Changing trends in utilization of neoadjuvant chemotherapy in muscle-invasive bladder cancer

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Introduction: *To reassess use of perioperative chemotherapy in muscle-invasive bladder cancer (MIBC) following implementation of monthly multidisciplinary meetings to facilitate optimal oncologic treatment. We previously reported from 2003 to 2008 17% of eligible patients with bladder cancer received cisplatin-based neoadjuvant chemotherapy (NAC) at our institution.*

Materials and methods: *A retrospective review of all patients who underwent radical cystectomy (RC) between 2008 and 2012 was performed. Information on clinical and pathologic stage, renal function, perioperative chemotherapy (CTX) use and oncologic outcomes was collected. Rationale for utilization decisions was obtained from physician encounter notes. Primary outcome was use of CTX among eligible patients. Secondary measures were type of CTX, pathologic and survival outcomes.*

Results: *Among 261 patients undergoing RC for bladder cancer, 162 were eligible for NAC. Overall 40.7% (n = 66) received NAC, and 86.4% were given platinum. Patients given NAC were younger and had more advanced clinical stage. The degree of chronic kidney disease (CKD) (0-3) did not impact likelihood of receiving NAC. NAC patients were more likely to be downstaged to non-muscle-invasive disease (21.2% versus 7.3% $p < 0.01$) or have a complete pathologic response (12.1% versus 3.1% $p = 0.025$). Receipt of NAC did not affect oncologic outcomes. Following RC 22.3% of high risk patients (n = 112) received adjuvant chemotherapy (AC).*

Conclusions: *Our use of cisplatin-based NAC improved from 17% to 35% and overall utilization of NAC increased from 22% to 41%. NAC led to improved pT0 rates and increased pathologic downstaging. The degree of CKD (0-3) did not impact likelihood of receiving NAC. AC use decreased in part due to higher utilization of NAC.*

Key Words: chemotherapy, radical cystectomy, bladder cancer, utilization, cisplatin

Introduction

In 2015, the American Cancer Society estimates there will be 74,000 new diagnoses and 16,000 deaths from bladder cancer.[1] Although the majority of new cases are non-muscle-invasive, 20%-40% of patients present with muscle-invasive bladder cancer (MIBC).[2] For these patients, radical cystectomy (RC) with bilateral lymphadenectomy is performed for tumor extirpation. Patients with pathologic organ-confined disease have 5 year survival rates greater than 70%; however 40%-70% of patients with clinical T2 (cT2) disease are upstaged due to extravesical extension and/or positive lymph nodes.[3-6] Survival rates drop significantly when these high risk features are present.[2-6]

In 2003, SWOG 8710 found that use of neoadjuvant chemotherapy (NAC) in patients with cT2/T3 disease increased median survival from 46 to 77 months.[7,8] Patients with a complete pathologic response received the greatest survival benefit, with 85% alive at 5 years.[7]

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Subsequent meta-analyses confirmed a 5% overall survival advantage and a 14% reduction in bladder cancer specific deaths with use of cisplatinum-based NAC.[9,10] Further, recently published long term results from the MRC/EORTC trials showed a significant reduction of risk of death of 16% after receipt of NAC and a 10 year survival advantage of 6% (36% versus 30%).[11]

While use of NAC has been rising, it remains underutilized.[7,8,12-14] A series from 2003-2008 at this institution reported that 17% of eligible patients received cisplatin-based NAC while 38% of patients received adjuvant chemotherapy (AC).[3] As a result of these sub-optimal findings, we instituted monthly multidisciplinary meetings with medical oncologists, radiation oncologists and urologists. Our intent was to optimize the treatment of urologic oncology patients encompassing all aspects of disease management including clinical trial enrollment. We evaluated the effects of this approach on utilization patterns of perioperative CTX in MIBC from 2008-2012.

Materials and methods

Following institutional review board (IRB) approval, we performed a retrospective chart review of all patients undergoing RC at this tertiary care center between 2008 and 2012. Patients undergoing RC for urothelial carcinoma (UC) with intention to cure were included in the initial cohort. Comprehensive clinical and pathological data was collected and entered into an IRB approved database. Perioperative CTX data including physician rationale for CTX utilization was ascertained by careful review of clinical encounter notes.

Exclusion criteria for the final cohort included pure non-transitional cell histology, clinical evidence of nodal or metastatic disease, partial or palliative cystectomy, previous chemo-radiation for UC, and partial or incomplete records of NAC, Figure 1. We previously reported that patients with an estimated glomerular filtration rate (eGFR) of > 30 mL/min routinely receive cisplatinum therapy following evaluation by medical oncology at this institution.[3] We used the MDRD equation to calculate the eGFR at the initial evaluation and 3 months postoperatively. Patients with an eGFR of > 30mL/min were considered eligible for perioperative chemotherapy and included in the final study cohort.

