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Original Article

Implications of micropapillary urothelial carcinoma variant on prognosis following radical cystectomy: A multi-institutional investigation

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Abstract

Purpose: To determine the association of micropapillary urothelial carcinoma (MUC) variant histology with bladder cancer outcomes after radical cystectomy.

Materials and Methods: Information on MUC patients treated with radical cystectomy was obtained from five academic centers. Data on 1,497 patients were assembled in a relational database. Tumor histology was categorized as urothelial carcinoma without any histological variants (UC; n = 1,346) or MUC (n = 151). Univariable and multivariable models were used to analyze associations with recurrence-free (RFS) and overall (OS) survival.

Results: Median follow-up was 10.0 and 7.8 years for the UC and MUC groups, respectively. No significant differences were noted between UC and MUC groups with regard to age, gender, clinical disease stage, and administration of neoadjuvant and adjuvant chemotherapy (all, $P \geq 0.10$). When compared with UC, presence of MUC was associated with higher pathologic stage (organ-confined, 60% vs. 27%; extravesical, 18% vs. 23%; node-positive, 22% vs. 50%; $P < 0.01$) and lymphovascular invasion (29% vs. 58%; $P < 0.01$) at cystectomy. In comparison with UC, MUC patients had poorer 5-year RFS (70% vs. 44%; $P < 0.01$) and OS (61% vs. 38%; $P < 0.01$). However, on multivariable analysis, tumor histology was not independently associated with the risks of recurrence ($P = 0.27$) or mortality ($P = 0.12$).

Conclusions: This multi-institutional analysis demonstrated that the presence of MUC was associated with locally advanced disease at radical cystectomy. However, clinical outcomes were comparable to those with pure UC after controlling for standard clinicopathologic predictors.

Keywords: Urinary bladder neoplasms; Micropapillary urothelial carcinoma; Cystectomy; Outcomes

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Abbreviations: UC, urothelial carcinoma; MUC, micropapillary urothelial carcinoma; RFS, recurrence-free survival; OS, overall survival

1. Introduction

Micropapillary urothelial carcinoma (MUC) is a histologic variant of bladder cancer that is under-reported in community practice [1,2]. It resembles papillary serous carcinoma of the ovary and accounts for $<1\%$ of all bladder urothelial carcinomas (UCs), although the presence of this pathologic variant is being increasingly recognized in recent years. Evidence suggests that MUC is an aggressive variant with poor prognosis [3–11]. These observations are primarily based on single-institution or population-based series that have limited numbers of clinical events or curated clinicopathologic data. Further, few studies have examined MUC histology as an independent prognostic factor after cystectomy. Comprehensive multicenter retrospective analysis of outcomes in MUC patients are needed as prospective studies for rare tumors are difficult to complete. Based on this rationale, we examined the impact of MUC histology on survival outcomes following radical cystectomy in a large multi-institutional cohort.

2. Materials and methods

2.1. Patient population

Fig. 1 provides an overview of the patient population accrual. The investigation was designed as a retrospective multi-institutional cohort study. Five academic centers across North America and Europe participated in the study that required identification of institutional patients with bladder UC who were assigned a diagnosis of MUC based on presence of any micropapillary component in their tumor specimen. Inclusion criteria stipulated identification of MUC patients who underwent open radical cystectomy, bilateral pelvic lymphadenectomy, and urinary diversion for primary bladder cancer at the respective institutions from 1980 through 2011. Extent of lymph node dissection and type of urinary diversion were performed according to surgeon preference; patients underwent a meticulous bilateral pelvic lymphadenectomy to include the standard template (i.e. external iliac and internal iliac/obturator nodal packets) at a minimum, if not higher. A medical oncologist evaluated patients for neoadjuvant or adjuvant chemotherapy at the surgeon's discretion. Choice of therapy was determined in consultation between the medical oncologist and patient. Exclusion criteria were (1) mortality within 30 days of cystectomy or during the postcystectomy hospital stay, whichever was longer; (2) presence of urethral or upper tract primaries, or distant metastasis at diagnosis; and (3) incomplete data on MUC patients for ≥ 1 variables.

