

Clinical risk stratification in patients with surgically resectable micropapillary bladder cancer

Mario I. Fernández*, Stephen B. Williams*, Daniel L. Willis*, Rebecca S. Slack†, Rian J. Dickstein*, Sahil Parikh*, Edmund Chiong*, Arlene O. Siefker-Radtke‡, Charles C. Guo§, Bogdan A. Czerniak§, David J. McConkey*, Jay B. Shah*, Louis L. Pisters*, H. Barton Grossman*, Colin P. N. Dinney* and Ashish M. Kamat*

*Departments of Urology, †Biostatistics, ‡Genitourinary Medical Oncology, and §Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Objective

To analyse survival in patients with clinically localised, surgically resectable micropapillary bladder cancer (MPBC) undergoing radical cystectomy (RC) with and without neoadjuvant chemotherapy (NAC) and develop risk strata based on outcome data.

Patients and Methods

A review of our database identified 103 patients with surgically resectable (\leq cT4acN0 cM0) MPBC who underwent RC. Survival estimates were calculated using Kaplan–Meier method and compared using log-rank tests. Classification and regression tree (CART) analysis was performed to identify risk groups for survival.

Results

For the entire cohort, estimated 5-year overall survival and disease-specific survival (DSS) rates were 52% and 58%, respectively. CART analysis identified three risk subgroups: low-risk: cT1, no hydronephrosis; high-risk: \geq cT2, no hydronephrosis; and highest-risk: cTany with

tumour-associated hydronephrosis. The 5-year DSS for the low-, high-, and highest-risk groups were 92%, 51%, and 17%, respectively ($P < 0.001$). Patients down-staged at RC $<$ pT1 regardless of the use of NAC had the best survival (5-year DSS of 96% vs 45% for those not down-staged; $P < 0.001$), while those who were not down-staged despite NAC had 5-year DSS of only 17%.

Conclusion

In patients with surgically resectable MPBC, NAC appears to confer benefit to patients with muscle-invasive disease without hydronephrosis, while patients with cT1 disease can proceed to upfront RC. Patients with hydronephrosis do not appear to respond well to NAC and have poor prognosis regardless of treatment paradigm. However, further external validation studies are needed to support the proposed risk stratification before treatment recommendations can be made.

Keywords

transitional cell carcinoma, cystectomy, multimodal treatment, neoadjuvant therapy, urinary bladder neoplasms

Introduction

Identification of histological subtypes in bladder cancer (BC) is particularly important because of their implications for prognosis and management. Micropapillary bladder cancer (MPBC) is considered an especially aggressive variant of BC and was first described by our institution in 1994. Since then, $>$ 500 cases have been reported in the literature, representing 6–10% of urothelial tumours in those series [1–4].

For patients with surgically resectable, muscle-invasive BC (MIBC), cisplatin-based combined neoadjuvant chemotherapy (NAC) is recommended, showing a 5% absolute benefit in overall survival (OS) [5,6]. However, NAC for such patients

remains underutilised [7]. Therefore, strategies have been developed to identify patients most likely to benefit. Previous work from our group identified higher clinical T category (cT3b or cT4), presence of lymphovascular invasion (LVI), and hydronephrosis as predictors of worse pathological findings at radical cystectomy (RC), and hence we offer NAC to these patients [8,9]. However, whether these factors are translatable to patients with variant histological subtypes, including MPBC, has not been studied.

At present, there are few reports on the role of NAC for MPBC. We previously reported the outcomes of 100 consecutive patients with MPBC seen at our institution [10]. Among these, 55 patients underwent RC for surgically

resectable disease (\leq cT4acN0 cM0) with no significant differences in stage distribution between groups. The 5-year OS for those treated with NAC was 63% and 71% for those undergoing RC alone. However, due to relatively small numbers in each group, we were unable to identify prognostic factors for patients with MPBC. In the present study, we expand on our cohort and report the outcomes in patients with surgically resectable MPBC undergoing RC with or without NAC, with a focus on risk group stratification.

