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Multicenter Assessment of Neoadjuvant Chemotherapy for Muscle-invasive Bladder Cancer

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Abstract

Background—The efficacy of neoadjuvant chemotherapy (NAC) for muscle-invasive bladder cancer (BCa) was established primarily with methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC), with complete response rates (pT0) as high as 38%. However, because of the comparable efficacy with better tolerability of gemcitabine and cisplatin (GC) in patients with metastatic disease, GC has become the most commonly used regimen in the neoadjuvant setting.

Objective—We aimed to assess real-world pathologic response rates to NAC with different regimens in a large, multicenter cohort.

Design, setting, and participants—Data were collected retrospectively at 19 centers on patients with clinical cT2–4aN0M0 urothelial carcinoma of the bladder who received at least three cycles of NAC, followed by radical cystectomy (RC), between 2000 and 2013.

Intervention—NAC and RC

Outcome measurements and statistical analysis—The primary outcome was pathologic stage at cystectomy. Univariable and multivariable analyses were used to determine factors predictive of pT0N0 and ≤pT1N0 stages.

Results and limitations—Data were collected on 935 patients who met inclusion criteria. GC was used in the majority of the patients (n = 602; 64.4%), followed by MVAC (n = 183; 19.6%) and other regimens (n = 144; 15.4%). The rates of pT0N0 and ≤pT1N0 pathologic response were 22.7% and 40.8%, respectively. The rate of pT0N0 disease for patients receiving GC was 23.9%, compared with 24.5% for MVAC (p = 0.2). There was no difference between MVAC and GC in pT0N0 on multivariable analysis (odds ratio: 0.89 [95% confidence interval, 0.61–1.34]; p = 0.6).

Conclusions—Response rates to NAC were lower than those reported in prospective randomized trials, and we did not discern a difference between MVAC and GC. Without any

evidence from randomized prospective trials, the best NAC regimen for invasive BCa remains to be determined.

Patient summary—There was no apparent difference in the response rates to the two most common presurgical chemotherapy regimens for patients with bladder cancer.

Keywords

Neoadjuvant chemotherapy; MVAC; GC; Cystectomy; Complete pathologic response; Partial pathologic response; Urothelial cancer

1. Introduction

Level 1 evidence indicates that neoadjuvant chemotherapy (NAC) prior to radical cystectomy (RC) improves the outcomes of patients with muscle-invasive bladder cancer (BCa) compared with RC alone [1–5]. Recent reports suggest that NAC does not increase the morbidity and mortality associated with RC [6,7]. Despite this evidence, there has been slow adoption of NAC by urology communities worldwide [8–10], although a recent population-based report suggests that NAC uptake is on the rise [11].

Owing to the outcome of the pivotal SWOG-8710 randomized controlled trial [2], methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) was established as the most effective regimen in the NAC setting. However, because of concerns regarding the toxicity of this regimen and based on equivalent long-term overall and progression-free survival of patients receiving MVAC or gemcitabine and cisplatin (GC) in a phase 3 trial involving patients with metastatic BCa [12], GC has been increasingly used in the NAC setting [13].

Although small retrospective single-institution series have reported comparative outcomes of these two chemotherapy regimens [14–17], there is a paucity of published data with regard to the efficacy of neoadjuvant GC. In this paper, we assess and compare pathologic response rates (complete and partial) and survival outcomes of GC, MVAC, and other NAC regimens in a multi-institutional series of patients with clinical stage T2–4aN0M0 urothelial carcinoma (UC) of the bladder. We hypothesized that outcomes would be different among these NAC regimens and that the real-world pathologic responses to NAC would be inferior to the responses reported in the setting of clinical trials. This hypothesis was based on our own experience with GC and anecdotal reports from other centers. Since the best evidence for NAC stems from trials using MVAC [2], and the use of GC is based on a negative trial testing for superiority (but not noninferiority) in the metastatic setting [12], we further postulated that the rate of pathologic response to GC would be inferior to the rate for MVAC.

2. Patients and methods

2.1. Study population

Institutional review board approval and data-sharing agreements were obtained at 19 North American and European institutions. Clinical records of patients who received NAC followed by open RC from 2000 to 2013 were reviewed retrospectively at each institution.

