Refining Patient Selection for Neoadjuvant Chemotherapy before Radical Cystectomy

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Abstract

Purpose—We evaluated the survival of patients with muscle invasive bladder cancer undergoing radical cystectomy without neoadjuvant chemotherapy to confirm the utility of existing clinical tools to identify low risk patients who could be treated with radical cystectomy alone and a high risk group most likely to benefit from neoadjuvant chemotherapy.

Materials and Methods—We identified patients with muscle invasive bladder cancer who underwent radical cystectomy without neoadjuvant chemotherapy at our institution between 2000 and 2010. Patients were considered high risk based on the clinical presence of hydroureteronephrosis, cT_{3b}-T_{4a} disease, and/or histological evidence of lymphovascular invasion, micropapillary or neuroendocrine features on transurethral resection. We evaluated survival (disease specific, progression-free and overall) and rate of pathological up staging. An independent cohort of patients from another institution was used to confirm our findings.

Results—We identified 98 high risk and 199 low risk patients eligible for analysis. High risk patients exhibited decreased 5-year overall survival (47.0% vs 64.8%) and decreased disease specific (64.3% vs 83.5%) and progression-free (62.0% vs 84.1%) survival probabilities compared to low risk patients (p <0.001). Survival outcomes were confirmed in the validation subset. On final pathology 49.2% of low risk patients had disease up staged.

Conclusions—The 5-year disease specific survival of low risk patients was greater than 80%, supporting the distinction of high risk and low risk muscle invasive bladder cancer. The presence

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of high risk features identifies patients with a poor prognosis who are most likely to benefit from neoadjuvant chemotherapy, while many of those with low risk disease can undergo surgery up front with good expectations and avoid chemotherapy associated toxicity.

Keywords

urinary bladder neoplasms; cystectomy; neoadjuvant therapy; risk; outcomes assessment

Radical cystectomy with pelvic lymph node dissection is the gold standard for muscle invasive bladder cancer. Advances in surgical technique and perioperative care have improved outcomes after RC, but many patients experience relapse after surgery, likely from micrometastasis present at RC.[1,2] The Intergroup trial (SWOG [Southwest Oncology Group]-8710) reported that patients randomized to 3 cycles of neoadjuvant methotrexate, vinblastine, doxorubicin and cisplatin followed by RC had an improved median survival of 77 months vs 46 months with RC alone.[3]

Although there was a clear survival benefit in the entire cohort that received NAC, the most dramatic improvement in median survival from 24 to 65 months was seen in patients with T_3 or greater disease. These data have been borne out in meta-analyses showing that cisplatin based NAC combinations significantly improve overall survival, translating into an approximate 6% risk reduction of death at 5 years.[4,5] However, this comes with some cost. SWOG-8710 reported grade 3 and 4 toxicity in 35% and 37% of patients, respectively, most of which was related to granulocytopenia and mucositis.[3] The International Collaboration of Trialists reported similar grade 3 and 4 hematological toxicity in comparable patients treated with cisplatin, methotrexate and vinblastine.[4]

If NAC always provided a clear survival advantage or was free of serious toxicity, the decision to treat all eligible patients would be simple. However, since multimodal therapy provides only modest benefit with notable toxicity and, at present, we cannot reliably identify likely responders, it is challenging to decide on the appropriate course of therapy.[3,4] Rather than recommending NAC for all patients with MIBC, we actively adopted a risk adapted approach to select individuals with high risk features for NAC, and in doing so, spared the morbidity and expense for those with low risk disease for whom RC alone should be curative. In the last 3 decades our approach to the clinical staging and risk assessment of MIBC was based on previous studies from our institution examining adjuvant chemotherapy in patients with BC,[6] and has evolved beyond AJCC (American Joint Committee on Cancer) criteria[7] to incorporate 3-D imaging, EUA and TUR to identify a 3-D palpable mass (cT_{3b}) or local invasion to adjacent viscera (cT_{4a}), the presence of hydroureteronephrosis, and histological evidence of LVI, micropapillary, and/or small cell features to meet our definition of high risk MIBC. Our published data revealed a 30% to 40% incidence of occult lymph node metastasis in the HR population, while the historical risk in those classified as LR was less than 10%.[8,9] In this study we defined clinical LR MIBC with outcomes comparable to those of organ confined MIBC when treated with RC alone, and validated the results in an independent subset from another institution.