A secure computerized database was implemented for data transfer. At data transfer, initial reports were generated for each variable to identify inconsistencies and other data integrity issues. Regular communication was maintained with all participating sites to resolve inconsistencies prior to analysis. After maximal resolution of all data points, the dataset was frozen from any additional modifications before final analysis.

Of the information received on 170 patients with confirmed MUC, data on 19 (11.2%) patients were excluded as

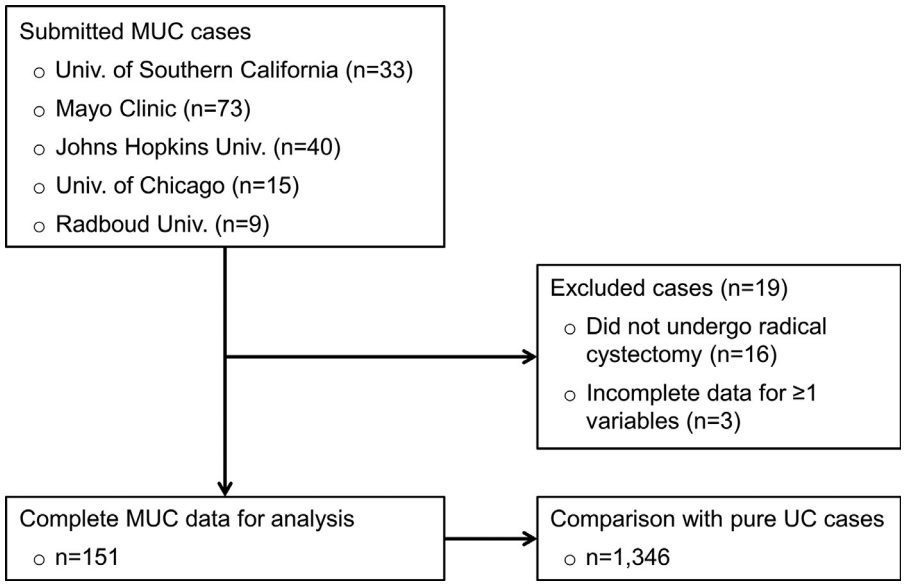

Fig. 1. Recruitment of study participants. MUC = micropapillary urothelial carcinoma; UC = urothelial carcinoma without any histological variants.

they did not meet the study criteria. The resulting final cohort consisted of 151 MUC patients. Clinical characteristics and outcomes for these subjects were compared with a group of patients with primary bladder UC devoid of any histological variants who were treated similarly at the primary sponsoring institution (University of Southern California) and otherwise met all other study criteria (n = 1,346). The investigation was approved by the University of Southern California Institutional Review Board, and all participating sites acquired the necessary institutional data use agreements before initiation of the study.

2.2. Pathological assessment and follow-up

All cystectomy specimens were processed and examined according to standard pathologic protocols. Anatomic pathologists at each institution reviewed all specimen slides; a second institutional genitourinary pathologist reviewed each case determined to be a MUC variant to ensure validity of the diagnosis. Centralized pathologic re-review was not performed. Tumor grading and histology were determined per World Health Organization/International Society of Urological Pathology classification; patients were categorized as pure UC (urothelial carcinoma with no histological variants, i.e., 0% micropapillary content) or MUC [12,13]. Patients were assigned a diagnosis of MUC if pathologic examination revealed any micropapillary component in the tumor. MUC patients were further subcategorized based on the absence (pure MUC) or presence (MUC with UC) of any urothelial carcinoma component in their primary tumor. Staging of tumor specimens was standardized to American Joint Committee on Cancer recommendations [14]. Disease stages were defined as organ-confined ($\leq$T2N0M0), extravesical (T3-4N0M0), and node-positive (TanyN1-3M0).

Patients were followed in accordance with individual site surveillance protocols. In general, routine postoperative follow-up was at 3-month intervals up to year 2, and annually thereafter. Physical examination and routine blood work were performed at each visit. Radiologic evaluation (chest radiography, computed tomography of abdomen and pelvis) was performed at 4 months postoperatively and every 6 months thereafter unless otherwise clinically indicated. Bone scans were performed when clinically indicated.