Clinical stage was determined from transurethral resection, exam under anesthesia, and preoperative imaging obtained within 4 weeks of diagnosis. For patients referred with a previously established MIBC diagnosis, original slides were obtained and re-reviewed by our pathologists to confirm histology and presence of muscle invasion. Patients were considered eligible for NAC if

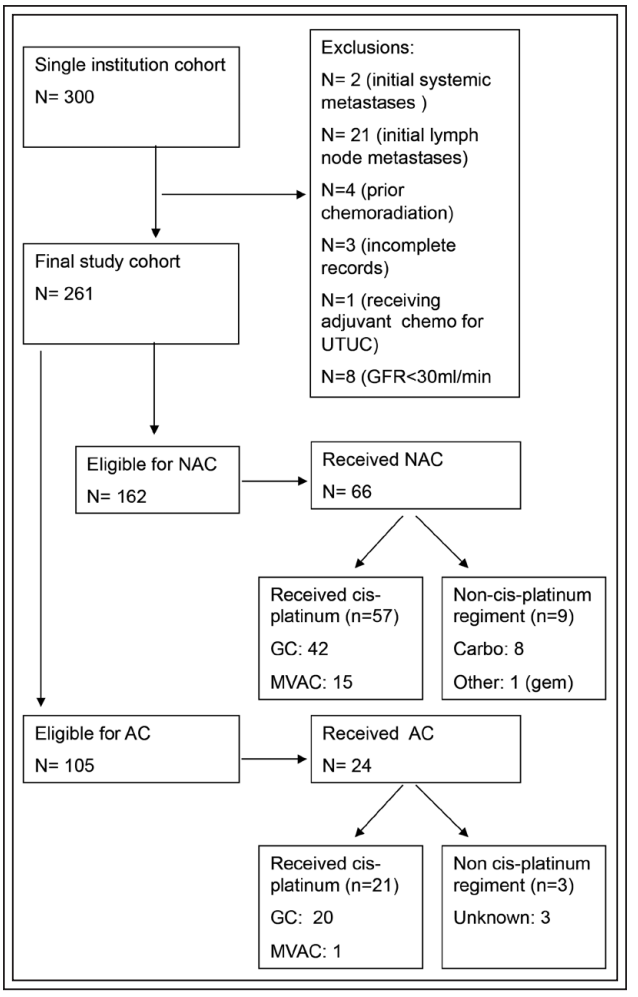

Figure 1. Flow chart; study inclusion and exclusion scheme.

their clinical stage was ≥ T2.[7] All patients underwent RC with bilateral pelvic lymph node dissection as previously described.[3] A genitourinary pathologist assessed pathologic characteristics and assigned stage using the AJCC 2010 TNM staging system.[15] Patients with a stage ≥ pT3 and/or positive lymph nodes were considered eligible for AC.[9,10,16]

During the initial evaluation, the urologic oncologist made treatment recommendations based on clinical judgment and patient preferences. Candidates for CTX were referred to a medical oncologist, either institutional or local, depending on patient preference. In all cases, records were reviewed to determine treatment regimen and protocol. All patients were re-evaluated after two cycles of CTX for response to treatment by cross-sectional imaging. For patients eligible but not given CTX encounter notes were reviewed to determine the reasons for this decision.

Patients were followed every 3 months for the first

year and semiannually thereafter. Assessments included basic labs, cross-sectional imaging, and physical exam. Development of local recurrences and distant metastases were assessed. Patients who died following RC prior to hospital discharge were considered to have died of bladder cancer. Cause of death was assessed by the treating physician and death certificate or death certificate alone. Multiple data reviews and quality assurance checks were conducted throughout the process.

Statistical analyses

The Student's t-test or Mann-Whitney-U test was used to compare continuous variables. Fisher's exact test and Pearson's chi-square test were used to compare categorical variables. Survival was estimated using the Kaplan-Meier method. Predictors of pT0 and survival were evaluated using binary logistic and Cox regression. Statistical significance was defined as $p \leq 0.05$ and all reported p values are two sided. Analyses were conducted using SPSS (Version 19, IBM, Armonk, NY, USA).

Results

Two hundred and sixty-one patients met the final inclusion criteria for this study and clinical characteristics are presented in Table 1. Median age at RC was 70.0 years (range 33-90 years). For patients alive at last follow up, median follow up was 24.9 months (range 1.0-74.0 months).

