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ORIGINAL ARTICLE

A risk-stratified approach to neoadjuvant chemotherapy in muscle-invasive bladder cancer: implications for patients classified with low-risk disease

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Abstract

Purpose To validate published risk criteria for informing use of neoadjuvant chemotherapy (NAC) in patients with muscle-invasive bladder cancer (MIBC), and to examine outcomes of low-risk (LR) patients treated with immediate radical cystectomy (RC).

Methods We identified 1931 patients who underwent RC for MIBC from 1980 to 2016. Patients were considered high risk (HR) with hydronephrosis, lymphovascular invasion, variant histology and/or cT3/4 disease. Kaplan–Meier survival estimates were compared to patients classified as LR, and logistic regression was used to examine factors associated with pathologic downstaging.

Results A total of 1025 LR and 906 HR patients were identified. Median follow-up was 6.3 years (IQR 2.6–12), during which time 1321 (68%) patients died, 753 (39%) from bladder cancer. HR patients had significantly lower 5-year CSS than LR patients (50% vs. 68%, $p=0.001$). Of 561 cisplatin-eligible LR patients treated with RC without NAC, 293 (52%) had pathologic non-organ confined disease; of these, 81 (14%) received adjuvant chemotherapy; 78 (14%) did not due to a perioperative event, while 134 (24%) did not due to patient/provider choice. NAC in LR patients was associated with greater odds of pT0 (OR 3.05; $p<0.001$) and < pT2 (OR 2.53; $p<0.001$) disease, but was not significantly associated with CSS ($p=0.31$).

Conclusions Our results validate the proposed risk groups. Among LR patients treated without NAC, 52% experienced pathologic upstaging, and 14% were unable to receive adjuvant chemotherapy due to a perioperative event. These data support offering NAC to both HR and LR MIBC patients, and may be useful for patient counseling.

Keywords Bladder cancer · Radical cystectomy · Neoadjuvant therapy

Introduction

The use of cisplatin-based neoadjuvant chemotherapy (NAC) prior to radical cystectomy (RC) for patients with muscle-invasive bladder cancer (MIBC) is supported by level 1 evidence, with a resultant 5% overall survival improvement [1–3]. However, it has been suggested that not all MIBC patients may in fact benefit from NAC [4]. Indeed, only approximately 30–40% of patients experience a pathologic response to NAC, and emerging data have indicated that the likelihood of response is influenced by molecular subtype [2, 5]. This is particularly notable in the context of recent data suggesting that patients treated with NAC who have residual cancer at the time of cystectomy have inferior survival compared to stage-matched controls treated without NAC [6]. Unfortunately, current clinical staging of bladder

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cancer remains poor, with rates of pathologic upstaging ranging from 50 to 70% for cT2 patients [7, 8]. Few clinical features predicting response to NAC have been identified, including the presence of pure urothelial histology and a high proliferation rate on transurethral resection specimen, and more robust tools to predict response are needed [9, 10].

To address this gap, investigators at MD Anderson Cancer Center proposed a clinical risk stratification scheme [11], whereby patients with any of the following features are classified as high risk (HR): hydroureteronephrosis, lymphovascular invasion (LVI), cT3b–4a disease, or variant histology. They suggest using NAC for HR patients given an observed 30–40% risk of occult node-positive disease in this cohort, and alternatively advised cystectomy without NAC for low-risk (LR) disease, which was associated with a less than 10% chance of nodal disease and an approximately 80% 5-year cancer-specific survival [11]. However, concern remains that upstaged LR patients may not be able to receive adjuvant chemotherapy (AC), for example due to perioperative complications or difficulties during recovery, and the degree to which such LR patients would miss an opportunity for cure with a strategy of immediate RC with selective AC requires further examination.

Herein, therefore, our objectives were to validate these HR vs. LR criteria within our institutional dataset and to specifically investigate the outcomes of clinically low-risk patients treated with RC without NAC.

