue margin status using multivariable Cox regression. OS was determined from the date of RC until death from any cause or last date known alive. All statistical analyses were conducted using STATA 13.0 (Stata Corp, College Station, TX, USA).

3. Results

Patient characteristics are displayed in Table 1. Patients with PCV were more likely to receive neoadjuvant chemotherapy (46% vs 22%, $p < 0.0001$). Patients with PCV tended to have higher pT3/pT4 stage (54% vs 38%, $p = 0.001$) and were more likely to have positive lymph nodes than patients with pure UC (30% vs 20%, $p = 0.038$). Although the rate of positive urothelial margins was similar between the two groups ($p = 0.2$), the rate of positive soft tissue surgical margins was over five times greater among those with plasmacytoid histology (21% vs 4.1%, respectively, $p < 0.0001$). The odds of having a soft tissue positive surgical margin was over five times greater among patients with plasmacytoid histology even after adjusting for pathologic stage (pT1 vs pT2 and pT1 vs pT3/pT4) using multivariable logistic regression (odds ratio = 5.25, 95% confidence interval [CI]: 2.83, 9.75, $p < 0.0001$). Of the 12 PCV patients who had clinical stage T1, the proportion upstaged to pT2 on RC was 42% (95% CI: 15%, 72%). Of the 86 PCV patients who had a clinical stage of pT2, the proportion downstaged to pT1 on RC was 22% (95% CI: 14%, 32%)

regardless of receipt of NACT (45 PCV patients had NACT and 41 PCV patients did not have NACT). Among the 98 patients with PCV UC, 12 developed peritoneal carcinomatosis based on a median follow-up time of 4.6 yr among PCV patients who did not develop peritoneal carcinomatosis.

A total of 742 patients—689 in the pure UC group and 53 in the PCV UC group—died. The median length of follow-up time for patients who were alive was 5.0 yr for the PCV UC group and 7.6 yr for the pure UC group. The Kaplan-Meier estimated probabilities of OS are displayed in Figure 1. Median OS was 4.1 yr greater among patients with pure UC (8 yr) compared with patients with PCV (3.8 yr). The largest difference observed in the probability of OS occurred 4 yr after cystectomy with a probability of 49% (38%, 59%) and 64% (62%, 67%) among the PCV and pure UC groups, respectively. On univariable analysis, we found that plasmacytoid histology was associated with an increased risk of mortality (hazard ratio [HR] = 1.34, 95% CI: 1.02–1.78, $p = 0.039$); however, after adjusting for age at RC, sex, NACT received, presence of positive lymph nodes, pathologic stage, and soft tissue margin status, the association was smaller and no longer significant (HR = 1.06, 95% CI: 0.78, 1.43, $p = 0.7$).

4. Discussion

In a large cohort of patients treated with RC, we found that the presence of PCV was associated with adverse pathologic features but was not associated with worse overall mortality compared with pure UC on multivariable analysis. This suggests that PCV histology cannot be used as an independent prognostic factor. Our study represents the largest series of PCV UC (46% treated with NACT) and highlights the importance of recognizing the local aggressiveness of PCV UC.

It is important to be aware of the presence of variant histology of UC due to the potential prognostic or therapeutic implications impacting clinical management [11]. However, studying the impact of variant histology has been challenging and outcome studies of variant histology are difficult to interpret due to the heterogeneity and percentage of each variant. In some patients, variant morphology was identified only on TURB, but not on final RC, or vice versa [2,12]. Additionally, it is not uncommon to have multiple patterns of variant histologies within the same tumor, and investigators may provide the relative percentage of each of the different components. In our study, one-third had plasmacytoid features only on the TURB specimen and one-third had other concurrent mixed histologies. Earlier PCV studies included only patients with a predominant (at least 50–90%) plasmacytoid component of the tumor [7,13]. A recent study by Kaimakliotis et al [2] included patients with any PCV component regardless of percentage or mixed-variant status and suggested any evidence of PCV may warrant aggressive therapy. Thus, in this study, we included patients with any PCV component in TURB and/or cystectomy specimens for analysis given the fact that PCV represents the poorly differentiated or undifferentiated end of the spectrum of UC [14].