2.3. Clinical outcomes and statistical analysis

Outcomes analyzed included recurrence-free survival (RFS) and overall survival (OS). RFS duration was calculated from date of cystectomy to first documented clinical recurrence based on imaging with/without directed biopsy; patients who were recurrence-free at end of the study were censored at death or last follow-up. OS duration was calculated from date of cystectomy to death due to any cause; surviving patients were censored at last follow-up.

Data were analyzed using SAS 9.1.3 (SAS Institute, Cary, NC). Categorical variables were evaluated by chi-square and Fisher's exact tests. Kruskal-Wallis test was used to evaluate continuous variables. Kaplan-Meier method and associated log rank statistic were used to estimate differences in clinical outcomes. Univariable and multivariable Cox proportional hazards regression analysis were performed to determine associations between patient variables and clinical outcomes. Cox regression hazards assumptions were tested and no violations of proportionality were found. All P values are two-sided; $P \leq 0.05$ was considered statistically significant.

3. Results

3.1. Baseline characteristics

A total of 151 patients with MUC who underwent radical cystectomy were included in the analysis and compared with 1,346 patients with UC without any histological variants. Median follow-up for the overall cohort was 10 years (range, 0–25 years). Median follow-up was 10.0 years for UC patients, and 7.8 years for MUC patients.

Table 1 presents the baseline characteristics. Median age was 67 years for both patient groups. No significant differences in patient proportions were noted between the UC and MUC groups with regard to gender, clinical disease stage, and administration of neoadjuvant and adjuvant chemotherapy (all, $P \geq 0.10$). Based on precystectomy clinical disease staging, 91% and 89% of UC and MUC patients respectively presented with organ-confined disease.

However, the presence of MUC at cystectomy was associated with greater proportion of higher pathologic disease stage when compared with UC patients (organ-confined, 27% vs. 60%; extravesical, 23% vs. 18%; node-positive, 50% vs. 22%; $P < 0.01$). MUC patients were also noted to have higher rates of lymphovascular invasion (58% vs. 29%, $P < 0.01$) and positive soft-tissue surgical margins (15% vs. 1%, $P < 0.01$).

3.2. Univariable associations with clinical outcomes

Across the entire cohort, high tumor grade, higher pathologic disease stage at cystectomy, and lymphovascular invasion were associated with increased risk of recurrence and overall mortality (all, $P < 0.01$; Table 2). Moreover, the presence of MUC was likewise associated with significantly worse RFS and OS (both, log rank $P < 0.01$; Fig. 2). Indeed, the estimated 5-year RFS probabilities for patients with UC and MUC were 70% and 44%, respectively. The corresponding 5-year OS probabilities were 61% and 38%, respectively. By univariable analysis, presence of MUC was associated with higher risk of recurrence and overall mortality (both, $P < 0.01$; Table 2).

Table 1
Univariable comparisons of baseline patient characteristics

	UC patients n (column %)*	MUC patients n (column %)*	*P*
All patients	1346 (100)	151 (100)	
FACTORS			
Demographic			
Age, median (range) years	67 (33–93)	67 (35–89)	0.81
Gender			0.39
Male	1077 (80)	126 (83)	
Female	270 (20)	25 (17)	
Smoking history			0.21
Absent	305 (23)	27 (18)	
Present	1041 (77)	124 (82)	
Clinical			
Disease stage precystectomy			0.35
Organ-confined	1228 (91)	134 (89)	
Extravesical	89 (7)	11 (7)	
Node-positive	29 (2)	6 (4)	
Chemotherapy administered			
Neoadjuvant	98 (7)	8 (5)	0.50
Adjuvant	285 (21)	41 (27)	0.10
Radiotherapy administered			
Neoadjuvant	28 (2)	4 (3)	0.56
Adjuvant	5 (0)	1 (1)	0.47
Pathologic			
Disease stage at cystectomy			<0.01
Organ-confined	806 (60)	41 (27)	
Extravesical	243 (18)	35 (23)	
Node-positive	297 (22)	75 (50)	
Histologic grade			0.07
Low	233 (17)	17 (11)	
High	1113 (83)	134 (89)	
Surgical margin status			<0.01
Negative	1332 (99)	128 (85)	
Positive	14 (1)	23 (15)	
Concomitant CIS			0.79
Absent	500 (37)	58 (38)	
Present	846 (63)	93 (62)	
Lymphovascular invasion			<0.01
Absent	956 (71)	64 (42)	
Present	390 (29)	87 (58)	