Materials and methods

Study population

Following Institutional Review Board approval, patients who underwent RC for cT2–4N0M0 urothelial carcinoma of the bladder between 1980 and 2016 were identified within the Mayo Clinic Cystectomy Registry. Patients received NAC at the discretion of their treating physician, which was typically based on patient performance status, underlying comorbidity, and preoperative renal function, although candidacy was not standardized. We excluded patients with nonurothelial histology, preoperative radiotherapy, and cT1 or less disease. According to the published risk criteria, patients were classified as HR if they had one or more of the following clinical features: hydroureteronephrosis, LVI, variant histology [specifically, only neuroendocrine carcinoma (encompassing small cell, large cell, and mixed small cell–large cell carcinoma) and micropapillary variants were included] in the transurethral resection specimen, or clinical T3/4 disease; otherwise, they were classified as LR [11]. Of note, we included all cT3/4 disease in the high-risk category, for although cT3b and cT4a disease were originally used to define high-risk disease [11], results of bimanual examination under anesthesia are frequently unavailable in our registry as many of the diagnostic transurethral resections were performed outside of our institution.

Given the retrospective nature of the study, postoperative surveillance was not standardized, but typically at our institution patients are followed with physical exam, laboratory studies, urine cytology, and cross-sectional imaging every 3 months for the first 2 years after surgery, every 6 months for the subsequent 2 years, and annually thereafter. Patients who follow up locally are contacted annually to gather follow-up details. Vital status is determined through either physician correspondence or death certificates. All pathologic specimens from RC were reviewed by a single genitourinary pathologist (J.C.C.), although transurethral resection specimens were not routinely re-reviewed.

Outcomes

Risk criteria were assessed by comparing cancer-specific survival (CSS) and overall survival (OS), stratified by risk group, among patients treated with RC without NAC, in an attempt to validate the original analysis [11].

To further examine the subset of LR patients, CSS and OS were compared between those treated with and without NAC. Among those who underwent RC without NAC, patients were further classified by whether they were eligible for neoadjuvant cisplatin, defined by a preoperative eGFR $\geq$ 60 mL/min/1.73 m^2 or if a patient with inadequate preoperative renal function experienced eGFR improvement to $\geq$ 60 mL/min/1.73 m^2 within 90 days of RC (in which case the preoperative value was assumed to reflect reversible acute kidney injury). Records for cisplatin-eligible LR patients who experienced pathologic upstaging to non-organ confined disease (pT3–4N0/X or pTanyN1–3) were examined to determine whether or not AC was administered within 90 days of RC. When AC was not used, patient records were individually reviewed by a single investigator blinded to survival outcome (T.D.L.) to determine reasons for reason for AC nonuse. These included a perioperative event (complication precluding use of chemotherapy within 90 days, renal function decline below 60 mL/min/1.73 m^2, functional status decline, or disease progression); provider choice (recommendation for surveillance over AC); or patient choice (consultation occurred with medical oncologist, but patient elected not to receive). If reasons were not clear, nonuse was attributed to a perioperative event if the patient experienced any complication within 90 days of RC, and to provider choice otherwise.

Statistical analysis

Continuous variables are reported with medians and interquartile range (IQR) and are compared using Mann–Whitney *U* test; categorical variables are reported as frequencies and