Patients who had resectable muscle-invasive BCa (cT2–4aN0M0) and received at least three cycles of NAC prior to RC were included. Patients with pure UC or mixed histology with squamous and/or glandular differentiation were included in the analysis. Patients with all other variant histology and cT4b disease were excluded from analysis. Patients were grouped as *MVAC*, *GC*, or *Other*, according to the NAC regimen that they received. The Other group consisted of patients receiving gemcitabine and carboplatin, taxanes, and other platinum-based regimens (other than cisplatin). Our primary outcome was pathologic response to chemotherapy, which was compared among different NAC regimens. Complete pathologic response (pCR) was defined as pT0N0, and pathologic partial response (pPR) was defined as pT≤1N0 (including pT1/Tis/Ta/T0). Secondary outcomes were overall survival (OS) and cancer-specific survival.

2.2. Analysis

Parameters related to demographics, clinical staging, NAC, surgery, histopathology, and survival outcomes were analyzed for the entire cohort. The assessed demographics included age, gender, smoking status (any prior history of smoking), and history of previous pelvic radiotherapy. Clinical staging data consisted of clinical and pathology staging based on initial transurethral resection of bladder tumor (TURBT) and cN staging based on preoperative imaging. NAC data encompassed type of regimen, number of cycles, time interval between TURBT and start of NAC, and time interval between commencement of NAC and RC. The operative data included extent of lymph node dissection (standard vs extended) and type of urinary diversion. Histopathology assessment entailed tumor classification, surgical margin status, presence of carcinoma in situ, and TNM staging according to the 2010 American Joint Committee on Cancer classification.

For variables with non-normal distribution, data were presented as median and interquartile range (IQR), and the respective groups were compared using the Mann-Whitney U test. Categorical variables were compared using the χ^2 test. Multivariable logistic regression analysis of selected variables (age, cT stage, gender, and type of chemotherapy regimen) was used to define factors predicting pCR and pPR. For comparison of adjusted pathologic response rates, the odds ratio (OR) is reported, and the 95% confidence interval (CI) was calculated with bootstrapping. The multivariable Cox proportional hazards regression model for survival was used to assess hazard ratios (HRs) for variables of interest (gender, type of chemotherapy regimen, surgical margin, extent of lymph node dissection, and presence of pPR). Significance was set at p value <0.05. Analyses were performed using SPSS v.21 software (IBM SPSS Statistics; IBM Corp, Armonk, NY, USA).

3. Results

A total of 1543 patients with histologically diagnosed UC who received NAC were identified (Fig. 1). Of these patients, 1130 (73.2%) were deemed clinically node negative (cN0) based on cross-sectional imaging, and 273 (17.7%) were clinically node positive (cN+). Another 140 cases had uncertain clinical node status (cNx) and were excluded from further analysis. Of the 1130 patients who were cN0, 108 (9.6%) received fewer than three cycles of NAC, and in 87 patients (7.7%), the number of chemotherapy cycles was not

available. Therefore, 935 patients with cN0 and a minimum of three cycles of NAC were included in the final analysis (Table 1).

3.1. Baseline characteristics

The median age of the cohort was 64 yr (IQR: 57–71), and the majority of the tumors were pure UC. GC was the most commonly used NAC regimen (64.4% of the cohort), followed by MVAC in 19.6% of the cohort and other regimens in 15.4%. Patients in the three chemotherapy regimens were similar with regard to age, gender, smoking, and radiation history. A higher proportion of the patients receiving MVAC had clinical T3/T4a disease (48.6%) compared with patients receiving GC (30.3%) or patients on other regimens (35%) ($p < 0.0001$).

3.2. Pathologic outcomes

Table 2 demonstrates the pathologic outcomes for each of the three chemotherapy regimens. The unadjusted pCR rate (pT0N0) for MVAC, GC, and other regimens was 24.5%, 23.9%, and 15.4%, respectively ($p = 0.05$). The unadjusted pPR rate (≤pT1N0) for the three groups was 44.8%, 43.7%, and 25.2%, respectively ($p < 0.0001$). The unadjusted pCR rate for cT2 (25.3%) was higher than the pCR rate for cT3–T4a tumors (18.7%) ($p = 0.023$).

A multivariable analysis of factors predicting pT0N0 is outlined in Table 3. Lower cT stage (≤cT2) and use of other regimens (compared with MVAC as reference) were predictors of pCR rate. Disease of cT3 or higher reduced the odds of pCR by 33% when compared with cT2 stage. On multivariable analysis, no difference between MVAC and GC in predicting pT0N0 pathologic response was detected (OR: 0.89 [95% CI, 0.61–1.34]; $p = 0.6$).