Materials and Methods

On approval from the MDACC internal review board, all patients who underwent RC without neoadjuvant chemotherapy for confirmed MIBC between January 2000 and December 2010 were identified. Patients dying of surgical complications and those with incomplete followup were excluded from the study. Patients were classified as HR or LR based on the presence of identifiable preoperative HR features (hydroureteronephrosis, cT_{3b}-T_{4a} disease [eg palpable 3-D mass on EUA, prostate stromal invasion], LVI or VH on TUR). VH was defined as histological evidence of neuroendocrine or micropapillary disease on biopsy.

Comprehensive clinical, pre-RC laboratory and final pathological data were collected, and extensively reviewed to ensure completeness and accuracy. As is standard practice at MDACC, all outside pathological and radio-graphic data were independently rereviewed, and all patients underwent repeat staging TUR and EUA before radical cystectomy. RC was performed with intent to cure, and included extended bilateral pelvic lymph node dissection with en bloc RC and urinary diversion. Tumor staging was based on the *AJCC Cancer Staging Manual*.[7]

Outcomes of interest included survival (OS, DSS and PFS) and rate of pathological up staging. Kaplan-Meier methods were used to calculate OS. Multivariable competing risks regression analysis, based on the model by Fine and Gray,[10] was used to calculate cause specific mortality and DSS and PFS probabilities, using death from nonBC as the competing variable. Followup was defined as time from RC to death or last known followup (OS and DSS), or to documented date of disease recurrence (PFS). Pearson chi-square analysis was used to identify variables differing between HR and LR patients. Independent predictors of pathological up staging were identified using multivariable logistic regression analysis. For the validation subset (USC) patients were grouped as high or low risk based on MDACC criteria, and identical survival analyses were performed as previously described. All analyses were performed using STATA® version 12 and p 0.05 was considered significant.

Results

Of 1,285 patients who underwent RC at MDACC between 2000 and 2010, a total of 98 HR and 199 LR eligible patients who underwent radical cystectomy without NAC were identified. Median followup was 40.6 months (IQR 19.3, 72.2) for the entire cohort and 56.7 months (IQR 29.7, 91.7) for those alive at the time of analysis. Demographic and clinical characteristics for the entire cohort and clinical characteristics of the HR cohort are listed in tables 1 and 2, respectively. A total of 36 (36.7%) HR and 37 (18.6%) LR patients died of BC (p = 0.001). On final pathology 26 (26.5%) HR cases were down staged to pT_2N_0 or less with no HR features (VH or LVI) present while 98 (49.2%) LR cases were reclassified to HR (pT_3 or greater, node positive disease and/or HR histological features), including 83 (84.7%) pT_3 or greater and 29 (29.6%) with positive nodes (table 3). On multivariable analysis including all preclinical variables, the sole predictor of pathological up staging in the LR cohort was a preoperative hemoglobin level less than the lower limit of normal (OR 2.35, 95% CI 1.29, 4.30, p = 0.005).

OS, and DSS and PFS probabilities were each significantly decreased, and CSM was increased in the high vs low risk patient cohorts (table 4 and fig. 1). Patients with multiple HR features (20) demonstrated an increased risk of CSM compared to those with only 1 HR feature (78) (SHR 2.22, 95% CI 1.09, 4.51, p = 0.028). Survival based on disease reclassification after RC is shown in table 5 and figure 2. On multivariable analysis HR patients with organ confined disease and no HR features on final pathology had a similar CSM (SHR 1.16, 95% CI 0.31, 4.32, p = 0.829) and DSS probability as clinically defined LR patients who remained LR on final pathology. However, pathological up staging in LR patients was independently associated with an increase in CSM (SHR 3.55, 95% CI 1.61, 7.84, p = 0.002) and decreased DSS probability compared to LR patients who remained LR. However, importantly, HR patients who remained HR exhibited the lowest DSS probability compared to all other groups (p <0.001).