TABLE 1. **Cohort demographics: radical cystectomy (RC) for muscle-invasive bladder cancer (MIBC)**

Demographic data	Entire cohort (n = 261)
Median age in years (range)	70.0 (33-90)
Sex	
Women	52 (19.9)
Men	209 (80.1)
Race	
White	164 (62.8)
Non-white	29 (11.1)
Unknown	69 (26.1)
Median BMI (range)	
BMI ≤ 25	96 (36.8)
BMI > 25	165 (63.2)
Baseline CKD stage (MDRD)	
0	3 (1.1)
1	41 (15.7)
2	139 (53.9)
3	78 (29.9)
Clinical stage	
< T2	99 (37.9)
≥ T2	162 (62.1)
Clinical grade	
Low grade	4 (1.5)
High grade	257 (98.5)
Received neoadjuvant CTX (if clinical stage ≥ T2)	
No	96 (59.3)
Yes	66 (40.7)
Pathologic T-stage (RC)	
T0	20 (7.7)
CIS	29 (11.1)
Ta	22 (8.4)
T1	40 (15.3)
T2	45 (17.2)
T3	75 (28.7)
T4	30 (11.5)
Grade (RC)	
Not applicable (T0 on specimen)	19 (7.3)
Low grade	2 (0.7)
High grade	240 (92.0)
N-stage (RC)	
N0	198 (75.9)
N1	63 (24.1)
M-stage (RC)	
M0	261 (100.0)
CIS present (RC)	
No	150 (57.5)
Yes	111 (42.5)
Lymphovascular invasion (RC)	
No	177 (67.8)
Yes	84 (32.2)
Positive margins at RC (including ureteral)	
No	219 (83.9)
Yes	42 (16.1)
Organ confined disease (≤ T2 and N0) (RC)	
Yes	149 (57.1)
No	112 (42.9)
Received adjuvant CTX (if > T2 and/or N1) (RC)	
No	87 (77.7)
Yes	25 (22.3)
Local/systemic recurrence	
No	191 (73.2)
Yes	70 (26.8)
Dead of urothelial carcinoma	
No	207 (79.3)
Yes	54 (20.7)

CKD = chronic kidney disease
MDRD = modification of diet in renal disease

Preoperative setting

Following initial evaluation, 162 (62.1%) patients were eligible for NAC (≥ cT2) and 66 (40.7%) received NAC, Table 2a and 2b. Median age at presentation was significantly lower among those who received NAC (68.5 versus 72.5 years, p = 0.028) and clinical stage was significantly higher among those given NAC (p = 0.011). Renal function did not differ between the two groups, (p = 0.161). Fifty-four patients had an initial eGFR of < 60mL/min (33.3%), and 28 (51.9%) were ultimately given NAC. Twenty of the 54 patients were seen by medical oncology at this institution and only 1 patient was considered too high risk for any NAC due to medical comorbidities. In total, a recommendation to see medical oncology was given to 59% (n = 95) of the 162 patients considered NAC eligible at this institution.

The majority (n = 57, 86.4%) received cisplatinum-based CTX (GC n = 42 (73.7%), MVAC n = 15 (26.3%)). Nine patients received non-cisplatinum regimens – eight received carboplatin-gemcitabine and one received gemcitabine only. Four (3 carboplatin-gemcitabine and 1 gemcitabine) received CTX from community providers prior to referral to our institution. The remaining five patients were evaluated by our medical oncologists and determined to be unfit for cisplatin due to medical comorbidities and given carboplatin.

Overall, the median number of cycles administered was 3 (range 1-5). Nine patients received two or less

TABLE 2a. **Clinico-pathological data: 162 neoadjuvant chemotherapy eligible patients**

	Received neoadjuvant chemotherapy (CTX)	**Did not receive neoadjuvant chemotherapy (CTX)**	**p value**
N in group (%)	66 (40.7)	96 (59.3)	-
Median age in years (range)	68.5 (46-85)	72.5 (33-88)	**0.028**
Sex			0.927
Women	12 (18.2)	18 (18.8)	
Men	54 (81.8)	78 (81.2)	
Race (if available)*			0.818
White	49 (87.5)	62 (86.1)	
Non-white	7 (12.5)	9 (13.9)	
Body mass index			0.085
< 25	22 (33.3)	45 (46.9)	
> 25	44 (66.7)	51 (53.1)	
Clinical stage			**0.011**
cT2	42 (63.6)	79 (82.3)	
cT3	20 (30.3)	11 (11.5)	
cT4	4 (6.1)	6 (6.3)	
CIS on TUR-BT specimen			0.482
Absent	49 (77.8)	79 (82.3)	
Present	14 (22.2)	17 (17.7)	
CKD stage (MDRD)			0.161
0	0 (0.0)	1 (1.0)	
1	10 (15.2)	14 (14.6)	
2	28 (42.4)	55 (57.3)	
3	28 (42.4)	26 (27.1)	
Received platinum based CTX			
No	9 (13.6)		
Yes	57 (86.4)		
-MVAC	-15 (26.3)		
-GC	-42 (73.7)		