Patients and methods

We performed an Institutional Review Board-approved review of patients treated with RC at our institution between 1989 and 2012 (1910 patients). We focused our attention to those who presented with surgically resectable (\leq cT4acN0 cM0) MPBC. We excluded those who had other concurrent variant histological subtypes and those treated on clinical trials of novel NAC regimens (to keep the study relevant to the community at large).

As previously reported, at our institution we consider a patient to have MPBC if review by our genitourinary pathologists reveals any component of micropapillary disease within the tumour, regardless of the percentage of MPBC [1,10,11]. This practice is based on our recognition of the aggressive behaviour of MPBC and the fact that referring hospitals frequently do not provide the entire specimen for review, which limits our ability to quantify the percentage of variant histology. However, in those patients who had a sufficient tumour block for assessment for this study, we assessed the percentage of MPBC in 94 patients (91%) and defined a micropapillary component of $<25\%$ of the total tumour as 'focal MPBC' and $\geq 25\%$ as 'extensive MPBC'. This was based on discussions among expert genitourinary pathologists, as it is thought to be a threshold that can be reproducibly translated into community practice as well.

Patient records were reviewed for demographic, clinical, and pathological data. Clinical stage at time of presentation was determined according to transurethral resection (TUR) and examination under anaesthesia findings, radiological studies (CT or MRI of the abdomen and pelvis and CT or radiography of the chest), and pathology reports after TUR. Tumour-associated hydronephrosis was defined as any grade of uni- or bilateral renal pelvis dilation in preoperative imaging.

Pathological downstaging at the RC specimen was defined as $<$ pT1 (i.e. pT0/pTa/pTis) and pN0 disease. Meanwhile, pathological upstaging at RC was defined as a shift to a higher T category and/or presence of lymph node metastases. Use of NAC was at the discretion of the treating physicians.

Survival analysis was performed and different risk subgroups were identified by multivariate classification and regression

tree (CART) analysis of all factors according to OS and disease-specific survival (DSS) risk. Minimum risk group size was set to 20 patients. Patient characteristics were compared using chi-square tests (with exact tests for small sample sizes), a Jonckheere–Terpstra test to address the natural ordering of TNM stage and treatment status, and independent *t*-tests for continuous variables. Survival was measured from RC or first NAC treatment until death. The 5-year survival estimates and median survival times were calculated using the Kaplan–Meier method and compared among groups using log-rank tests [12]. The effects of age and time between diagnosis and treatment were tested using proportional hazards regression [13]. Due to relatively small numbers, a limited subset of clinically meaningful characteristics that did not overlap with the CART groups were combined in a Cox regression model (full model), with a backward selection procedure to reduce the model to only factors remaining significantly different in combination with each other (reduced model). CART analyses were performed and Kaplan–Meier plots were created in Stata/SE 13 (StataCorp, College Station, TX, USA). All other analyses were performed in SAS 9.3 (SAS Institute Inc., Cary, NC, USA) using a two-sided 5% significance level. Unadjusted *P* values were presented for hypothesis generation, and a *P* $<$ 0.05 was considered statistically significant.

Results

Of the 103 patients, 29 (30%) received NAC before RC and 74 (70%) underwent RC upfront. Patient demographics are summarised in Table 1. Of the 29 patients treated with NAC, most (75%) received cisplatin-based regimens, while seven did not (ifosfamide/doxorubicin/gemcitabine four, paclitaxel/doxorubicin/gemcitabine one, gemcitabine/docetaxel one and paclitaxel/carboplatin one). As is our published treatment paradigm for NAC [9], patients with a higher clinical T category (*P* = 0.002), LVI (*P* = 0.01), or tumour-associated hydronephrosis (*P* = 0.02) were more likely to receive NAC.