Table 1 Clinicopathologic features of the study cohort

	No NAC $n=1631$	NAC $n=300$	p value
Age (years), median (IQR)	69 (62–76)	65 (58–73)	< 0.001
Male, *n* (%)	1320 (81)	254 (85)	0.13
ECOG status, *n* (%)			0.04
0	1343 (82)	249 (83)	
1	227 (14)	48 (16)	
≥ 2	61 (3.7)	3 (1.0)	
Charlson Comorbidity Index, *n* (%)			0.047
0	785 (48)	160 (53)	
1	466 (29)	65 (22)	
≥ 2	380 (23)	75 (25)	
BMI (kg/m^2), median (IQR)	27 (24–30)	28 (25–31)	0.01
Smoking status, *n* (%)			0.32
Never	334 (21)	65 (22)	
Former	825 (51)	161 (54)	
Current	472 (29)	74 (25)	
Preoperative eGFR < 60 ml/min/1.73 m^2, *n* (%)	704 (46)	130 (45)	0.74
Postoperative eGFR < 60 ml/min/1.73 m^2, *n* (%)	483 (30)	104 (35)	0.10
Preoperative LVI, *n* (%)	143 (8.8)	45 (15)	0.001
Preoperative hydronephrosis, *n* (%)	442 (27)	92 (31)	0.20
Variant histology on biopsy, *n* (%)	13 (0.8)	6 (2.0)	0.052
Carcinoma in situ on biopsy, *n* (%)	341 (21)	76 (25)	0.09
Prior intravesical therapy, *n* (%)	351 (22)	56 (19)	0.26
Clinical T stage, *n* (%)			< 0.001
T2/T2a	1282 (79)	167 (56)	
T2b	69 (4.2)	5 (1.7)	
T3	182 (11)	86 (29)	
T4	98 (6.0)	42 (14)	
Risk category, *n* (%)			< 0.001
Low	921 (56)	104 (35)	
High	710 (44)	196 (65)	
Pathologic T stage, *n* (%)			< 0.001
T0	190 (12)	90 (30)	
< T2	290 (18)	64 (21)	
T2	376 (23)	46 (15)	
T3	650 (40)	72 (24)	
T4	125 (7.7)	28 (9.3)	
pN+, *n* (%)	360 (22)	69 (23)	0.53
Total lymph nodes removed, median (IQR)	13 (7–22)	23 (13–31)	< 0.001
Positive surgical margin, *n* (%)	45 (2.8)	6 (2.0)	0.45

IQR interquartile range, *ECOG* Eastern Cooperative Oncology Group, *BMI* body mass index, *GFR* glomerular filtration rate, *LVI* lymphovascular invasion, *SD* standard deviation

percentages and compared with Chi-square or Fisher's exact tests. CSS and OS were estimated using the Kaplan–Meier method and compared with the log rank test. Associations between clinical features and pathologic downstaging to pT0 and < pT2 disease were evaluated using multivariable logistic regression. Due to a large percentage of the patients missing data on the presence of carcinoma in situ at biopsy, sensitivity analysis was performed analyzing models with and without this feature. Cox proportional hazards models were built for CSS and OS among the LR patient subset, with features with $p < 0.1$ on univariable analysis included in the multivariable models. Significance was defined as $p \leq 0.05$ using two-tailed tests. Statistical analyses were performed using SAS, version 9.4 (SAS Institute Inc., Cary, NC).