*race available for n = 128

TUR-BT = transurethral resection of bladder tumor; CKD = chronic kidney disease; MDRD = modification of diet in renal disease; MVAC = methotrexate, vinblastine, doxorubicin, cisplatin; GC = gemcitabine-cisplatin

TABLE 2b. **Clinico-pathological data: 162 neoadjuvant chemotherapy eligible patients**

	Received neoadjuvant chemotherapy (CTX)	Did not receive neoadjuvant chemotherapy (CTX)	p value
Pathologic stage on RC specimen			**0.010**
pT0	8 (12.1)	3 (3.1)	
pTis,pTa,pT1	14 (21.2)	7 (7.3)	
pT2	12 (18.2)	21 (21.9)	
pT3	23 (34.8)	47 (49.0)	
pT4	9 (13.6)	18 (18.7)	
Nodal stage			0.380
pN0	45 (68.2)	59 (61.5)	
pN1	21 (31.8)	37 (38.5)	
LVI on RC specimen			0.136
Absent	41 (62.1)	49 (51.0)	
Present	25 (37.9)	47 (49.0)	
CIS on RC specimen			0.541
Absent	43 (65.2)	58 (60.4)	
Present	23 (34.8)	38 (39.6)	
Positive margins on RC specimen			0.449
No	56 (84.8)	77 (80.2)	
Yes	10 (15.2)	19 (19.8)	
Local or systemic recurrence			0.174**
No	44 (66.7)	58 (60.4)	
Yes	22 (33.3)	38 (39.6)	
Death of disease			0.193**
No	50 (75.8)	65 (67.7)	
Yes	16 (24.2)	31 (32.3)	

**log-rank statistic
RC = radical cystectomy; LVI = lymphovascular invasion

CTX cycles. Eight patients receiving GC were unable to tolerate the side effects. One developed renal insufficiency and GC was stopped. The remainder had systemic issues (urosepsis, ongoing hematuria) severe enough to require hospitalization and/or lead to a decline in performance status. One patient receiving carboplatin had evidence of disease progression following restaging studies done after cycle 2. All nine patients proceeded to RC. Two patients received five cycles of GC. One received chemotherapy in the community, the other at our institution. The remaining patients received either three or four cycles at the discretion of medical oncology.

Among the 96 patients who were eligible for NAC but did not receive it, reasons included patient choice (n = 27), favorable tumor characteristics (clinical T2, no LVI) (n = 25), concerns about age and/or comorbidities (n = 17), transfusion-dependent hematuria (n = 4) and chemotoxicity concerns (n = 3). For 20 patients no reason was documented. Only 2 of the 96 patients were evaluated by medical oncology and determined to be unfit for NAC.

Patients who received NAC were more likely to have a complete pathologic response (pT0) (12.1% versus 3.1%, p = 0.025) or to be downstaged to non-muscle-invasive disease (21.2% versus 7.3%, p = 0.001) than those who did not.

Postoperative setting

Following RC, 112 of 261 (40.2%) patients were eligible for AC due to high risk pathological features (≥ pT3 and/or pN+), Table 3. Twenty-five of 105 (22.3%) patients with high risk disease received AC and the majority (89.0%) received cisplatinum (GC n = 21 (95.5%), MVAC n = 1 (4.0%)). For three patients, their chemotherapy protocol was unknown. The median number of cycles administered was 3 (range 1-6).

Nodal stage (p = 0.002) and the presence of LVI on RC specimen (p = 0.025) differed significantly between those given AC and those who were not, Table 3. Patients receiving AC were significantly less likely to have been given NAC (16% versus 36.8%, p = 0.05).