Pathological findings at RC are shown in Table 2. The overall incidence of lymph node metastases at RC was 40%. Only one patient in our cohort had a positive surgical margin and there were no differences between groups concerning lymph node yield (*P* = 0.98). There was pathological downstaging to $<$ pT1pN0 in 29% of patients and, as expected, was significantly more common among patients who received NAC (52% vs 19%; *P* = 0.002). Conversely, patients who underwent upfront RC had higher pathological T categories and a higher rate of upstaging at RC (60% vs 34% with NAC; *P* = 0.03).

With a median follow-up of 6.0 years, the 5-year OS and DSS rates were 52% and 58%, respectively. When we analysed preoperative factors associated with OS and DSS, the following were associated with worse survival: extensive

Table 1 Patients' characteristics overall and according to treatment.

Characteristic	All	RC	NAC + RC	P*
All patients, N (%)	103 (100)	74 (70)	29 (30)	
Baseline characteristics				
Age at RC, years, median (range)	67 (30-88)	67 (30-88)	70 (43-80)	0.92
Sex, n (%)				
Female	15 (15)	10 (14)	5 (17)	0.76
Male	88 (85)	64 (86)	24 (83)	
Extent of MPBC in TUR specimen, n (%)				
Extensive	25 (24)	16 (22)	9 (31)	0.61
Focal	69 (67)	52 (70)	17 (59)	
Unknown	9 (9)	6 (8)	3 (10)	
Hydronephrosis, n (%)				
Yes	22 (21)	11 (15)	11 (38)	0.02
No	79 (77)	61 (82)	18 (62)	
Missing	2 (2)	2 (3)	0	
Clinical T category, n (%)				
T1	38 (37)	31 (42)	7 (24)	0.002
T2	52 (50)	39 (53)	13 (45)	
T3/T4a	13 (12)	4 (5)	9 (31)	
LVI, n (%)				
Yes	29 (28)	15 (20)	14 (48)	0.01
No	74 (72)	59 (80)	15 (52)	
CIS at diagnosis, n (%)				
No	81 (79)	55 (74)	26 (90)	0.11
Yes	22 (21)	19 (26)	3 (10)	
ASA score, n (%)				
3	66 (64)	48 (65)	18 (62)	0.87
4	1 (1)	1 (1)	0 (0)	
NA	36 (35)	25 (34)	11 (38)	
Time to treatment [†] , months, median (IQR)	1.8 (1.0, 3.2)	2.1 (1.3, 3.4)	1.0 (0.5, 2.4)	0.003
Treatment after RC, n (%)				
Adjuvant chemotherapy				0.79
None	67 (65)	46 (62)	21 (72)	
Cisplatin	32 (31)	25 (34)	7 (24)	
Non-cisplatin	3 (3)	2 (3)	1 (3)	
Missing	1 (1)	1 (1)	0	

*Patients with missing values were not included in comparisons. P values are based on exact tests because counts were <5 in some categories, and those in bold are significant. [†]Time to treatment was defined as time from MPBC diagnosis at TUR to either upfront RC or NAC. ASA, American Society of Anesthesiologists; IQR, interquartile range.

MPBC on TUR specimen (5-year OS 26% vs 58%, $P = 0.01$; and 5-year DSS 34% vs 62%, $P = 0.02$), higher clinical T category (5-year OS 34%, 38% and 81% for cT3/4, cT2 and cT1 respectively, $P = 0.001$; and 5-year DSS 34%, 45% and 90% for cT3/4, cT2 and cT1, respectively, $P < 0.001$), presence of tumour-associated hydronephrosis (5-year OS 15% vs 60%, $P < 0.001$; and 5-year DSS 17% vs 68%, $P < 0.001$) and presence of carcinoma *in situ* (CIS; 5-year OS 30% vs 58%, $P = 0.02$; and 5-year DSS 33% vs 65%, $P = 0.02$) (Table 3).

Using CART analysis, we were then able to identify three distinct risk subgroups (Fig. S1): low-risk: cT1, no hydronephrosis; high-risk: \geq cT2, no hydronephrosis; and highest-risk: cTany with tumour-associated hydronephrosis based on survival outcomes [5-year OS rates were 82%, 45%,

Table 2 Pathological findings in RC specimen.