Previous case series studies of PCV ranged from nine to 32 cases. These studies show that PCV is an aggressive variant associated with a high percentage of advanced disease (39–

100%), positive surgical margins (6–40%), the presence of positive lymph nodes (35–80%), and poor survival (median survival 18–37 mo) [2,7,8,13,15–17]. In this study, we extended our analysis to compare the pathologic features and outcomes between PCV UC and pure UC. Similarly, we found that the presence of PCV was associated with locally advanced stage disease (54% vs 37%), a higher rate of positive surgical margins (21% vs 4%), and more positive lymph node involvement (30% vs 20%) compared with pure UC. In a cohort of 1589 patients, Dotan et al [9] found that the rate of positive soft tissue surgical margins was associated with nonpure UC histology, 4% and 10% in pure UC, and nonpure UC groups, respectively ($p < 0.001$). This portends an increased risk of disease-specific death [9]. In our study, we found a similar rate of positive soft tissue surgical margins in pure UC and a five times greater rate of positive soft tissue surgical margins in PCV UC (4% vs 21%, respectively). The discrepancy of positive soft tissue surgical margins between pure UC and PCV UC suggests that tumor presence at the margins is unlikely due to a surgical error (cutting through gross tumor), but rather it is associated with infiltration of the adjacent soft tissue (microscopic disease not seen by the surgeon at the time of RC) [9]. These findings suggest that the presence of any PCV may warrant more accurate preoperative staging and a wider perivesical dissection to avoid a positive surgical margin and achieve local pelvic control. The median survival for our patients with any PCV was 3.8 yr, similar to the median survival (3.1 yr) of the 16 patients with resectable predominant PCV from an MD Anderson series [7]. Notably, the largest difference of overall mortality between patients with PCV UC and those with pure UC occurred 4 yr following cystectomy. This suggests that a subset of patients with PCV UC can achieve long-term cure similar to patients with pure UC using surgical resection and adequate treatment.

It remains unclear whether worse prognosis associated with other variant histologies is largely driven by tumor stage or by a disparate biology of tumor type. Earlier studies suggest that variant histology, for example, micropapillary, nested, or nonsquamous, are associated with cancer-specific mortality in univariable analysis, but they are not independent predictors of outcomes [5,18–21]. Moon et al [X] recently reported that PCV is independently associated with twice the risk of all-cause mortality (HR = 2.0, $p = 0.016$) compared with nonvariant histology after adjusting for age, sex, nonorgan confined disease, and systemic chemotherapy. The authors suggested that PCV may be a driver of disease. However, we found the association between PCV and OS to be smaller and no longer significant (HR = 1.06, 95% CI: 0.78, 1.43, $p = 0.7$) upon multivariable analysis adjusted for age, sex, NACT received, presence of positive lymph nodes, pathologic stage, and soft tissue margin. Thus, histology was not statistically significant in patients with PCV UC despite having more adverse pathologic features, suggesting that the poor prognosis associated with PCV UC on univariable analysis may be largely driven by adverse pathologic features. This disparity between univariable analysis and multivariable analysis has been reported in multiple variant histology studies [19,21] and may also be explained by other confounding factors, such as different regimens of NACT, receipt of adjuvant chemotherapy, the quality of RC, and the variability of surgeon experience. However, due to many confounding factors in this retrospective study, no clear conclusion could be made regarding the impact of the quality of RC and neoadjuvant or adjuvant chemotherapy on the OS of patients with PCV.

The management of various variant histologies in UC remains controversial, except for adenocarcinoma, pure squamous cell carcinoma, and small cell carcinoma, in which disease-specific management strategies have been developed [22]. Management of variant histology in UC fundamentally relies on the accurate staging and how these subtypes respond to nonsurgical therapy (systemic therapy, intravesical therapy, radiation therapy, etc.) prior to radical extirpative treatment. It remains unknown whether patients with PCV UC should be treated with early RC or NACT followed by cystectomy [2,7,23,24]. Kaimakliotis et al [2] showed that 80% of patients with PCV UC on clinically staged nonmuscle-invasive disease were upstaged to pT3 at RC and that 60% had lymph node involvement. The authors suggested that any evidence of PCV UC during TURB may warrant aggressive surgical therapy regardless of having clinically nonmuscle-invasive disease. We found that 42% of patients with PCV UC on clinically T1 disease were upstaged to pT2 or greater. Moreover, poor outcomes of patients with PCV UC were reported if cisplatin-based chemotherapy was given in the adjuvant setting [23]. Given the similar OS for patients with PCV UC in our study, there is no definitive clinical evidence to alter the current treatment recommendations for patients based on PCV histology. Further studies are required to determine the responsiveness of PCV to novel systemic therapy. Refining patient selection for novel neoadjuvant systemic therapy or early cystectomy may improve clinical outcomes using an optimized multimodal treatment approach.