A total of 51 patients, 32 (16.2%) LR and 19 (19.4%) HR, received adjuvant chemotherapy, the majority of whom (98.0%) were high risk based on final pathology. Reasons for not receiving adjuvant chemotherapy included patient comorbidity (45%), physician choice (38%) or patient choice (16%). Overall, patients at MDACC who were selected for adjuvant chemotherapy had a decreased CSM (SHR 0.42, 95% CI 0.21, 0.87, p = 0.019). However, 5-year DSS probabilities were higher in HR patients who received adjuvant chemotherapy than for those who were observed, with 82.7% vs 67.3% (LR up staged to HR) and 73.3% vs 52.4% (HR remaining HR). A total of 37 (37.8%) HR and 35 (17.6%) LR patients experienced progression (p <0.001) at a median of 10.7 (95% CI 6.8, 17.8) and 9.1 (95% CI 5.6, 14.9) months, with a median time from RC to death of 18.2 (95% CI 13.5, 29.5) and 18.1 (95% CI 12.2, 27.4) months, respectively. The progression rate was lowest in LR cases that remained LR and highest in HR cases that remained HR on final pathology (table 5). Of those with progression 23 (65.7%) HR and 22 (64.7%) LR patients underwent salvage chemotherapy. There was no significant survival difference based on the delivery of salvage chemotherapy.

The MDACC criteria for preoperative high vs low risk disease were applied to an independent subset of patients who underwent RC without NAC at another institution (USC) during a 25-year period. This independent cohort consisted of 1,138 LR and 644 HR patients (tables 6 and 7). Consistent with our data, patients with pre-RC HR features demonstrated decreased OS and increased CSM compared to LR patients (fig. 3). Five-year OS, DSS and PFS probabilities were all significantly lower in patients with HR features present before RC compared to LR patients. Importantly, the percentage of HR patients with each pre-RC high risk feature and 5-year survival probabilities was similar between the MDACC and USC cohorts.

Discussion

While NAC has become the accepted standard of care for the treatment of MIBC on the basis of convincing level I evidence, contemporary studies show dramatic underuse of this approach, with less than 20% of patients receiving the recommended care.[3,11] Possible explanations include the modest overall benefit in 5-year survival afforded by NAC to an unselected population with MIBC, since only 30% to 40% of cases are rendered pT_1 or less

and reliable identification of those who respond this dramatically is not yet feasible.[4,5] Perioperative mortality rates are low, but morbidity is not insignificant and is unacceptable if there is no benefit to be gained from NAC.[3,4] Not everyone seems to require NAC, as patients with organ confined MIBC, who account for up to 50% of those in contemporary surgical series, have approximately 80% durable DSS.[1] The dilemma is articulated by the inadequacy of current clinical staging strategies that leave more than 50% of patients with extravesical disease clinically under staged. We face the quandary of offering NAC to every eligible patient with MIBC regardless of risk, or the challenge of improving clinical staging to accurately identify those patients with HR features likely to experience progression despite RC. A more selective approach to NAC should translate into a higher rate of prescribing such care to those most likely to benefit.

Numerous studies have highlighted the inaccuracy of clinical staging in BC with the incidence of pathological up staging ranging from 49% to 72% and patients with up staged disease more likely to die of BC.[12–15] The pathological stage of those cases we designate as HR at MDACC is of particular concern, as those with LVI on TUR or cT_3-cT_{4a} disease had an 86% rate of nonorgan confined disease at RC. A pooled analysis of 778 patients who underwent RC at 4 different academic medical centers found pathological up staging in 42% with only 36% of patients considered to have clinical nonorgan confined disease (pT_3N_0 or greater, or pT_xN+) at diagnosis.[17] Most recently, in studying patients with suspected cT_2 disease only, Canter et al found a 73% rate of up staging to pT_3/T_4 or pN+ with 5-year recurrence-free survival and disease specific survival of 56.5% and 59.5%, respectively.[18] In comparison, 49% of our LR patient cohort was reclassified as HR at radical cystectomy with a DSS probability of approximately 75% at 5 years. Surprisingly we found that a preoperative hemoglobin less than the lower limit of normal was the only independent predictor of pathological up staging, which may indicate that baseline anemia may be a surrogate for occult aggressive disease in addition to other HR features, and has recently been described by other investigators as well.[19]