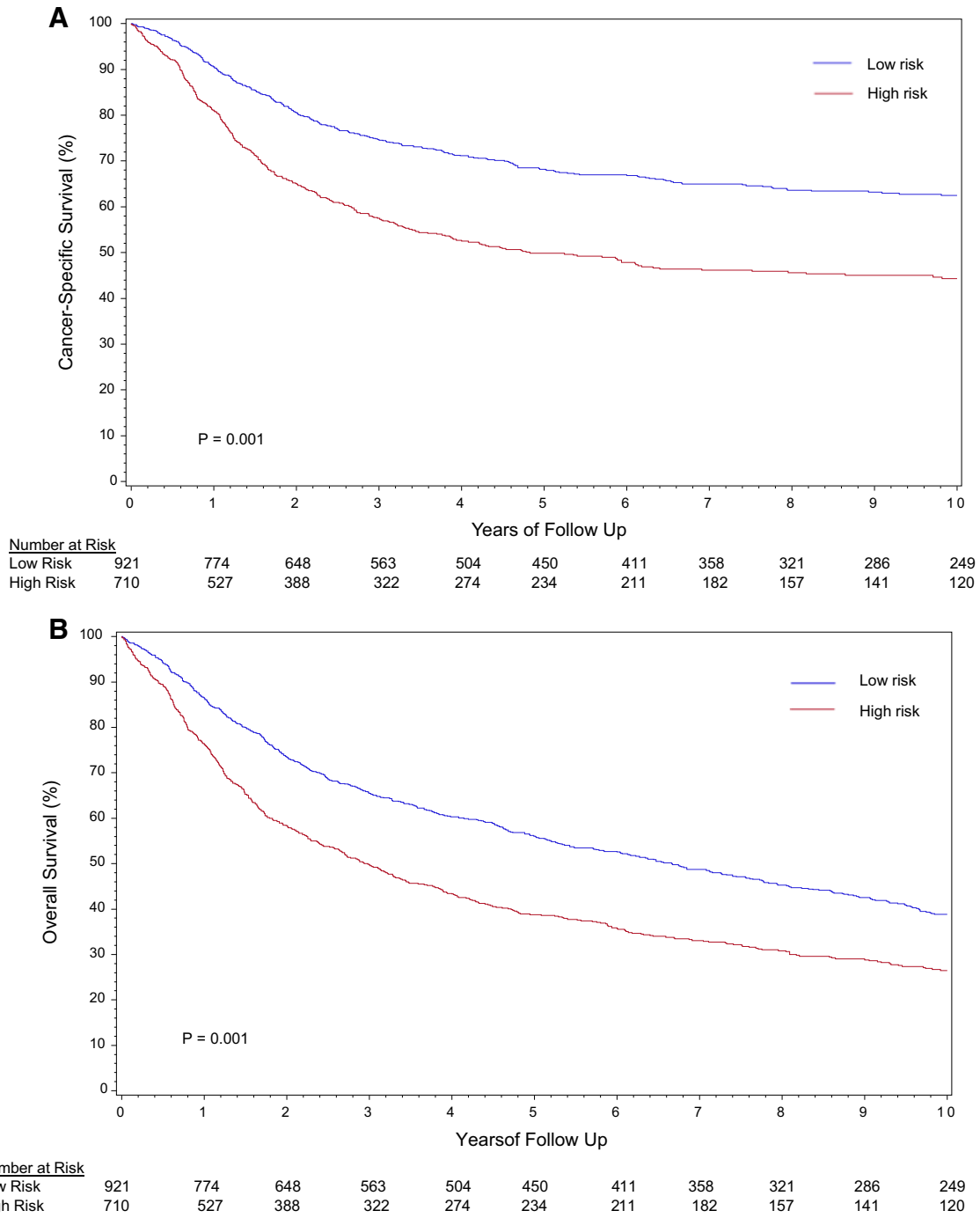

Fig. 1 Cancer-specific survival (**a**) and overall survival (**b**) estimates for patients treated with upfront radical cystectomy, stratified by risk group

Results

A total of 1931 patients were identified for study, including 1025 classified as LR and 906 as HR. Median follow-up among patients alive at last follow-up was 6.3 years (IQR 2.6–12 years), during which time 1321 patients died, including 753 from bladder cancer. Baseline characteristics for the study population are summarized in Table 1. There was no evidence of a changing trend in the rate of pathologic non-organ confined disease over the study period (Cochran–Armitage $p = 0.21$). Overall, 300 patients were treated with NAC, including 104 LR patients. Median time from last dose of NAC to RC was 59 days (IQR 39–95). A summary of chemotherapy regimens can be found in Supplementary Table 1.

Table 2 Multivariable logistic regression of features associated with pathologic downstaging among low-risk patients

Feature	No residual disease (pT0 N0)		Pathologic downstaging (< pT2 N0)	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age	1.01 (0.99–1.03)	0.21	1.00 (0.99–1.02)	0.79
Male sex	0.81 (0.52–1.27)	0.35	1.09 (0.76–1.56)	0.64
Smoker (current/former vs. none)	0.93 (0.60–1.42)	0.73	0.99 (0.71–1.40)	0.99
Charlson Comorbidity Index				
0	Ref		Ref	
≥ 1	0.61 (0.42–0.88)	0.01	0.69 (0.52–0.90)	0.01
BMI	1.01 (0.97–1.04)	0.73	1.02 (0.99–1.04)	0.26
Neoadjuvant chemotherapy	3.05 (1.89–4.93)	< 0.001	2.53 (1.64–3.89)	< 0.001
Clinical T stage				
T2/T2a	Ref		Ref	
T2b	0.71 (0.29–1.72)	0.45	0.55 (0.28–1.07)	0.08
Prior intravesical therapy	1.21 (0.78–1.86)	0.39	0.92 (0.66–1.29)	0.63
Carcinoma in situ on biopsy	0.82 (0.52–1.28)	0.38	1.91 (1.39–2.63)	< 0.001
Number of lymph nodes dissected	1.0 (0.99–1.01)	0.98	0.99 (0.98–1.00)	0.06

Ref reference

Among the 1631 patients treated with immediate RC, we found that patients classified as HR had a significantly worse 5-year CSS (50% vs. 68%, $p = 0.001$) and OS (39% vs. 56%, $p = 0.001$) compared to patients classified as LR (Fig. 1).