Characteristic	All	RC alone	NAC + RC	P*
No. of patients, N (%)	103 (100)	74 (100)	29 (100)	
Pathological T category, n (%)				
T0	33 (32)	17 (23)	16 (55)	<0.001
T1	14 (14)	14 (19)	0	
T2	10 (10)	8 (11)	2 (7)	
T3	45 (44)	34 (47)	11 (38)	
LVI, n (%)				
Yes	43 (42)	31 (46)	12 (67)	0.12
No	42 (41)	36 (54)	6 (33)	
CIS at RC, n (%)				
Yes	49 (48)	40 (59)	9 (50)	0.50
No	37 (36)	28 (41)	9 (50)	
Surgical margin, n (%)				
None	102 (99)	73 (99)	29 (100)	>0.99
Focal ureteric	1 (1)	1 (1)	0	
Nodes examined				
Number	14	14	13	0.98
Median(IQR)	(8, 25)	(8, 26)	(9, 23)	
Pathologic N category, n (%)				
N+	40 (40)	32 (45)	8 (28)	0.12
Downstaging to <pT1pN0 at RC, n (%)				
Yes	29 (29)	14 (19)	15 (52)	0.002
No	72 (71)	58 (81)	14 (48)	
Upstaging at RC, n (%)				
Yes	54 (53)	44 (60)	10 (34)	0.03
No	48 (47)	29 (40)	19 (66)	

*Patients with missing values were not included in comparisons. P values are based on exact tests because counts were <5 in some categories and those in bold are significant.

and 15%, respectively ($P < 0.001$); 5-year DSS rates were 92%, 51%, and 17%, respectively ($P < 0.001$) (Fig. 1). For patients classified as having low-risk disease, the 5-year OS and DSS rates were 87% and 95%, respectively, for upfront RC, and 67% and 83%, respectively, for NAC+RC. For those patients classified as having high-risk disease, the 5-year OS and DSS rates were 39% and 43%, respectively, for upfront RC, and 64% and 79%, respectively, for NAC+RC. The outcome for patients with highest-risk disease was poor with 5-year OS and DSS rates of 24% and 27%, respectively, for upfront RC, and could not be estimated for patients treated with NAC because no patients survived or were followed for 5 years. Note that we did not perform intra-group statistical comparisons due to inherent errors that would be introduced by limited numbers of patients.

As expected downstaging to <pT1 disease at RC was prognostic of outcome with those that were down-staged having significantly better survival (5-year OS 76% vs 42%, $P = 0.003$; 5-year DSS 96% vs 45%, $P < 0.001$). Interestingly, while DSS was almost identical for those down-staged to <pT1 either by NAC or by TUR alone (RC only group), for those patients who were not down-staged by NAC, the prognosis was especially dismal with a 5-year DSS rate of only 17% (Fig. 2). Notably, 45% patients in the NAC group and 46% in the upfront RC group who were not down-staged received adjuvant chemotherapy, with no discernable impact on outcomes.

Table 3 OS and DSS by patient characteristics.