LVI is widely accepted as a HR feature for BC, as multiple studies have shown LVI to be associated with higher pathological stage, higher grade, positive surgical margins, and worse overall survival and recurrence-free survival.[20–22] It is possible that our practice of repeat TUR before RC identifies more patients with LVI than was appreciated by review of the original pathology. As with LVI, multiple studies have demonstrated that the presence of hydroureteronephrosis or VH is associated with more advanced disease on final pathology as well as being an independent predictor of decreased DSS.[23–26] In support of the inclusion of small cell histology in HR MIBC, we can look to our own experience. In a review of 46 patients who underwent RC for small cell BC, the 5-year DSS was 36%. However, in those patients treated with NAC, survival approached that of our LR group at 78%.[27,28] This stark trend served as the basis of a phase 2 clinical trial of NAC in the setting of small cell BC.[29] Due to the overlap of this phase 2 trial with the cohort used in the present study, there were no patients included in our present analysis with pre-RC small cell histology.

While there are inherent limitations of single center retrospective reviews, our results were confirmed using an independent cohort from another high volume institution. Not only did we find that HR patients identified from this independent cohort exhibited decreased

survival and increased CSM compared to LR patients, we found that 5-year overall, and disease specific and progression-free survival probabilities were remarkably similar between the 2 institutions. These data indicate that this iteration of our risk stratification is consistent across institutions. Although we lack a control group of LR patients treated with NAC, given an 80% 5-year DSS and the appreciated survival benefits to NAC identified by randomized prospective trials, until we can prospectively identify likely responders to NAC, the advantage to the LR group would likely be trivial. We also did not present data showing that patients with HR features benefit from NAC as this is outside the scope of the current report.

Our objective was to define a clinical LR disease state with a disease specific survival after RC comparable to that of organ confined MIBC to justify our two-pronged approach to the management of MIBC (fig. 4). Our results indicate that carefully selected patients with low risk MIBC achieve a DSS probability of approximately 80% at 5 years after RC, which is comparable to those with pT_2 disease. Notably if patients remain LR after RC, 5-year DSS probability is greater than 90%. The 5-year DSS probability of those with disease pathologically up staged or found to harbor HR histological features decreased significantly to approximately 75%, but was still far superior to HR patients who remained HR after RC.

Our greatest concern is that despite a concerted effort to refine clinical staging, we still fail to identify a significant number of HR patients who may be candidates and might benefit from NAC. Our published experience provides assurance that this limitation does not necessarily compromise survival since we reported that adjuvant was as effective as neoadjuvant chemotherapy in the high risk setting.[16] Indeed 31 of the 98 patients with disease pathologically up staged received adjuvant chemotherapy with 5-year DSS probabilities greater than 80%, indicating that adjuvant chemotherapy offers an acceptable 5-year DSS even with pathological up staging. However, this off protocol practice does not match the level of commitment to adjuvant chemotherapy that we anticipated from previous experience.[16] Regardless, patients classified as LR before RC should be counseled that they may still need adjuvant chemotherapy given the high risk of pathological up staging.

Conclusions

The accumulation of experience at our institution and in the literature directed our current strategy of risk adapted NAC. Weighing the modest survival advantage with the potential toxicity led us to offer NAC to those patients at highest risk and most likely to benefit from treatment. Our results indicate that patients with MIBC without high risk features can achieve a DSS comparable to those with organ confined MIBC despite the fact that approximately 50% have disease under staged. Nonetheless, an important challenge remains to further refine clinicopathological assessment to limit clinical under staging and assure that HR individuals are identified for NAC.