When we specifically evaluated LR patients, we noted that receipt of NAC was associated with significantly increased odds of downstaging to pT0 (OR 3.05, 95% CI 1.89–4.93, $p < 0.001$) as well as < pT2 (OR 2.53, 95% CI 1.64–3.89, $p < 0.001$) disease at RC (Table 2). LR patients who were downstaged experienced significantly improved CSS and OS compared to those who did not ($p < 0.001$ for both; Supplementary Figure). Despite this higher likelihood of downstaging, however, we did not observe a significant difference in CSS or OS between LR patients who did vs. did not receive NAC (Fig. 2). Sensitivity analysis excluding carcinoma in situ did not change the significance of reported results (data not shown). Features significantly associated with CSS and OS on Cox proportional hazards modeling are shown in Table 3. Of note, NAC was not univariately associated with either survival outcome ($p > 0.1$).

Meanwhile, outcomes for the 921 LR patients treated with immediate surgery are summarized in Fig. 3. A total of 561 of these patients were eligible for cisplatin-based NAC, of whom 268 (48%) had pathologic organ-confined disease; of the 293 with non-organ confined disease, 81 (14%) received AC, 78 (14%) were unable to receive AC due to perioperative events, and 134 (24%) did not receive AC due to patient/provider choice. Additional details on specific perioperative complications which precluded receipt of AC, as well as AC regimens utilized, are found in Supplementary Tables 2 and 3.

Discussion

In the present study, we validated the clinical risk groups previously proposed by investigators at MD Anderson [11]. In addition, we observed a 68% 5-year CSS among LR patients who underwent RC without NAC. Moreover, we found that for the LR patients treated with immediate RC who were candidates for NAC, 14% had an indication for AC but were unable to receive it due to a perioperative event—and thus missed an opportunity to receive timely perioperative cisplatin. Taken together, these data support continuing to offer NAC to LR patients, and may be useful for counseling patients who are considering foregoing NAC due to concerns over toxicity and/or the perception of modest benefit.

Current guidelines recommend offering NAC to all patients with MIBC [1–3]. However, such a strategy remains imperfect, as reports have suggested that patients who do not respond to NAC may experience inferior survival compared to stage-matched patients treated with RC without NAC [4, 6, 12]. Further, the noted 35% risk of grade 3 or chemotherapy-related toxicity [1, 2] emphasizes the importance of refining selection criteria for NAC in MIBC. Given that cisplatin-based NAC is the current standard of care for MIBC patients, it unlikely that a randomized trial of clinical risk-based NAC use will be undertaken in the future, and therefore observational data such as these will remain useful