Patient characteristic	OS			DSS		
	Deaths, n/N	5-year (SE)	P	Deaths, n/N	5-year (SE)	P
All	55/103	51.7 (5.3)		41/103	58.3 (5.5)	
Age, years						
30–59	13/26	58.2 (10.2)	0.19	12/26	58.2 (10.2)	0.10
60–69	15/35	61.5 (8.8)		8/35	74.7 (8.3)	
≥70	27/42	37.8 (8.5)		21/42	43.4 (9.3)	
Sex						
Female	8/15	57.1 (13.2)	0.74	4/15	68.6 (13.2)	0.41
Male	47/88	50.8 (5.8)		37/88	56.7 (6.0)	
Extent of MPBC in TUR specimen						
Extensive	17/25	26.4 (9.7)	0.01	13/25	34.2 (11.6)	0.02
Focal	34/69	57.7 (6.4)		27/69	62.3 (6.5)	
Clinical T category						
T1	10/38	80.8 (7.1)	0.001	4/38	89.5 (5.8)	<0.001
T2	36/52	38.3 (7.0)		29/52	44.8 (7.7)	
T3/T4	9/13	34.2 (13.8)		8/13	34.2 (13.8)	
LVI						
No	38/74	54.7 (6.4)	0.41	27/74	62.3 (6.5)	0.18
Yes	17/29	44.7 (9.7)		14/29	48.0 (10.1)	
Hydronephrosis						
No	35/79	60.4 (6.0)	<0.001	25/79	68.1 (6.0)	<0.001
Yes	18/22	15.2 (8.9)		15/22	16.7 (9.7)	
CIS						
No	39/81	57.8 (5.9)	0.02	28/81	65.2 (6.0)	0.02
Yes	16/22	29.8 (10.9)		13/22	33.1 (11.8)	

P values in bold are significant.

Finally, on multivariate analysis (Table 4), risk groups (low vs highest-risk, HR 0.2, 95% CI 0.1, 0.4; high vs highest-risk, HR 0.5, 95% CI 0.2, 0.9; $P < 0.001$) and the presence of extensive MPBC in the TUR specimen (HR 2.1, 95% CI 1.1, 3.8; $P = 0.02$) were significantly associated with OS. Similarly, the risk groups were also predictive of DSS: low vs highest-risk, HR 0.1, 95% CI 0.0, 0.3; high vs highest-risk, HR 0.3, 95% CI 0.2, 0.7; $P < 0.001$. However, extensive MPBC in the TUR specimen did not remain significant while presence of CIS did (yes vs no, HR 2.3, 95% CI 1.1, 4.9; $P = 0.03$).

Discussion

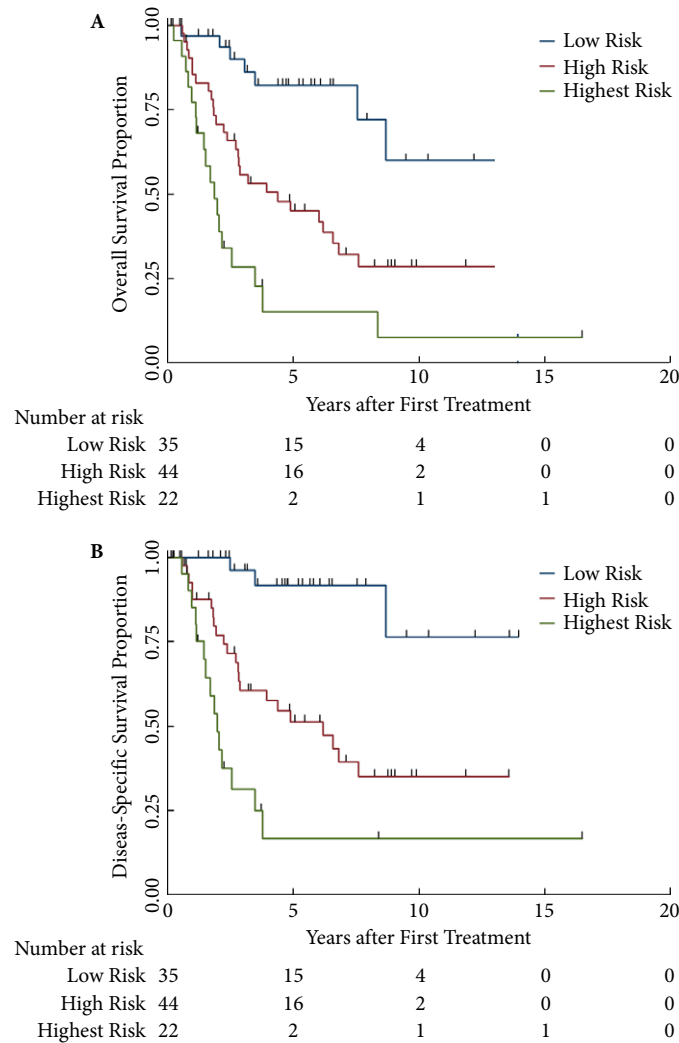
MPBC is an aggressive variant of urothelial carcinoma and because of its relative low incidence optimal treatment paradigms remain to be defined. In the present study, which expands on our prior reports and is the largest series to date, we were able to identify three distinct risk subgroups of surgically resectable MPBC with distinct survival outcomes at 5-years as follows: low-risk, 92%; high-risk, 51%; and highest-risk, 17%, respectively ($P < 0.001$). This is also the largest series assessing the role of NAC in patients with MPBC; the overall 5-year DSS rate was 54% for patients who received NAC and 60% for patients treated with upfront RC ($P = 0.54$). When survival differences were examined within risk groups, patients with high-risk disease appeared to derive benefit from NAC (5-year DSS rate, 79% vs 43%). Our present finding that NAC did not appear to have a positive