A similar multivariable analysis of factors predicting pPR is outlined in Table 4. Again, lower cT stage (≤cT2) and the type of NAC regimen were predictors of higher pPR rates.

When comparing MVAC with GC, the adjusted pCR rate (pT0N0) for MVAC and GC was 25.1% and 24.5%, respectively ($p = 0.86$). The OR of pCR for GC compared with MVAC after bootstrapping was 0.96 (95% CI, 0.67–1.40).

3.3. Incomplete treatment

Assessment of the 108 patients receiving fewer than three cycles of NAC found that the proportions of patients receiving incomplete treatment (fewer than three cycles of NAC) and proceeding to RC were similar between MVAC ($n = 28$; 13.3%), GC ($n = 64$; 9.6%), and other NAC regimens ($n = 16$; 10%) ($p = 0.5$).

3.4. Survival outcomes

The median follow-up time for the entire cohort was 11 mo (IQR: 3–27). The median follow-up after RC in patients alive at last follow-up was 14 mo (IQR: 3–35). The Kaplan-Meier estimated mean survival time for the cohort was 5.8 yr (95% CI, 5.4–6.3).

In the Cox proportional hazards regression model for survival, positive surgical margin (HR: 2.2 [95% CI, 1.4–3.6]), receiving other NAC regimens (HR: 1.6 [95% CI, 1.01–2.7]), and

achieving pPR (HR: 0.25 [95% CI, 0.16–0.4]) were significant predictors of survival (Table 5). This finding supports the validity of pPR as a surrogate measure of survival.

A difference between GC and MVAC was not detected (HR: 1.25 [95% CI, 0.80–1.93]). Since cT stage was a significant predictor of pathologic response, we did not include this variable in our Cox regression model.

4. Discussion

Level 1 evidence has demonstrated that NAC with MVAC followed by RC improves survival in patients with muscle-invasive BCa compared with RC alone [1–5,18]. Although such evidence does not exist for GC in the NAC setting, GC has become the most commonly used regimen based on extrapolation of data from patients with metastatic BCa and owing to a better toxicity prolife [13]. This pattern of practice has been confirmed in our series, in which 64.5% of patients received GC. Since the use of GC over MVAC is not clearly supported by evidence, we aimed to assess response rates in real-world practice with the hypothesis that response to MVAC would be higher than response to GC. This analysis in 935 patients, however, does not demonstrate a difference in efficacy.

The pCR rate (pT0N0M0) after NAC has been shown to be strongly associated with OS and recurrence-free survival and is therefore commonly considered a surrogate end point to evaluate treatment efficacy [19,20]. The pCR for our entire series (22.7%) was considerably lower than the pCR rate of 38% observed in the pivotal SWOG study and other prospective trials [2,21]. This was observed although the proportion of patients with cT3–T4a stage was higher in the SWOG trial (Table 6), which could be due in part to differences in staging techniques. In our series, the pathologic response rate was higher with lower clinical T stage. Differences seen in response rates relative to the pivotal SWOG trial may reflect the real-world nature of our patient cohort compared with the highly select cohort in the SWOG trial. In the SWOG trial, 317 patients were recruited over 11 yr from 126 institutions, which translates into an accrual rate of two to three patients per institution per year. Our results may better inform clinicians and patients about the potential benefits of NAC in routine practice. However, our results would be less favorable if we had conducted an intention-to-treat analysis and included patients who failed to complete three cycles of chemotherapy and/or did not go on to surgery.

The pCR rates for studies comparing MVAC and GC are summarized in Table 7. The pCR for MVAC among published series outside randomized controlled trials is variable and has been reported to be between 9% and 46% [19,22–24]. For GC, the reported rate of pCR among published series is within the range of 10–50% [14–17,24–29]. The variability arises from the heterogeneity of the trials with respect to clinical TNM stage of included patients and the number of cycles and dosing regimen of NAC administration. The lack of randomization and the small patient numbers likely led to significant selection bias. In a pooled analysis of seven studies incorporating 164 patients receiving GC, Yuh et al [27] reported a pCR rate of 25.6%. Few studies have assessed the factors predicting pCR after NAC on multivariable analysis; however, cT stage has been shown to be a predictor of OS and recurrence in patients receiving NAC followed by RC [14]. In our study, cT3 or higher

staging reduced the probability of pathologic response (complete or partial) by nearly 40%. Nevertheless, the accuracy of clinical staging is limited [25].