P value based on Kruskal-Wallis, chi-square or Fisher's exact tests.
Abbreviations: CIS = carcinoma in situ; MUC = micropapillary urothelial carcinoma; UC = pure urothelial carcinoma.
* Unless indicated otherwise.

An exploratory analysis was then performed to assess the prognostic importance of extent of micropapillary component involvement when compared with patients with pure UC. Patients with pure MUC (n = 62) experienced poorer RFS (recurrence risk, 1.78; 95% CI, 1.21–2.64; $P < 0.01$) and OS (mortality risk, 1.72; 95% CI, 1.28–2.31; $P < 0.01$) when compared with patients with pure UC. Similarly, MUC with UC patients (n = 89) also experienced poorer RFS (recurrence risk, 2.23; 95% CI, 1.61–3.09; $P < 0.01$), and OS (mortality risk, 1.56; 95% CI, 1.17–2.09; $P < 0.01$). Indeed, presence of MUC histology was associated with significantly worse RFS and OS compared with those with pure UC, irrespective of whether micropapillary features comprised part or the entirety of the tumor (both, log rank $P < 0.01$; Fig. 3). However, outcomes between MUC patients without/with any urothelial carcinoma component in their primary tumors were not significantly different. Predicted 5-year RFS probabilities for MUC with UC vs. pure MUC patients were 43% and 45%, respectively. The corresponding 5-year OS probabilities were 42% and 34%, respectively.

3.3. Multivariable associations with clinical outcomes

Multivariable Cox proportional hazards models confirmed that higher pathologic disease stage at cystectomy and lymphovascular invasion were associated with increased risk of recurrence and overall mortality across the entire cohort (all, $P < 0.01$; Table 3). Administration of adjuvant chemotherapy was associated with improved RFS and OS (both, $P < 0.01$). In addition, advanced age was associated with higher overall mortality risk ($P < 0.01$). After inclusion in multivariable models that incorporated pathologic disease stage at cystectomy and lymphovascular invasion, presence of MUC histology was not independently associated with recurrence ($P = 0.27$) or mortality ($P = 0.12$; Table 3).

4. Discussion

The presence of micropapillary components in UC has been associated with aggressive behavior and poor prognosis [4]. However, nonregistry multi-institutional efforts comparing outcomes of MUC patients with those devoid of this histologic variant have not been reported. We herein performed a multi-institutional analysis evaluating the impact of MUC histology on outcomes following radical cystectomy. Our findings suggest that presence of MUC is associated with several adverse features such as advanced pathologic disease stage at cystectomy and higher rates of lymphovascular invasion. These features portend poor prognosis, as indicated by the comparatively higher probabilities of disease recurrence and mortality in MUC patients by unadjusted survival analysis. However, in multivariable models that accounted for pathologic disease stage at cystectomy and lymphovascular invasion, the presence of MUC was not independently associated with clinical outcomes. This suggests that MUC patients have more aggressive disease at presentation, but do not otherwise experience worse outcomes when controlled for standard pathologic predictors.