Acknowledgments

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Abbreviations and Acronyms

3-D	3-dimensional
BC	bladder cancer
CSM	cause specific mortality
DSS	disease specific survival
EUA	examination under anesthesia
HR	high risk
LR	low risk
LVI	lymphovascular invasion
MDACC	University of Texas M.D. Anderson Cancer Center
MIBC	muscle invasive bladder cancer
NAC	neoadjuvant chemotherapy
OS	overall survival
PFS	progression-free survival
RC	radical cystectomy
TUR	transurethral resection

| **USC** | University of Southern California |
| **VH** | variant histology |

Figure 1.
Survival of patients with MIBC who underwent radical cystectomy without NAC based on clinical high vs low risk (MDACC 2000 to 2010). *A*, Kaplan-Meier survival curve demonstrating overall survival. *B*, cumulative incidence of bladder cancer specific mortality, accounting for competing risk of nonbladder cancer death, and adjusted for age at surgery, gender, race, preoperative anemia, smoking history and year of surgery.
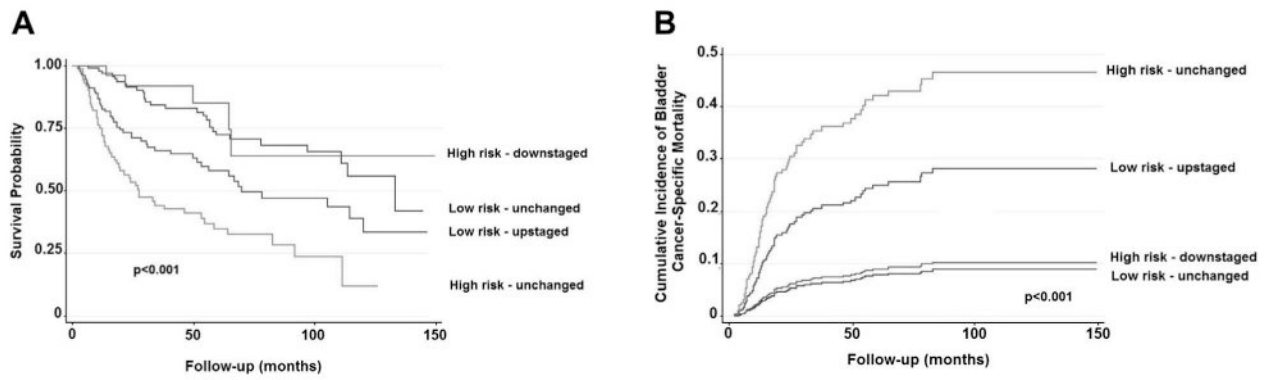
Figure 2.