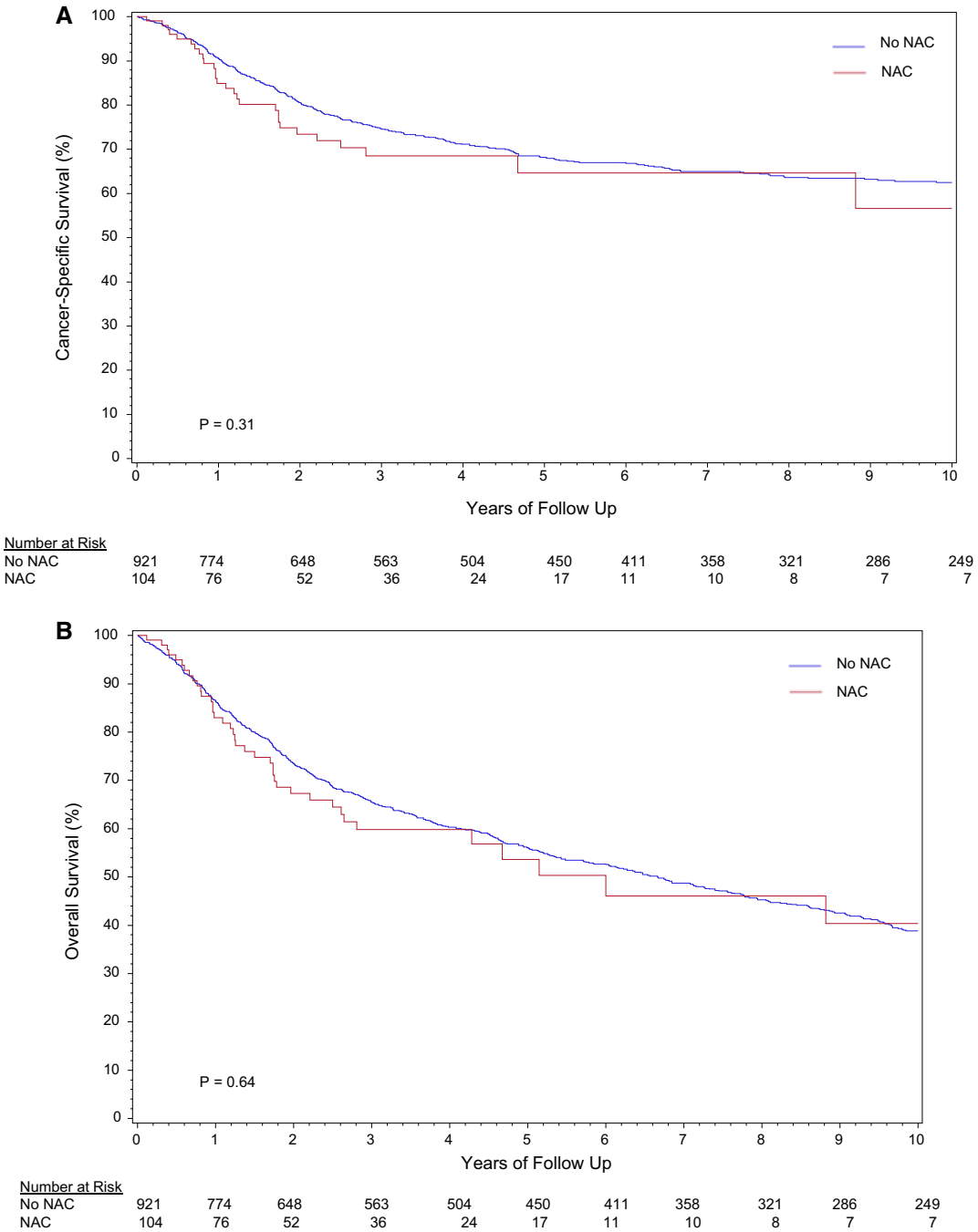

Fig. 2 Cancer-specific survival (**a**) and overall survival (**b**) estimates for low-risk patients, stratified by receipt of neoadjuvant chemotherapy

for helping LR patients contextualize the range of potential postoperative outcomes following RC.

The MD Anderson clinical risk stratification schema were developed to predict the likelihood of occult nodal metastases at RC, based on the reasoning that such patients are the most likely to benefit from NAC [11]. In their initial report of patients treated with RC without NAC, 5-year CSS was 83.5% among LR patients, similar to literature-reported rates in patients with pathologic organ-confined disease, despite a 49% upstaging rate in these patients [13]. Indeed, 5-year CSS rates of 77–100% have been observed among LR patients treated without NAC in validation sets from several other institutions [11, 14, 15]. On the basis of these data, the authors propose a management approach where LR patients would be treated with immediate RC and adjuvant AC as indicated, whereas HR patients are given NAC [11].