impact on DSS in the low-risk group matches our previous finding that early RC offers the best survival in this group [11]. However, we urge the community to further study this in a prospective manner or at least validate it with external multicentre data sets in order to overcome biases inherent to single-centre reports. Unfortunately, patients in the highest-risk category (those with tumour-associated hydronephrosis) had poor outcomes regardless of mode of therapy.

MPBC has gained recognition as a variant with an aggressive clinical behaviour. Micropapillary tumours in other organ sites, e.g., ovary, lung, and breast, usually present at advanced stage and are reported to not respond well to chemotherapy [14–18]. For MPBC, reported clinical outcomes have consistently been poor. For example, in the first ever report of MPBC from our institution in 1994, 39% of patients had died of disease at a mean follow-up of 44 months [1]. More recently, analyses of larger series of patients with MPBC treated with RC showed 10-year cancer-specific mortality rates of 37–61% and 10-year DSS rates up to 31% [19–21]. In our present cohort the 5- and 10-year DSS rates were 58% and 46%, respectively.

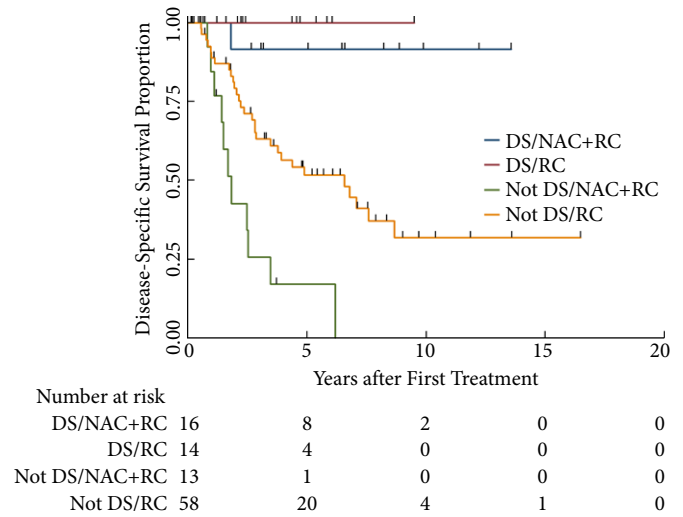
The poor outcomes of patients with MPBC appear to be associated with several factors, most significantly tumour stage. In our previous report of 100 patients with MPBC, 56% of patients had MIBC at presentation [10]; consistent with reports from other smaller series showing that 38–92% of cases are invasive at presentation [1,3,19,22–24]. Notably,

Fig. 1 OS and DSS survival by risk group. Low-risk was defined as no hydronephrosis, T1; high-risk, as no hydronephrosis, \geq T2; and highest-risk, as hydronephrosis, any T category. **(A)** OS estimates (standard error) at 5 years were 82.4% (7.2%), 45.1% (7.9%), and 15.2% (8.9%) for low, high, and highest risk groups, respectively ($P < 0.001$). **(B)** DSS estimates (standard error) at 5 years were 91.8% (5.6%), 51.4% (8.4%), and 16.7% (9.7%) for low, high, and highest risk groups, respectively ($P < 0.001$).