Survival of patients with MIBC who underwent radical cystectomy without NAC based on clinical high vs low risk and reclassification based on final pathology (MDACC 2000 to 2010). *A*, Kaplan-Meier analysis demonstrating overall survival. *B*, cumulative incidence of bladder cancer specific mortality, accounting for competing risk of nonbladder cancer death, and adjusted for age at surgery, gender, race, preoperative anemia, smoking history, history of intravesical therapy, margin status, total lymph nodes resected, adjuvant chemotherapy and year of surgery.
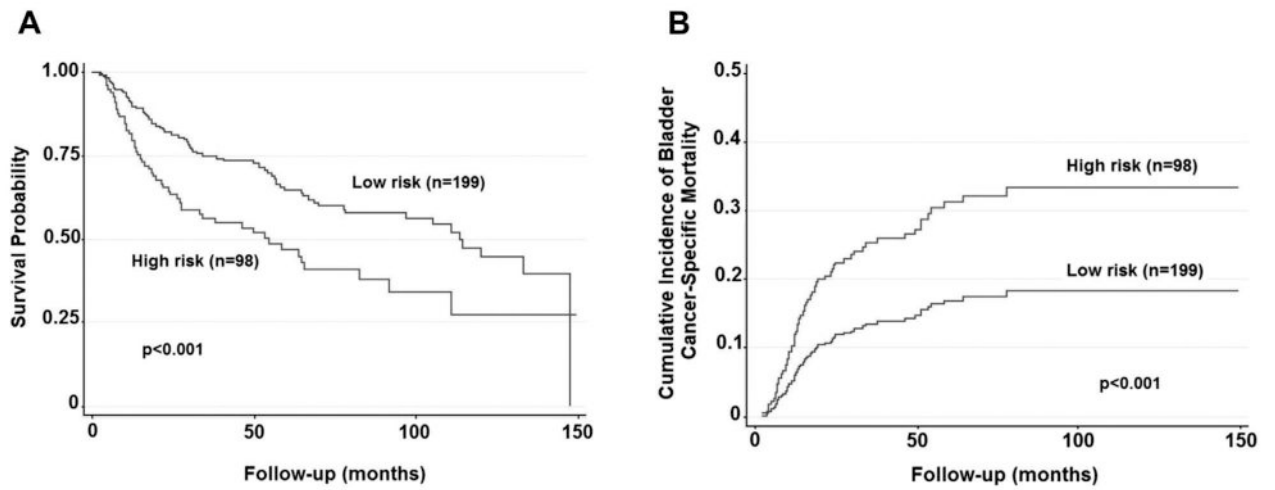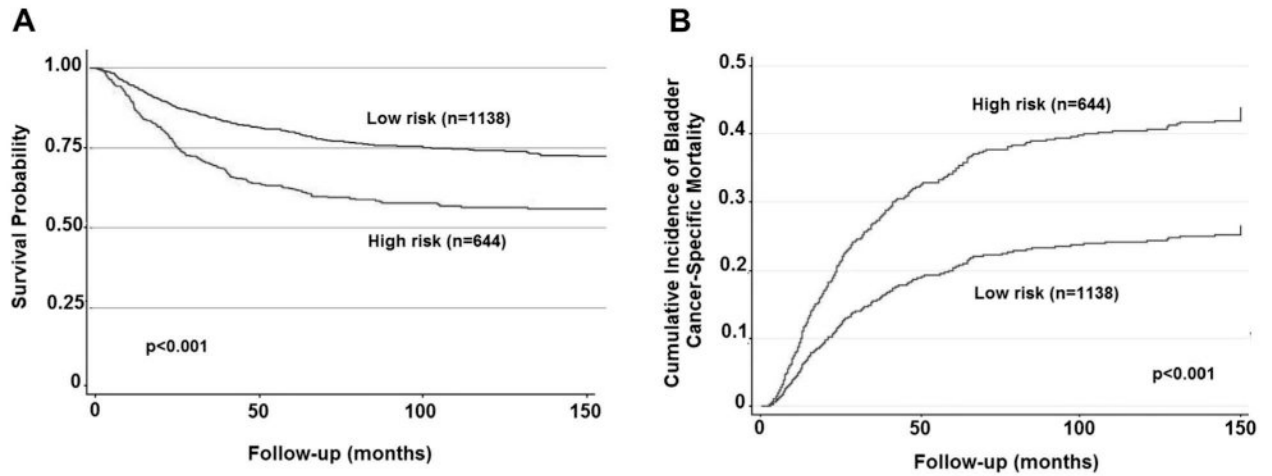
Figure 3.
Survival of patients with MIBC who underwent radical cystectomy without NAC based on clinical high vs low risk (USC 1983 to 2008). *A*, Kaplan-Meier survival curve demonstrating overall survival. *B*, cumulative incidence of bladder cancer specific mortality, accounting for competing risk of noncancer death, and adjusted for age at surgery, gender, race, preoperative anemia, smoking history and year of surgery.