Table 3 Multivariable Cox proportional hazards models for survival outcomes among low-risk patients

Feature	Cancer-specific survival		Overall survival	
	Adjusted HR (95% CI)	*p* value	Adjusted HR (95% CI)	*p* value
Age	1.00 (0.99–1.01)	0.81	1.03 (1.02–1.04)	< 0.001
BMI			0.99 (0.98–1.01)	0.34
Charlson Comorbidity Index				
0	Ref	–	Ref	–
≥ 1	1.23 (0.98–1.54)	0.07	1.45 (1.24–1.70)	< 0.001
Adjuvant chemotherapy	0.62 (0.42–0.91)	0.01		
Pathologic T stage				
< T2	Ref	–	Ref	–
T2	2.21 (1.59–3.08)	< 0.001	1.52 (1.24–1.85)	< 0.001
T3/4	4.10 (3.04–5.54)	< 0.001	1.97 (1.63–2.38)	< 0.001
pN+	2.00 (1.46–2.74)	< 0.001	1.42 (1.14–1.77)	0.002
Total number nodes dissected			0.99 (0.98–1.01)	0.07
Positive margin	1.74 (1.09–2.75)	0.02	1.46 (1.01–2.14)	0.048

Ref reference

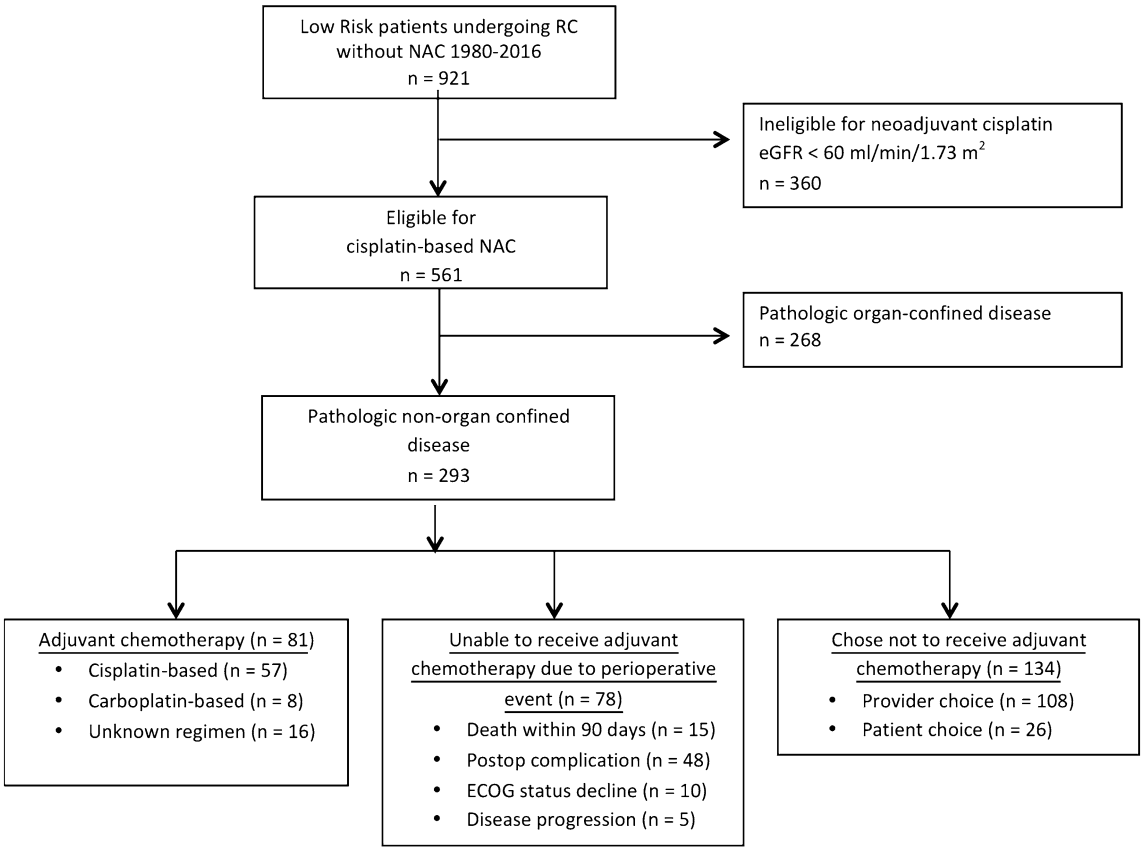

Fig. 3 Flow diagram demonstrating outcomes for 921 clinically low-risk patients treated with upfront radical cystectomy without neoadjuvant chemotherapy