Use of GC or MVAC was a predictor of pathologic response to chemotherapy when compared with other regimens, but we did not detect a statistically significant difference between the two regimens. For GC, the adjusted OR of cPR compared with MVAC following bootstrapping was 0.96 (95% CI, 0.67–1.40), and given the relatively wide CI, we do not have sufficient evidence to conclude that one regimen is better than the other in our series.

The utility of no-cisplatin–based NAC is controversial. Carboplatin has been shown to be inferior to cisplatin in the metastatic setting in several studies [30,31], so its use for NAC would seem ill-advised without further evidence of its efficacy. Some early-stage trials have been completed, but mostly without comparator arms. In a prospective phase 2 trial of NAC in patients with locally advanced BCa, 31 patients were treated with three cycles of paclitaxel, carboplatin, and gemcitabine (PCaG) over 5 yr [32]. The rate of pCR in this study was 32% (22% for intention-to-treat analysis). Because of the mortality associated with chemotherapy, the trial was closed prior to reaching the planned enrollment goal. A subsequent study in 77 patients treated with PCaG and TURBT achieved a clinical cT0 rate of 46%, but 6 of 10 patients deemed to be cT0 had persistent cancer at the time of RC [33].

A more recent phase 2 trial of NAC using three cycles of nab-paclitaxel, carboplatin, and gemcitabine (ACaG) in 29 patients with locally advanced BCa (T2–4N0–2) reported a pT0N0 of 27.3% and a ≤pT1N0 rate of 54.5% [34]. The use of ACaG was associated with a high incidence of grade 3–4 myelotoxicity. In a retrospective series (cT2–4Nx) comparing MVAC with carboplatin and gemcitabine (CaG), Iwasaki et al reported a ≤pT1 rate of 53% for CaG, comparable to MVAC (62%; $p = 0.6$). The hematologic grade 3–4 complications for CaG were higher than for MVAC.

The question remains whether every patient with high-risk muscle-invasive BCa should receive NAC regardless of the regimen, or whether only cisplatin-based therapy should be offered to patients who can tolerate it while cisplatin-ineligible patients proceed directly to surgery [35]. In contrast, in a small comparative series by Mertens et al [36], the rate of pCR for patients with non–organ-confined BCa receiving CaG was 30.4%. The authors concluded that CaG might be a reasonable alternative to cisplatin in unfit patients.

The rate of pCR for patients with cT2 was 25% and 27% for GC and MVAC, respectively. On multivariable analysis, cT2 stage was a predictor of pT0 stage at cystectomy. Given the limitations of the clinical staging and the variability in extent of TURBT, it is difficult to discriminate the pT0 rate because of complete surgical resection at the time of TURBT. However, it is possible to speculate that the relatively higher rate of pT0 for cT2 disease is at least in part is because of completeness of TURBT in some cases. The rate of pCR for cT3–T4a patients showed a trend toward favoring MVAC compared with GC (24.4% vs 15.4%; $p = 0.07$). This information could be useful in further tailoring NAC administration.

On survival analysis, we did not detect a difference between GC and MVAC; however, they were both superior to other chemotherapy regimens. In our series, similar to previously

published data [18,20], pathologic response was associated with improvement in OS. After adjusting for relevant variables in a Cox regression model (Table 5), treatment with other NAC, presence of positive soft tissue surgical margin, and lack of pPR after NAC were associated with an increased risk of death from all causes.

Our study has important limitations, including its retrospective nature, the lack of randomization, the lack of standardization of NAC administration across centers, the variability of indications for NAC, and selection bias in the choice of chemotherapy regimen. Lack of centralized radiologic and pathologic assessment is an additional potential confounding factor. We did not assess NAC dose density, dose adjustment, growth factor support, or drug-related toxicity, morbidity, and mortality. Also, using pathologic response as a primary end point, we were not able to assess the outcome of patients who received NAC but never underwent cystectomy because of disease progression or change in performance status. We acknowledge the short follow-up for the survival data and have therefore focused on the pathologic response rates. Some risk factors, such as performance status, renal function, and the presence of hydronephrosis, were not captured. Despite these limitations, this is the largest series assessing the pathologic response to NAC and represents the real-world experience with NAC outside clinical trials.