Figure 4.
Neoadjuvant platform for clinical based staging and therapy for bladder cancer.

Table 1

Baseline demographic and clinical characteristics of patients undergoing RC

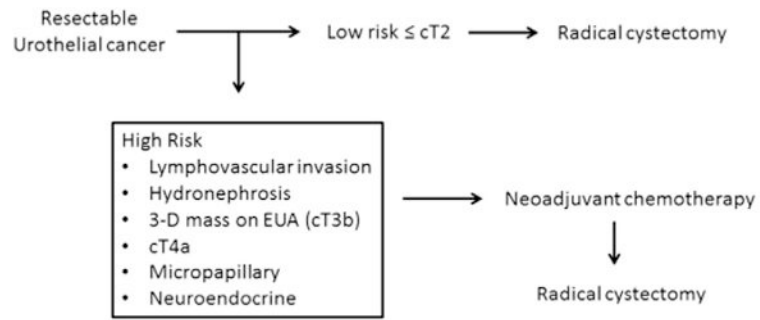|	Low Risk	High Risk	p Value
Median age (IQR)	69.6 (61.3, 74.8)	72.6 (63.1, 79.6)	0.366
No. gender (%):			0.05
F	22 (11.1)	19 (19.4)	
M	177 (88.9)	79 (80.6)	
No. race (%):			0.829
Caucasian	180 (90.5)	86 (87.0)	
African-American	5 (2.5)	4 (4.1)	
Hispanic	13 (6.5)	7 (7.1)	
Asian	1 (0.5)	1 (1.0)	
No. smoking history (%):			0.557
Never	43 (21.9)	23 (23.5)	
Former	115 (58.7)	61 (62.2)	
Current	38 (19.4)	14 (14.3)	
No. body mass index (kg/m^2) (%):			0.150
Less than 25.0	47 (24.9)	38 (35.5)	
25.0–29.9	84 (44.4)	41 (38.3)	
30.0–34.9	43 (22.8)	17 (15.9)	
35.0 or Greater	15 (7.9)	11 (10.3)	
No. prior intravesical treatment (%)	46 (23.1)	18 (18.4)	0.349
No. concomitant carcinoma in situ (%)	52 (26.1)	28 (28.6)	0.656
No. clinical tumor stage (%):			<0.001
cT$_1$	0 (0)	29 (29.6)	
cT$_2$	199 (100.0)	50 (51.0)	
cT$_{3b}$	0	14 (14.3)	
cT$_{4a}$	0	5 (5.1)	
Median mos from TUR to RC (IQR)	1.5 (1.0, 2.4)	1.4 (0.9, 1.9)	0.321
No. preop hemoglobin (%):			0.063
12-16 (female) or 14-18 (male)	104 (52.3)	42 (42.0)	

	Low Risk		High Risk		p Value
Less than 12 (female) or less than 14 (male)	95	(47.7)	58	(59.2)	
Median pre-RC laboratory values (IQR):					
Glomerular filtration rate	74.5	(62, 83.5)	69	(50, 85)	0.585
Platelet count	229	(193, 277)	248	(210, 326)	0.161
Creatinine	1.0	(0.9, 1.3)	1.0	(0.9, 1.4)	0.928
Albumin	4.1	(4.0, 4.4)	4.1	(3.8, 4.4)	0.530
Calcium	9.1	(8.9, 9.4)	9.1	(8.8, 9.4)	0.988
Alkaline phosphatase	77.5	(66, 89)	77	(63, 97)	0.960
Lactate dehydrogenase	447.5	(397.5, 514)	432	(393, 505)	0.461
No. history of malignancy (%)	22	(11.1)	18	(18.4)	0.090

Table 2

Baseline clinical characteristics of HR patients

	No. (% of HR cohort)
Hydroureteronephrosis	39 (39.8)
LVI on TUR	38 (38.8)
cT_3 or cT_4 disease	20 (20.4)
Micropapillary on biopsy	25 (25.5)
Total HR features:	
1	77 (78.6)
2	18 (18.4)
3	3 (3.1)
Reason for not undergoing NAC:	
Comorbidity	38 (38.8)
Physician choice	31 (31.6)
Pt choice	11 (11.2)
Unknown	18 (18.4)

Table 3

Final pathological data of patients with MIBC

	Low Risk		High Risk		p Value
No. pathological tumor status (%):					0.003
T_0	24	(12.1)	2	(2.0)	
Tis	25	(12.6)	9	(9.2)	
T_a	5	(2.5)	6	(6.1)	
T_1	9	(4.5)	7	(7.1)	
T_2	53	(26.6)	16	(16.3)	
T_3	74	(37.2)	48	(49.0)	
T_4	9	(4.5)	10	(10.2)	
No. pos lymph nodes (%):					0.025
0	158	(79.4)	64	(65.3)	
1–2	27	(13.6)	20	(20.4)	
3 or More	14	(7.0)	14	(14.3)	
Median lymph nodes examined (IQR)	15	(9, 24)	15.5	(9, 29)	0.934
No. extranodal extension in N+ (%)	12	(29.3)	15	(44.1)	0.012
No. pos surgical margin (%)	5	(2.5)	5	(5.1)	0.245
No. concomitant carcinoma in situ (%)	98	(49.3)	54	(55.1)	0.342
No. LVI (%)	46	(23.1)	46	(46.9)	<0.001
Median cc estimated blood loss (IQR)	975	(600, 1,500)	900	(675, 1,300)	<0.001
No. diversion (%):					0.096
Ileal conduit	107	(53.4)	62	(63.9)	
Studer neobladder	88	(44.2)	31	(32.0)	
Indiana pouch	4	(2.0)	4	(4.1)	
Median mins surgical duration (IQR)	405	(329, 492)	383	(322, 477)	0.445
No. blood transfusion at surgery (%)	108	(54.3)	68	(69.4)	0.013