TABLE 3. **Clinico-pathological data: 112 adjuvant chemotherapy eligible patients**

	Received adjuvant (CTX)	**Did not receive adjuvant (CTX)**	**p value**
N in group (%)	25 (22.3)	87 (77.7)	-
Median age in years (range)	68.0 (48-84)	73.0 (33-90)	0.107
Sex			0.819
Women	6 (24.0)	68 (78.2)	
Men	19 (76.0)	19 (21.8)	
Race (if available)*			0.739
White	18 (84.4)	58 (85.3)	
Non-white	4 (15.6)	10 (14.7)	
Body mass index			0.779
< 25	12 (48.0)	39 (44.8)	
> 25	13 (52.0)	48 (55.2)	
Received neoadjuvant CTX			**0.050**
No	21 (84.0)	55 (63.2)	
Yes	4 (16.0)	32 (36.8)	
Pathologic stage on radical cystectomy specimen			0.870
pT0	0 (0)	1 (1.1)	
pTis,pTa,pT1	0 (0)	2 (2.3)	
pT2	1 (4.0)	3 (3.4)	
pT3	16 (64.0)	59 (67.8)	
pT4	8 (32.0)	22 (25.3)	
Nodal stage			**0.002**
pN0	4 (16.0)	45 (51.7)	
pN1	21 (84.0)	42 (48.3)	
Lymphovascular invasion on radical cystectomy specimen			**0.025**
Absent	4 (16.0)	35 (40.2)	
Present	21 (84.0)	52 (59.8)	
CIS on radical cystectomy specimen			0.384
Absent	14 (56.0)	57 (65.5)	
Present	11 (44.0)	30 (34.5)	
Positive margins on radical cystectomy specimen			0.115
No	16 (64.0)	69 (79.3)	
Yes	9 (36.0)	18 (20.7)	
Chronic kidney disease stage (modification of diet in renal disease) post radical cystectomy			0.641
0	2 (8.0)	6 (6.9)	
1	3 (12.0)	16 (18.4)	
2	15 (60.0)	39 (44.8)	
3	5 (20.0)	26 (29.9)	
Received adjuvant platinum based CTX			
No	3 (12.0)		
Yes	22 (89.0)		
-MVAC	-1 (4.5)		
-GC	-21 (95.5)		
Local or systemic recurrence			0.367**
No	7 (28.0)	45 (51.7)	
Yes	18 (72.0)	42 (48.3)	
Death of disease			0.563**
No	12 (48.0)	52 (59.8)	
Yes	13 (52.0)	35 (40.2)	

*race available for n = 90; ** log-rank statistic

Primary reasons for not giving AC included age or functional status concerns (n = 29), death or rapidly progressive disease (n = 20), patient choice (n = 7), and cancer characteristics (n = 4). For 27 patients no reason was documented, but 17 (62.9%) had received NAC.

Among the 54 patients with a preoperative eGFR of < 60mL/min, there was no difference in postoperative eGFR between those who were given NAC and those who were not. Of 28 patients given NAC, 24 had unchanged or improved CKD. Twenty-six of 26 patients not given NAC had unchanged or improved CKD (p = 0.1120).

Following RC, 70 patients (26.8%) had a local or systemic recurrence at a mean time of 9.3 months (range: 0.6-34.2 months) and 54 (20.7%) died of UC at a mean time of 12.8 months (range: 0.3-37.8). Of 112 patients with high risk disease 60 (53.6%) had a local and/or systemic recurrence while 10 of 149 (6.7%) patients with pathologically organ-confined disease recurred. Among 70 patients who recurred, 35 (50.0%) received salvage chemotherapy and 21 (30.0%) received radiotherapy.

Survival analysis

Among 166 patients eligible for NAC, clinical stage was an independent significant predictor of all oncologic outcomes (recurrence-free, cancer-specific and overall survival) in univariate and multivariate analyses except recurrence-free survival, where no multivariate analysis was computed since clinical stage was the only significant predictor in univariate analysis, Table 4a. Further, a body mass index (BMI) of less than or equal to 25 was also an independent predictor for worse cancer-specific and overall survival in both univariate and multivariate analysis, Table 4a. The receipt of

TABLE 4a. **Uni and multivariate analysis: patients eligible for neoadjuvant chemotherapy (CTX) because of muscle-invasive bladder cancer (n = 166)**

Recurrence-free survival	**Univariate analysis**	**Multivariate analysis**
Male versus female	1.4 (0.8-2.6) p = 0.266	-
Age ≤ 65 yr versus > 65 yr	1.2 (0.6-2.1) p = 0.590	-
BMI ≤ 25 versus > 25	0.7 (0.4-1.1) p = 0.110	-
Clinical stage T2 versus > T2	**1.8 (1.1-3.2) p = 0.030***	-
GFR ≥ 60 mL/min versus < 60 mL/min	0.7 (0.4-1.2) p = 0.211	-
Neoadj. CTX not received versus received	0.7 (0.4-1.2) p = 0.230	-