The observation that patients present with more aggressive disease, but have similar outcomes given comparable clinicopathologic characteristics has been documented for other histologic variants of UC [15]. The association of MUC with aggressive pathologic features has also been noted in other studies [16-18]. The micropapillary portion is the invasive and most deeply infiltrated tumor component at time of initial diagnosis in a majority of cases, especially

Table 2
Univariable associations with clinical outcomes

	Relative risk of recurrence (95% CI)	*P*	Relative risk of mortality (95% CI)	*P*
Tumor histology				
UC	1.00 (Reference)		1.00 (Reference)	
MUC	2.02 (1.56–2.63)	<0.01	1.64 (1.32–2.02)	<0.01
Age				
≤65 years	1.00 (Reference)		1.00 (Reference)	
>65 years	1.20 (1.00–1.44)	0.054	2.23 (1.92–2.58)	<0.01
Gender				
Male	1.00 (Reference)		1.00 (Reference)	
Female	1.20 (0.96–1.49)	0.12	1.15 (0.98–1.36)	0.09
Disease stage at cystectomy				
Organ-confined	1.00 (Reference)		1.00 (Reference)	
Extravesical	3.20 (2.49–4.12)	<0.01	2.16 (1.81–2.58)	<0.01
Node-positive	5.54 (4.48–6.86)	<0.01	3.07 (2.63–3.59)	<0.01
Lymphovascular invasion				
Absent	1.00 (Reference)		1.00 (Reference)	
Present	3.18 (2.65–3.82)	<0.01	2.18 (1.90–2.51)	<0.01
Histologic grade				
Low	1.00 (Reference)		1.00 (Reference)	
High	2.71 (1.95–3.78)	<0.01	1.83 (1.48–2.27)	<0.01
Adjuvant chemotherapy				
Not administered	1.00 (Reference)		1.00 (Reference)	
Administered	1.89 (1.55–2.29)	<0.01	1.06 (0.90–1.24)	0.52

P value based on Cox regression analysis.
Abbreviations: CI = confidence interval; MUC = micropapillary urothelial carcinoma; UC = pure urothelial carcinoma.

in patients with advanced-stage disease [5,6]. Our exploratory analyses also suggest that presence of any proportion of micropapillary component in urothelial carcinoma specimens confers poorer RFS and OS as compared with UC without any histological variants. These findings are consistent with the biologically aggressive nature of this histologic variant.

Despite its adverse features, multivariable analyses indicated that MUC histology was not independently associated with poor outcomes. A prior study reported lack of significant differences in outcomes between patients with MUC and pure UC, although these findings were not based on multivariable models and may have been impacted by diminished statistical power [16]. A single-institution analysis reported poor cancer-specific survival in MUC patients when compared with unmatched pure UC patients [18]. However, this prognostic difference was not observed when patients were matched based on pathologic disease stage at cystectomy. Other single-institution and population-based analyses have also corroborated these findings [17,19]. This present multi-institutional effort supports and extends the results of such prior efforts, and confirms that MUC outcomes are comparable to those of patients with UC without histological variants when controlled for disease stage and other pathologic parameters.

Our results have implications for research and clinical practice. As a multi-institutional retrospective investigation of the clinical behavior of MUC patients, these findings underscore the importance of identifying the presence of aberrant micropapillary differentiation in primary bladder tumors, and their impact on survival outcomes. Although challenging, ongoing multi-institutional collaborations are useful and necessary to study this rare tumor. The disease's clinical course makes early pathologic diagnosis imperative to identify these subjects who may need more aggressive management. Additional research is also required to determine whether MUC patients will benefit from multimodal therapy. Such studies may be particularly important in optimizing outcomes of radical surgery given that patients with variant histology bladder cancer are often clinically understaged [15]. Evidence suggests that administration of intravesical therapy may be ineffective against non-muscle-invasive MUC, and delaying cystectomy until progression may result in poorer outcomes [20,21]. However, other small series have reported reasonable outcomes with bladder-preserving therapies, especially in carefully selected patients and when the non–muscle-invasive micropapillary component is relatively small [22,23]. Although neoadjuvant chemotherapy administration may result in significant downstaging of tumors with micropapillary histology, its overall value in improving oncologic outcomes also remains controversial [24-26]. This is reflected in the lack of consensus regarding neoadjuvant chemotherapy use for