Table 4

Survival outcomes of patients with MIBC undergoing radical cystectomy without NAC based on preoperative high vs low risk classification

	Low Risk	High Risk
Overall survival OR (95% CI):		
1-Yr	90.3 (85.2, 93.7)	80.5 (71.2, 87.1)
3-Yr	75.0 (68.0, 80.7)	56.3 (45.5, 65.6)
5-Yr	64.8 (56.7, 71.8)	47.0 (35.8, 57.4)
% DSS probability:[*]		
1-Yr	94.3	88.8
3-Yr	85.9	73.7
5-Yr	82.7	68.2
% PFS probability:[*]		
1-Yr	90.7	78.3
3-Yr	86.2	69.0
5-Yr	83.6	63.9

All values p <0.001.

[*] Calculated using stepwise competing risks regression analysis with nonbladder cancer death as competing variable. Adjusted for age at surgery, gender, race, preoperative anemia, year of surgery and smoking history.

Table 5

Outcome data of patients with MIBC undergoing RC without NAC based on preoperative high vs low risk classification and final pathology

	LR + Remained LR	LR but Up Staged	HR but Down Staged	HR + Remained HR
No. pts	101	98	26	72
No. progression rate (%)	11 (10.9)	24 (24.5)	6 (23.1)	31 (43.1)
Overall survival OR (95% CI):				
1-Yr	96.9 (90.7, 99.0)	83.7 (74.7, 89.7)	100	73.5 (61.6, 82.2)
3-Yr	84.1 (74.6, 90.3)	66.0 (55.4, 74.7)	91.6 (70.5, 97.9)	44.3 (32.4, 55.5)
5-Yr	72.2 (60.6, 80.9)	57.8 (46.1, 67.7)	85.1 (56.4, 95.1)	35.0 (23.5, 46.7)
% DSS probability:[*]				
1-Yr	97.7	92.1	97.4	85.6
3-Yr	93.7	79.4	92.8	64.7
5-Yr	92.2	74.9	91.0	57.9
% PFS probability:[*]				
1-Yr	94.6	87.0	88.1	74.1
3-Yr	91.8	80.9	82.4	63.2
5-Yr	90.3	77.6	79.3	56.6

[*] Calculated using multivariable competing risks regression analysis with nonbladder cancer death as competing variable. Adjusted for age at surgery, gender, race, preoperative anemia, year of surgery, smoking history, total lymph nodes resected, margin status and adjuvant chemotherapy.

Table 6

Characteristics of patients with MIBC at USC (1983–2008) considered high risk before surgery

	No. (% of HR cohort)
Hydroureteronephrosis	313 (48.6)
LVI on TUR	292 (45.3)
cT_3 or cT_4 disease	154 (23.9)
Micropapillary or small cell on biopsy	19 (3.0)
Total HR features:	
1	521 (80.9)
2	112 (17.4)
3	11 (1.7)

Table 7

Survival of patients with MIBC at USC (1983–2008) based on the presence or absence of preoperative high risk features

	Low Risk	High Risk
Overall survival OR (95% CI):		
1-Yr	90.1 (88.3, 91.9)	85.3 (82.5, 88.1)
3-Yr	76.2 (73.6, 78.8)	63.2 (59.2, 67.2)
5-Yr	67.9 (64.9, 70.9)	52.4 (48.0, 56.8)
% DSS probability:[*]		
1-Yr	95.0	90.7
3-Yr	84.5	72.9
5-Yr	79.8	65.6
% PFS probability:[*]		
1-Yr	89.3	80.7
3-Yr	79.3	64.6
5-Yr	75.8	59.3

All values p <0.001.

[*] Calculated using multivariable competing risks regression analysis with non-bladder cancer death as competing variable.