Several limitations should be considered when interpreting our data. First, misclassification bias may exist due to the lack of comprehensive pathologic reanalysis of the presence and percentage of PCV in each patient. However, under-recognition of PCV is unlikely in this study because all specimens were examined by dedicated genitourinary pathologists in a large referral hospital [25]. Second, selection and referral bias exist in this retrospective study of patients treated with cystectomy at a high-volume tertiary center. This selection possibly overestimated OS of patients with PCV UC because patients who were amenable to radical surgery may have had significantly better survival than those who were unable to undergo RC due to presenting with de novo metastasis or secondary to rapid disease progression. Third, given that the cases were collected over a prolonged period of time, changes in practice patterns (increased utilization of NACT and extended lymph node dissections) may have impacted our findings. However, we noted no difference in the number of lymph nodes removed between the PCV UC and pure UC groups and the use of NACT which were adjusted for in analyses. Finally, the impact of other concurrent mixed histology cannot be determined in this study. One third of our PCV UC cohort had concurrent divergent differentiation including PCV. Our conclusion was drawn based on the same assumption in previous studies that any component of PCV represents the poor undifferentiated end of the spectrum of UC regardless of other concurrent variant histologies [2]. Despite these limitations, this large retrospective series highlighted the local aggressive characteristics of PCV.

5. Conclusions

The presence of PCV in the TURB or cystectomy specimen is associated with locally advanced disease, positive surgical margins, and positive lymph nodes compared with pure UC. However, PCV was not an independent predictor of long-term survival after RC on

multivariable analysis, suggesting that PCV histology should not be used as an independent prognostic factor. Further studies of novel biomarkers, novel systemic therapies, or better clinical staging tools are in urgent need to improve clinical outcome in UCB patients with aggressive pathologic features.

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Fig. 1 —. Kaplan-Meier probability of overall survival by histology.
RC = radical cystectomy.

Table 1 —

Patient characteristics by histology type (values are displayed as median [interquartile range] or frequency [percentage])

Characteristics	Pure urothelial (<i>N</i> = 1312; 93%)	Plasmacytoid (<i>N</i> = 98; 7.0%)	<i>p</i> value ^a
Age at radical cystectomy	69 (61, 75)	66 (58, 73)	0.012
Male	1056(80)	71 (72)	0.066
Smoker	933 (71)	74 (76)	0.4
Neoadjuvant chemotherapy	292 (22)	45 (46)	<0.0001
Consensus stage			
pT1	463 (35)	11(11)	<0.0001
pT2	356 (27)	34 (35)	
pT3/pT4	493 (38)	53 (54)	
Pathologic stage			
pT1	570 (43)	26 (27)	0.001
pT2	256 (20)	19 (19)	
pT3/pT4	486 (37)	53 (54)	
Pathologic grade			
Low	50(3.8)	0(0)	0.070
High	1141(87)	82 (84)	
Unknown	121 (9.2)	16 (16)	
Lymph node status			
NO	982 (75)	65(66)	0.038
N1/N2	266 (20)	29 (30)	
Unknown	64 (4.9)	4(4.1)	
No. of lymph nodes removed (<i>N</i> = 1330)	16 (9, 24)	19 (9, 25)	0.2
Soft tissue positive surgical margins	54 (4.1)	21 (21)	<0.0001
Urothelial positive surgical margins	254 (19)	13 (13)	0.2
Unknown	107 (8.2)	10 (10)	

^a All *p* values determined by Wilcoxon rank sum test for continuous variables and Fisher's exact test for categorical variables.