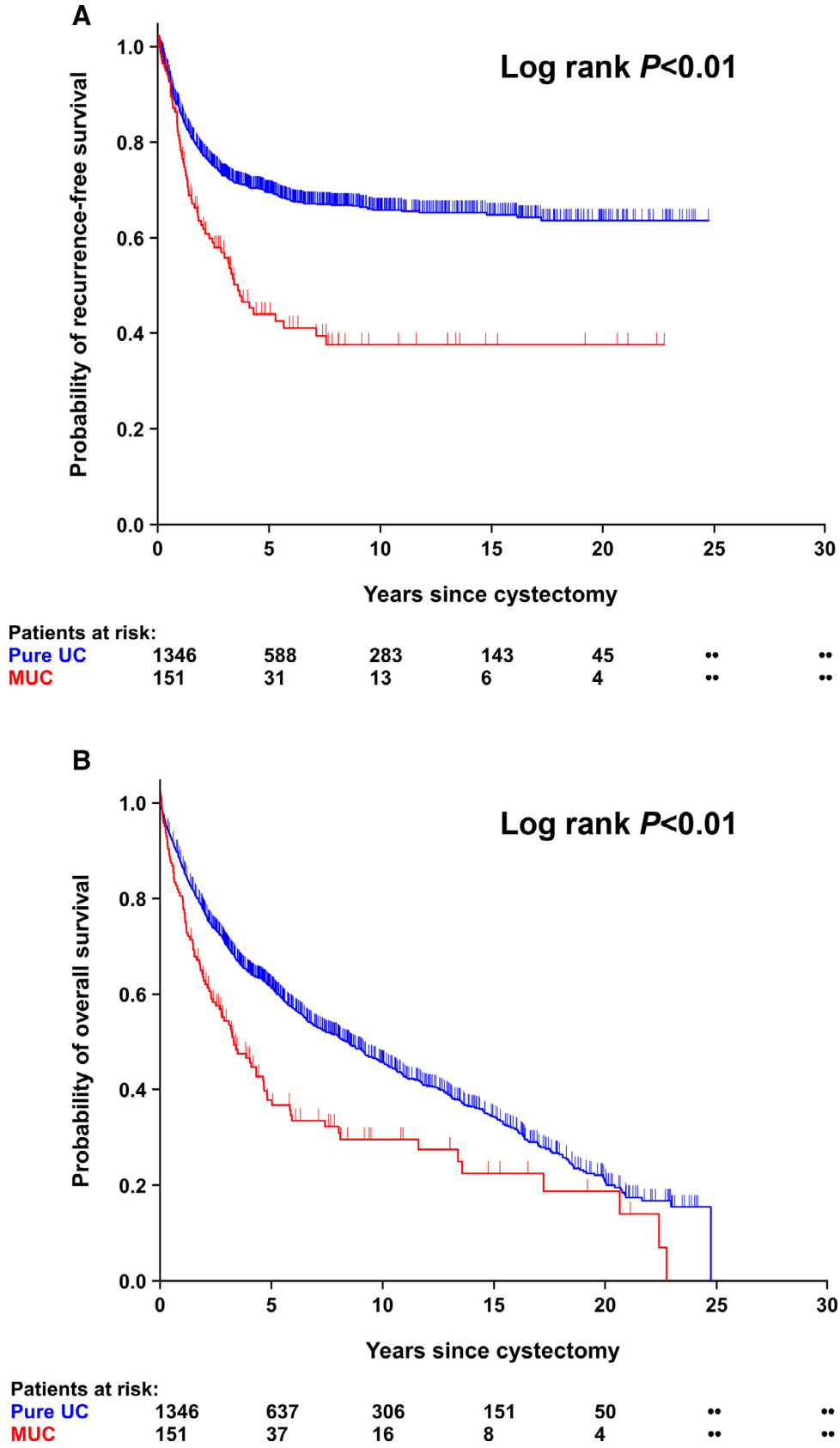

Fig. 2. Kaplan-Meier curves demonstrating probabilities of (A) recurrence-free and (B) overall survival of the study population stratified by tumor histology. MUC = micropapillary urothelial carcinoma; UC = urothelial carcinoma.