*no multivariate analysis computed since only one variable predictive

Cancer-specific survival	**Univariate analysis**	**Multivariate analysis**
Male versus female	1.7 (0.9-3.3) p = 0.113	-
Age ≤ 65 yr versus > 65 yr	0.8 (0.5-1.5) p = 0.575	-
BMI ≤ 25 versus > 25	**0.5 (0.3-0.9) p = 0.018**	**0.5 (0.3-0.95) p = 0.033**
Clinical stage T2 versus > T2	**2.1 (1.2-3.9) p = 0.014**	**2.0 (1.1-3.7) p = 0.028**
GFR ≥ 60 mL/min versus < 60 mL/min	0.6 (0.3-1.2) p = 0.133	-
Neoadj. CTX not received versus received	0.7 (0.4-1.3) p = 0.244	-

Overall survival	**Univariate analysis**	**Multivariate analysis**
Male versus female	1.5 (0.9-2.6) p = 0.152	-
Age ≤ 65 yr versus > 65 yr	1.0 (0.6-1.6) p = 0.960	-
BMI ≤ 25 versus > 25	**0.6 (0.4-0.99) p = 0.043**	0.7 (0.4-1.1) p = 0.081
Clinical stage T2 versus > T2	**2.3 (1.4-3.8) p = 0.001**	**2.2 (1.4-3.7) p = 0.001**
GFR ≥ 60 mL/min versus < 60 mL/min	1.0 (0.6-1.7) p = 0.976	-
Neoadj. CTX not received versus received	0.8 (0.5-1.3) p = 0.293	-

BMI = body mass index; GFR = glomerular filtration rate

TABLE 4b. **Uni and multivariate analysis: patients eligible for adjuvant chemotherapy (CTX) of non-organ confined bladder cancer (n = 109)**

Recurrence-free survival	**Univariate analysis**	**Multivariate analysis**
Male versus female	1.3 (0.7-2.3) p = 0.447	-
Age < 65 yr versus > 65 yr	0.9 (0.5-1.6) p = 0.642	-
BMI < 25 versus > 25	0.9 (0.5-1.5) p = 0.624	-
≤ pT3 versus pT4	1.1 (0.6-1.9) p = 0.748	-
pN0 versus pN1	**1.7 (1.0-2.9) p = 0.048**	1.0 (0.6-1.9) p = 0.913
LVI absent versus present	**2.8 (1.5-5.1) p = 0.001**	**2.7 (1.3-5.5) p = 0.006**
Concomitant CIS absent versus present	1.2 (0.6-1.9) p = 0.609	-
Margin status negative versus positive	1.4 (0.8-2.5) p = 0.207	-
Adj. CTX not received versus received	1.3 (0.7-2.3) p = 0.345	-
Disease-specific survival	**Univariate analysis**	**Multivariate analysis**
Male versus female	1.5 (0.8-2.9) p = 0.221	-
Age < 65 yr versus > 65 yr	0.7 (0.4-1.4) p = 0.317	-
BMI < 25 versus > 25	0.7 (0.4-1.2) p = 0.221	-
≤ pT3 versus pT4	1.2 (0.6-2.3) p = 0.582	-
pN0 versus pN1	**2.3 (1.2-4.3) p = 0.007**	1.2 (0.6-2.5) p = 0.536
LVI absent versus present	**4.2 (1.9-9.0) p < 0.001**	**4.3 (1.5-8.8) p = 0.003**
Concomitant CIS absent versus present	1.1 (0.6-1.9) p = 0.863	-
Margin status negative versus positive	1.6 (0.8-2.9) p = 0.173	-
Adj. CTX not received versus received	1.2 (0.6-2.4) p = 0.549	-
Overall survival	**Univariate analysis**	**Multivariate analysis**
Male versus female	1.4 (0.8-2.5) p = 0.207	-
Age < 65 yr versus > 65 yr	0.8 (0.5-1.4) p = 0.445	-
BMI < 25 versus > 25	0.8 (0.5-1.3) p = 0.374	-
≤ pT3 versus pT4	1.2 (0.7-2.0) p = 0.564	-
pN0 versus pN1	**2.0 (1.2-3.3) p = 0.007**	1.2 (0.7-2.2) p = 0.503
LVI absent versus present	**3.1 (1.7-5.6) p < 0.001**	**3.3 (1.4-5.5) p = 0.004**
Concomitant CIS absent versus present	0.4 (0.5-1.4) p = 0.490	-
Margin status negative versus positive	1.4 (0.8-2.4) p = 0.209	-
Adj. CTX not received versus received	0.9 (0.5-1.7) p = 0.764	-

BMI = body mass index; LVI = lymphovascular invasion

NAC was not significantly associated with survival in this dataset.