these rates differ significantly from the 15–25% rate of MIBC at presentation among patients with conventional urothelial carcinoma [25]. Furthermore, MPBC is almost always present in a milieu of high-grade tumour, and LVI is reported in many cases (28% in present study). Note that rates of LVI must be interpreted with caution given that stromal retraction spaces around tumour cell clusters are common in the invasive component of MPBC and may mimic LVI [3,26]. The extent of MPBC in the TUR specimen is also gaining relevance. Our present finding that extensive MPBC (>25%) is significantly associated with a reduced OS is consistent with our previous study in patients with T1 MPBC, where patients with extensive MPBC were more likely to die of

Fig. 2 DSS by pathological downstaging and treatment. DS indicates that disease was down-staged at RC to $<$ pT1pN0.



disease progression (5-year DSS 42% vs 73%, $P = 0.033$) [11]. Further evidence for the aggressive nature of MPBC is the high incidence of pathological upstaging at RC, putatively due to rapid growth of tumour [10,19,21,23]. In our present series, 54% of patients were upstaged at RC including occult lymph node metastases in 40%. Given all these data regarding the aggressiveness of MPBC and lack of established risk stratifiers, the optimal approach for patients with surgically resectable MPBC remain a matter of debate [10,27].

Cisplatin-based NAC is currently established as the standard approach before local treatment for MIBC [6]. While a secondary analysis of the Southwest Oncology Group (SWOG) trial 8710 suggested that squamous and glandular differentiation did not confer resistance to cisplatin-based NAC [28], results could not be generalised to mixed urothelial tumours with other non-urothelial components, such as MPBC. For example, in a phase 2 clinical trial of sequential NAC with ifosfamide, doxorubicin, and gemcitabine followed by cisplatin, gemcitabine, and ifosfamide in locally advanced urothelial carcinoma, variant histology was associated with an inferior 5-year DSS rate (50% vs 83% in pure TCC; $P = 0.02$) [29]. These findings suggest different patterns of response to chemotherapy for variant histologies but prior studies analysing NAC in patients with MPBC including our own resulted in more questions than answers [19,22]. The three risk subgroups we have identified based on clinically relevant and easily obtained information prior to initiation of therapy (RC or NAC) should help in this regard: low-risk: cT1, no hydronephrosis; high-risk: \geq cT2, no hydronephrosis; and highest-risk: cTany with tumour-associated hydronephrosis.

Pathological downstaging has been proposed as a surrogate marker for survival after NAC for MIBC because it is

Table 4 Multivariate analysis of factors associated with OS and DSS by patient characteristics (N = 92).*

Patient characteristics	Full model		Reduced model	
	HR (95% CI)	P	HR (95% CI)	P
OS (49 Events)				
Extensive vs focal disease in TUR specimen	1.8 (1.0, 3.4)	0.06	2.1 (1.1, 3.8)	0.02
Risk group [†]				
Low vs highest	0.2 (0.1, 0.5)	<0.001	0.2 (0.1, 0.4)	<0.001
High vs highest	0.4 (0.2, 0.7)		0.5 (0.2, 0.9)	
High vs low	2.0 (0.8, 5.0)		3.0 (1.3, 6.9)	
CIS				
Yes vs no	1.9 (0.9, 3.9)	0.08		
NAC				
Yes vs no	0.9 (0.5, 1.7)	0.75		
Time to Treatment				
1 year increase	0.6 (0.2, 1.8)	0.35		
DSS (39 Events)				
Extensive vs focal disease in TUR specimen	1.7 (0.8, 3.4)	0.14		
Risk group [†]				
Low vs highest	0.1 (0.0, 0.3)	<0.001	0.1 (0.0, 0.3)	<0.001
High vs highest	0.3 (0.2, 0.8)		0.3 (0.2, 0.7)	
High vs low	4.2 (1.1, 15.8)		4.7 (1.3, 16.3)	
CIS				
Yes vs no	2.1 (0.9, 4.1)	0.07	2.3 (1.1, 4.9)	0.03
NAC				
Yes vs no	0.9 (0.5, 1.7)	0.75		
Time to treatment [‡]				
1 year increase	0.8 (0.2, 2.7)	0.68		