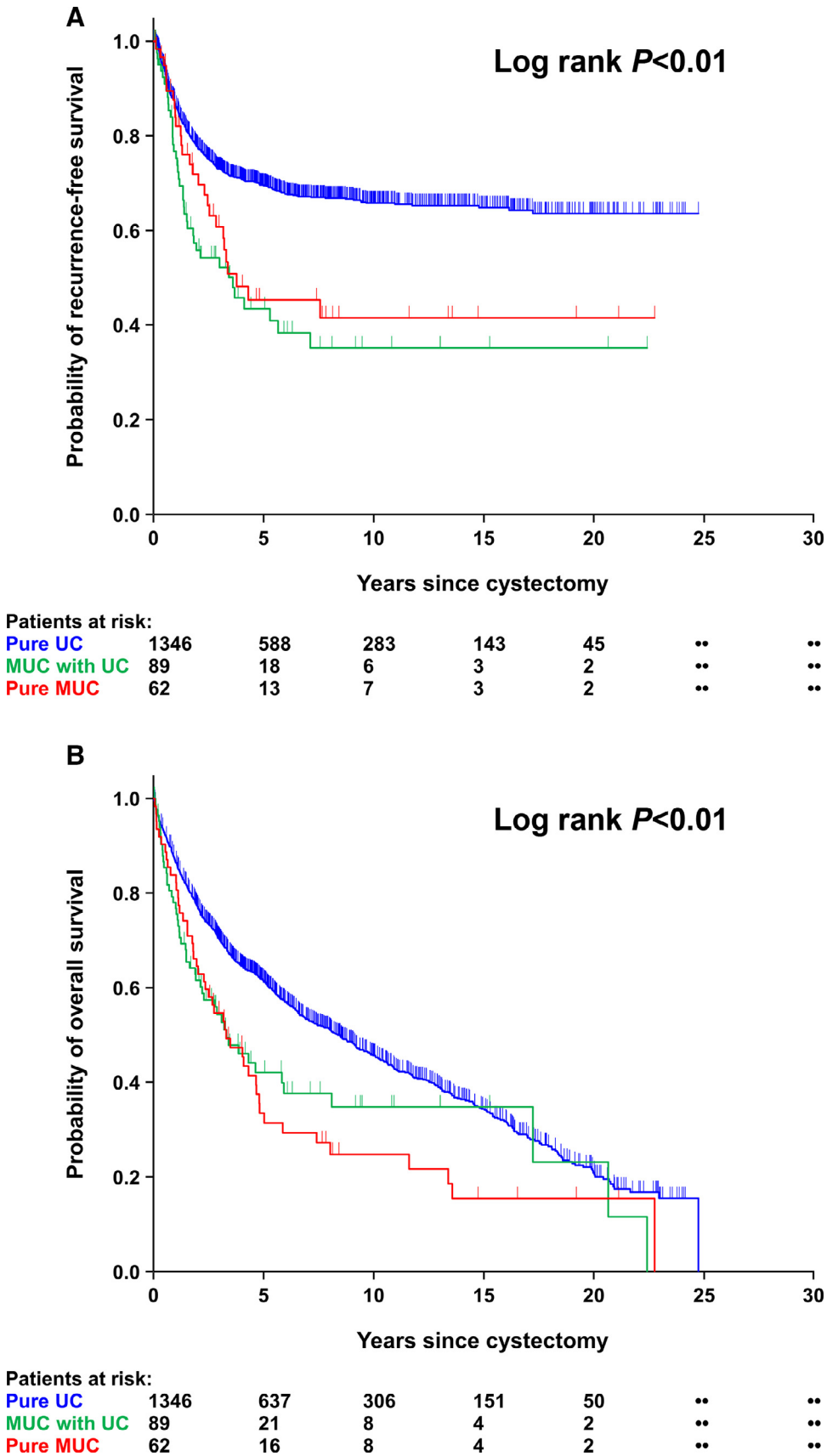

Fig. 3. Kaplan-Meier curves demonstrating probabilities of (A) recurrence-free and (B) overall survival of the study population stratified by extent of micropapillary component in the primary tumor. MUC = micropapillary urothelial carcinoma; UC = urothelial carcinoma.