Among patients eligible for AC, the presence of LVI was the only independent predictor of worse survival across all oncologic outcomes, Table 4b. The receipt of AC was not associated with significantly improved or worse survival in this dataset.

Prediction of pT0 disease

Further we assessed the predictive parameters of pT0 disease at time of RC as a surrogate for a survival benefit in the cohort of patients with clinical MIBC eligible for NAC (n = 166), Table 5. In uni- and multivariate analyses, receipt of NAC (OR 4.57 (1.15-18.26), p = 0.031) and concomitant CIS at time

TABLE 5. **Binary logistic regression for prediction of pT0 at time of radical cystectomy for patients eligible for neoadjuvant chemotherapy due to muscle-invasive bladder cancer (n = 166)**

Prediction of pT0 at RC	Univariate analysis	Multivariate analysis
Male versus female	0.42 (0.51-3.38) p = 0.413	-
Age ≤ 65 yr versus > 65 yr	1.27 (0.32-5.00) p = 0.732	-
BMI ≤ 25 versus > 25	1.98 (0.51-7.74) p = 0.327	-
Time TUR-B to RC (months)	1.08 (0.91-1.28) p = 0.385	-
Clinical stage T2 versus > T2	0.66 (0.14-3.19) p = 0.606	-
Concomitant CIS no versus yes	**3.86 (1.10-13.57) p = 0.035**	**3.72 (1.02-13.51) p = 0.046**
GFR ≥ 60 mL/min versus < 60 mL/min	0.68 (0.17-2.68) p = 0.583	-
Neoadj. CTX not received versus received	**4.46 (1.14-17.48) p = 0.032**	**4.57 (1.15-18.26) p = 0.031**
Number of cycles of NAC	1.13 (0.39-3.25) p = 0.882	

RC = radical cystectomy; BMI = body mass index; TUR-B = transurethral resection of bladder; GFR = glomerular filtration rate

of last TUR-BT (OR 3.86 (1.10-13.57), p = 0.035) were independent predictors of pT0 disease at time of cystectomy.

Discussion

Current guidelines recommend cisplatin-based NAC be 'strongly considered' for all patients with cT2 and higher disease, and Level I evidence demonstrates a 5% survival benefit.[7,9-11,16,17] Although still underutilized, institutions are reporting increased use of NAC, often following the implementation of a multidisciplinary model.[18] Larger data sets reflect this, with analysis of the National Cancer Database showing use of NAC in MIBC increased from 13% in 2007 to 21% in 2010.[12,19] At this center, 17% of patients received cisplatin-based NAC between 2003 and 2008.[3] Following the institution of monthly multidisciplinary oncology meetings, cisplatin-based NAC usage improved to 36% and overall NAC use to 40.7%. Over the same time period, AC use decreased from 38% to 23% in part due to increased utilization of NAC.[3]

Currently there is no clear definition of cisplatinum based NAC eligibility.[20] Cisplatin is renally excreted and nephrotoxic, which limits the applicability in patients with pre-existing renal insufficiency.[21] A 2011 consensus definition of patients unfit for cisplatinum used a creatinine clearance cutoff of < 60 mL/min, but the true proportion of patients ineligible for cisplatin is unknown.[3,21,22] The International Bladder Cancer study reported 45.3% of patients were ineligible for NAC, while other series have reported rates between 24%-52% depending on the method used to assess renal function.[3,22-25]

Calculated creatinine clearances have been shown to be unreliable as nearly 40% of patients ineligible by calculated creatinine clearance become eligible for cisplatinum by evaluating measured creatinine clearance.[26] Therefore we do not use eGFR < 60 as exclusion for cisplatinum-based CTX, and refer potential candidates to medical oncology for further evaluation. In our study, one third (54/162, 33.3%) of patients had an eGFR < 60 mL/min by MDRD at the time of evaluation. More than half were ultimately given NAC (28/54, 51.9%), the majority receiving cisplatinum (21/28, 75.0%). Postoperatively, among patients with an initial eGFR less than 60 mL/min, there was no significant difference (p = 0.1120) in eGFR between those who received NAC and those who did not. Therefore in patients with MIBC and an eGFR < 60 mL/min referral to medical oncology for further evaluation and measured creatinine clearance may help identify additional patients eligible for NAC.