*Patients had to have complete information in all of these variables to be included in these models. [†]Low-risk was defined as no hydronephrosis, T1; high-risk, as no hydronephrosis, \geq T2; and highest-risk, as hydronephrosis, any T category. [‡]Time to treatment was defined as time from MPBC diagnosis at TUR to either upfront RC or NAC. P values in bold are significant.

associated with improved survival [29,30]. A recent study from the Memorial Sloan-Kettering Cancer Center (MSKCC), which reported a 45% rate of downstaging in 29 patients with MPBC treated with NAC, also suggested that downstaging was associated with higher survival rates at 24-month follow-up [24]. In the present study, we too found that downstaging was associated with improved OS and DSS, and essentially patients with MPBC down-staged to $<$ pT1pN0 at RC did well regardless of whether downstaging was achieved with NAC or TUR alone. However, it is interesting that among patients whose disease was not down-staged, those undergoing upfront RC had better outcomes than those treated with NAC (5-year DSS rate, 52% vs 17%), a difference that cannot be explained by adjuvant chemotherapy because implementation was similar in the two groups. This observation underscores the need for identification of markers for aggressiveness and chemosensitivity (e.g. molecular profiling) to avoid delay of RC in patients who are not likely to respond to chemotherapy. In fact, the significant activation of miR-296 target genes in MPBC identified by our group in a recent study represents an attractive target considering the previously described role of miR-296 in cisplatin-chemosensitivity [31,32].

We acknowledge the limitations inherent in the present study. Selection bias for treatment cannot be excluded in a retrospective study and lead-time bias may account for

differential outcomes. Nonetheless, we minimised the potential for lead-time bias in terms of time from diagnosis to definitive therapy by evaluating survival times from the first date of NAC or RC and including it in the multivariate model.

In conclusion, in patients with surgically resectable MPBC, NAC appears to confer benefit to patients with MIBC without tumour-associated hydronephrosis, while patients with cT1 disease present no reason to change standard practice of proceeding to upfront RC. Patients with hydronephrosis do poorly regardless of treatment paradigm, as do those who are not down-staged after NAC. However, further external validation studies are needed to support the proposed risk stratification before treatment recommendations can be made within the strata.

Conflicts of interest

The following authors had no conflicts of interest to declare: Mario I. Fernández, Stephen B. Williams, Daniel L. Willis, Rebecca S. Slack, Sahil Parikh, Charles C. Guo, and Louis L. Pisters. Rian J. Dickstein: Consulting or Advisory Role: Pacific Edge; Endo Pharmaceuticals. Edmund Chiong: Stock or Other Ownership: Tianjin Pharmaceuticals and Co., Ltd (China; Immediate Family Member), Honoraria: Janssen; Bayer; Astellas Pharma; Sanofi; AstraZeneca, Research Funding:

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Correspondence: Ashish M. Kamat, Department of Urology, Unit 1373, The University of Texas MD Anderson Cancer Center, 1155 Pressler, Houston, TX 77030, USA.

e-mail: akamat@mdanderson.org

Abbreviations: (MI)(MP)BC, (muscle-invasive) (micropapillary) bladder cancer; CART, classification and regression tree; CIS, carcinoma in situ; DSS, disease-specific survival; LVI, lymphovascular invasion; NAC, neoadjuvant chemotherapy; OS, overall survival; RC, radical cystectomy; TUR, transurethral resection.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Fig. S1 Risk groups as identified in CART analysis. The sample size is 101, as two patients had an unknown hydronephrosis status.