Table 3
Multivariable associations with clinical outcomes

	Relative risk of recurrence (95% CI)	*P*	Relative risk of mortality (95% CI)	*P*
Tumor histology				
UC	1.00 (Reference)		1.00 (Reference)	
MUC	1.16 (0.89–1.53)	0.27	1.19 (0.96–1.49)	0.12
Age				
≤65 years	1.00 (Reference)		1.00 (Reference)	
>65 years	1.00 (0.82–1.21)	1.00	1.95 (1.67–2.26)	<0.01
Gender				
Male	1.00 (Reference)		1.00 (Reference)	
Female	1.11 (0.89–1.39)	0.36	1.06 (0.89–1.25)	0.52
Disease stage at cystectomy				
Organ-confined	1.00 (Reference)		1.00 (Reference)	
Extravesical	3.09 (2.36–4.03)	<0.01	2.21 (1.83–2.67)	<0.01
Node-positive	5.32 (3.99–7.09)	<0.01	3.66 (2.97–4.51)	<0.01
Lymphovascular invasion				
Absent	1.00 (Reference)		1.00 (Reference)	
Present	1.62 (1.31–2.01)	<0.01	1.39 (1.18–1.64)	<0.01
Adjuvant chemotherapy				
Not administered	1.00 (Reference)		1.00 (Reference)	
Administered	0.65 (0.51–0.82)	<0.01	0.49 (0.40–0.60)	<0.01

P value based on Cox proportional hazards model.
Abbreviations: CI = confidence interval; MUC = micropapillary urothelial carcinoma; UC = pure urothelial carcinoma.

muscle-invasive MUC [27]. While this study was not designed to test the impact of multimodal therapy or surgical delay on MUC outcomes, but rather to investigate overall prognosis as compared with pure UC, the results in aggregate highlight the need for identifying more aggressive therapeutic modalities for these tumors beyond merely offering early radical surgery. Nevertheless, early identification of presence of MUC in transurethral bladder tumor resection specimens may give pause to the surgeon of potentially advanced disease, and providers should be more wary of possible clinical understaging and consider more aggressive management at the outset. It is conceivable that future management may involve clinical risk stratification and novel biomarkers to identify candidates who may respond to chemotherapy vs. those who may benefit from early cystectomy [28-30].

This study has some limitations that merit comment. These involve caveats inherent to any retrospective multicentric study, including potential variations due to treatment by multiple surgeons and oncologists. MUC cases from multiple institutions were compared with pure UC cases from a single institution. However, comparing the MUC cases with pure UC cases from all participating institutions presented challenges with respect to data transfer and comparison between two unevenly balanced patient subgroups. In addition, while specimens were originally reviewed by expert anatomic pathologists at each participating institution, reporting of data accrued over a period of more than three decades posed a logistical challenge for performing centralized pathologic re-review. However, all participating institutions are academic centers of excellence for treatment of aggressive bladder cancer where patient diagnosis and management protocols are in accordance with internationally accepted guidelines. While the interpretation and understanding of MUC variant has evolved over the duration of cohort accrual and is therefore subject to standard biases associated with retrospective review, we believe that histopathologic diagnostic accuracy, patient management, and post-radical cystectomy outcomes are comparable across these centers. The study was also not designed to assess whether presence of MUC on clinical staging (i.e., transurethral resection specimen) was associated with outcomes. Given the limited number of patients who received perioperative chemotherapy and the retrospective nature of this analysis, we also refrained from assessing the impact of such therapy on MUC prognosis.

In conclusion, while MUC is associated with advanced disease at cystectomy, clinical outcomes are comparable to patients with pure UC after controlling for pathologic features. These multi-institutional data support the continued use of radical cystectomy for treating MUC patients, but highlights the importance of early identification of this aggressive variant that may forebode locally advanced and possible nodal metastatic disease at cystectomy. Moving forward, prospective evaluations are needed to define optimal treatment strategies for patients with aberrant micropapillary differentiation.

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