While carboplatin has been investigated as an alternative in patients with renal dysfunction, multiple trials indicate inferiority to cisplatin thus it remains investigational in the neoadjuvant setting.[13,27] With our multidisciplinary approach, we have become more aggressive in administering cisplatinum-based therapy with no detrimental effects. We found that with referral to medical oncology, only with severe medical comorbidites such as a solitary kidney, carboplatin was recommended. Overall nine patients received non-cisplatinum regimens. Four had received CTX from community providers prior to referral to our institution. The remaining five patients had severe medical comorbidities and our medical oncologists recommended they be given carboplatin. For patients

who opted to receive treatment locally, the eligibility for cisplatinum-based therapies was less stringent.

Overall, a recommendation to see medical oncology was given to 59% (n = 95) of the 162 patients considered NAC eligible at this institution. Among those who did not receive NAC, 28% of patients (n = 27) declined to be further evaluated by medical oncology, preferring immediate RC. For 21% (n = 20) no reason was found in the chart. Of the remaining 49 patients (51%), only two were referred to medical oncology and deemed medically unfit. The physician rationale for proceeding directly to cystectomy was split between patient factors (age, functional status, n = 24) and favorable disease characteristics (cT2, no LVI, n = 25). This is consistent with the data, which showed that younger patients and those with higher clinical stages were more likely to receive NAC.

Pathologic stage is significantly associated with oncologic outcomes in patients with MIBC.[2,28] Downstaging to NMIBC after RC confers significant survival benefits compared to patients with residual muscle invasive disease.[4,6,7,29] The pT0 rate is used as a surrogate marker for treatment efficacy.[13] Following TURBT, 5%-15% of patients have a complete pathologic response; with NAC the pT0 rate increases to 30%-40% (although it has been reported as low as 7%).[3,7,30] In our study, patients given NAC were significantly more likely to be downstaged to NMIBC and obtain a complete pathologic response. On binary logistic regression analyses, receipt of NAC as well as concomitant CIS at time of last TUR-BT before RC were independent predictors of a higher likelihood for pT0 disease at time of cystectomy. While lower than previously reported at this institution, we found 12.1% of patients given NAC had a complete response and 21.2% of patients were downstaged to NMIBC (compared to 27% and 45.8% previously reported).[3] Possible reasons for the lower pT0 rate may include patient selection (cT2 in 69% versus 63.6% of patients receiving NAC in the previous and current cohort, respectively), referrals for higher stage cancer, high volume disease precluding complete resection on initial TURBT, or improved pathologic evaluation allowing detection of smaller residual tumor. At our institution, we do not routinely re-TUR patients before cystectomy if the original specimen was adequate for diagnosis (with review and confirmation by our pathologists for outside biopsies), however this may result in higher rates of residual disease.

While Level I evidence supports using neoadjuvant MVAC, the polychemotherapy regimen of gemcitabine-cisplatin (GC) is commonly used due to its more favorable safety profile.[29] While meta-analyses suggest that other cisplatin-containing regimens have similar utility to MVAC, variable pT0 rates have been reported.[8,27,30] Therefore choice of chemotherapeutic agents may also contribute to lower pT0 rates. Despite higher clinical stages before RC, those that received NAC had a lower overall recurrence rate (67.7% versus 53.6%), although this did not translate into improved survival on our analysis. Failure to show a survival benefit may be attributable to our small cohort size, short follow up and the difference in disease severity due to lack of randomization between the groups. Further, since this is a limited size retrospective cohort, it does seem that survival benefits are better assessed in prospective trials.

BMI was independently associated with cancer-specific and overall survival in patients with clinical MIBC; however it was not independently associated with outcomes in patients with pathologic high risk disease. Previous reports have shown a BMI > 22 is associated with improved outcomes in upper tract disease.[31] In contrast, obese patients with high-grade cT1 disease have worse outcomes and increased perioperative risks.[32,33] Obese patients have a 28% overall increased risk for developing BC.[31] Improved survival may be related to disease severity since patients with worse disease may have increased cytokine levels causing "cancer cachexia." In addition, a higher BMI may indicate greater physiologic reserve and thus implicate quicker recovery after RC amongst other benefits.

Due to the retrospective nature of the study, recall bias exists in determining reasons for not giving NAC or AC. In addition, we only included patients who underwent RC; therefore we may be underestimating the actual number of patients who received chemotherapy for clinical MIBC. Finally, a single creatinine value was used to estimate GFR pre and postoperatively, which may miss trends in renal function.

Conclusion

Our use of cisplatin-based NAC improved from 17% to 35% and overall utilization of NAC increased from 22% to 41%. NAC led to improved pT0 rates and increased pathologic downstaging to NMIBC. The degree of CKD (0-3) did not impact likelihood of receiving NAC. AC use decreased from 38% to 23% in part due to higher utilization of NAC. □

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