The noted adverse survival among HR patients here supports use of NAC for this cohort. Among LR patients, we found that the use of NAC was associated with significantly higher odds of pathologic downstaging to < pT2 and pT0 disease. We did not observe a corresponding difference in survival, which may admittedly have been due to insufficient power for this outcome. The 14% of LR patients eligible for neoadjuvant cisplatin who were instead treated with

immediate RC and met pathologic eligibility for AC but could not receive it due to a perioperative event is considerably lower than the 45% rate of nonuse of AC attributed to comorbidity reported previously [11]. This difference is most likely explained by the fact that the present analysis only considered LR patients and those with adequate renal function to receive neoadjuvant cisplatin. Further, the 68% 5-year CSS observed here among LR patients treated without NAC is somewhat lower than the CSS reported previously [11, 14, 15]. One potential explanation for this discrepancy is the low number of patients in our cohort who were classified as having variant histologies on biopsy (19/1931, 1.0%). The reasons for this low rate of identified variant histology are several-fold. For one, these biopsy specimens did not undergo contemporary re-review at our institution. Moreover, risk classification relies on histologic examination of biopsy specimens, which have been shown to have a low sensitivity for detecting variant histologies [16]. In addition, inclusion of patients treated as far back as 1980 likely also contributed to misclassification, as awareness of several histologic subtypes did not occur until more recently [17]. As the presence of variant histology has been associated with a poor prognosis, a decrease in observed survival of patients classified as LR would occur if the variant histology was not recognized [17, 18].

Characterization of molecular subtypes of urothelial carcinoma and their associated chemosensitivity may improve patient selection for NAC [5, 19, 20]. In fact, the finding that tumors with a basal subtype respond most favorably to cisplatin [5, 19] has led to the development of a commercial testing platform designed to prospectively identify patients most likely to benefit from NAC [21]. The role of clinical parameters such as the risk criteria evaluated here for informing the optimal sequencing of therapy for patients with MIBC in the future continues to evolve, while data in the prostate cancer literature have demonstrated that including clinical variables can improve the discrimination of similar genome-based biomarkers on predicting outcome [22].

We recognize that interpretation of the data presented here is limited by nonrandomized allocation to NAC. The lack of a significant difference in survival outcomes in the LR group was likely attributable to the small number of LR patients who received NAC ($n = 104$), as NAC was associated with pathologic downstaging among the LR group, which has been recognized as a surrogate marker of survival [4, 12]. Other limitations include missing data on need for dose reduction with adjuvant chemotherapy and potential misclassification of risk group or adjuvant therapy use due to retrospective data analysis. Similarly due to the retrospective nature of the study, some patients with postoperative performance status decline but without overt complications may have been incorrectly classified as not receiving AC by provider choice instead of a perioperative event, biasing towards an underestimation of the number of patients who could not receive AC. Further, our assessment of cisplatin candidacy was based upon renal function alone, and we recognize that in clinical practice such decisions are more nuanced, taking into account patient age and performance status, as well as preexisting hearing loss or peripheral neuropathy.

Conclusion

Despite data supporting use of NAC in patients with MIBC, many patients or providers conclude that the toxicities of NAC are greater than its demonstrated benefits, and opt for immediate surgery with selective AC as indicated [23–26]. The noted adverse survival among HR patients here supports use of NAC for this cohort. Further, we observed that LR patients experienced a 5-year CSS of 68%, and that 14% of LR patients treated without NAC experienced pathologic upstaging at RC but could not receive timely AC postoperatively. These data support offering NAC to all eligible MIBC patients irrespective of risk classification, and may aid in informed discussion of treatment sequencing for LR patients.

Author contributions Protocol/project development: TDL, IF, VS, PHS, PT, SAB. Data collection or management: TDL, IF, PT, JCC, SAB. Data analysis: TDL, PT, SAB. Manuscript writing/editing: TDL, IF, VS, PHS, MKT, RHT, RJK, PT, JCC, SAB.

Compliance with ethical standards

Conflict of interest All authors certify they have no conflicts of interest to disclose.

Ethical approval Study was approved by the Mayo Clinic Institutional Review Board: 17-005856.

Informed consent Due to retrospective nature of study, waiver of informed consent was obtained by the Institutional Review Board.

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