5. Conclusions

Despite our clinical suspicion to the contrary, this analysis of outcome data from 19 centers does not suggest a difference in efficacy between MVAC and GC, although a clinically relevant difference cannot be excluded. The argument remains that MVAC, but not GC, has been proven effective in prospective randomized controlled trials. However, routine clinical practice has shifted more toward GC, and our data do not weigh against this shift. Response rates to NAC in our international, retrospective, real-world patient cohort are clearly lower than those reported in prospective randomized trials. We must be guarded in drawing conclusions from these data for clinical practice given the retrospective nonrandomized study design. It is important that these results not be misconstrued to suggest that NAC is not effective, as its effectiveness has been shown definitively in prospective randomized clinical trials.

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Take-home message

Response rates to neoadjuvant chemotherapy in our international cohort are clearly lower than those rates reported in prospective randomized trials. There was no statistically significant difference between the MVAC regimen (methotrexate, vinblastine, doxorubicin, cisplatin) and gemcitabine and cisplatin in terms of complete pathologic response (pT0N0) and partial pathologic response (pT≤1N0).

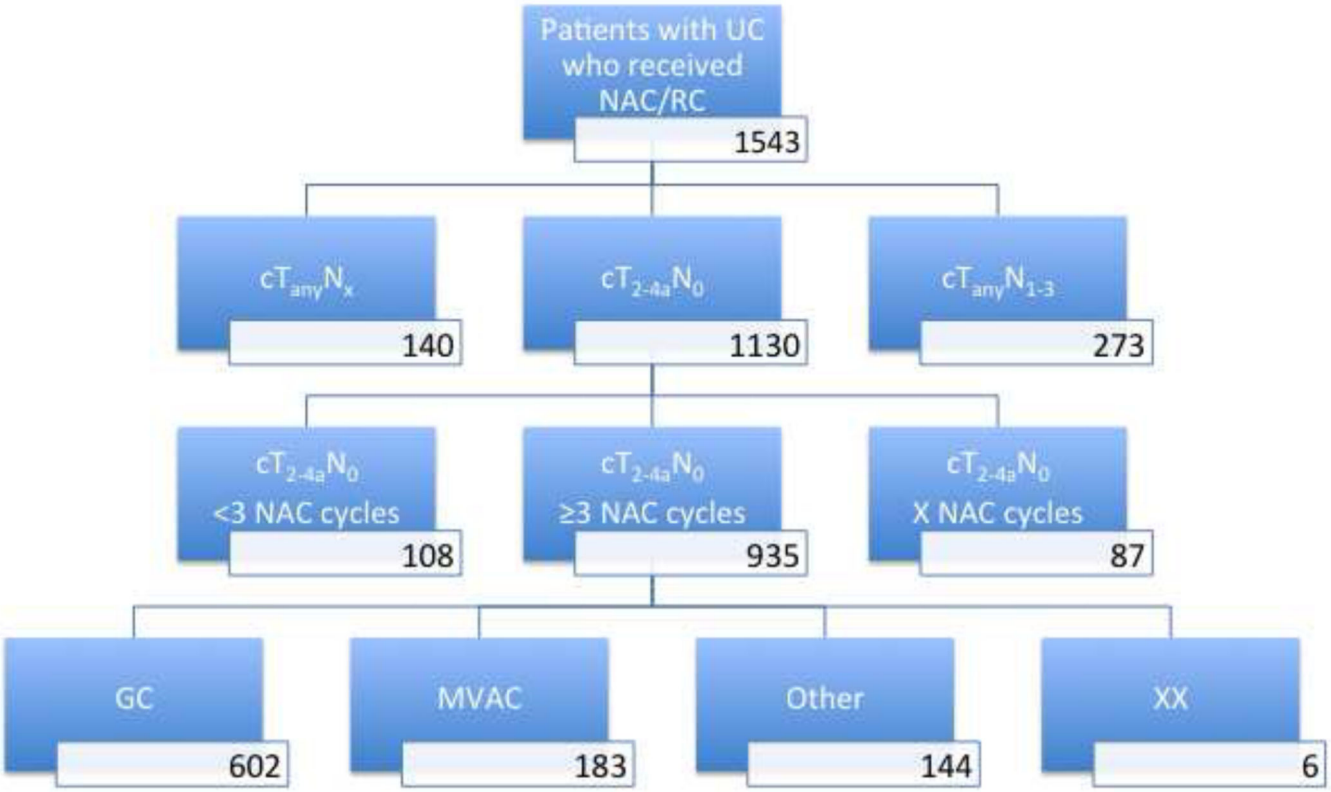

Fig. 1.

Flowchart demonstrating the selection of patients for the analysis.

GC = gemcitabine and cisplatin; MVAC = methotrexate, vinblastine, doxorubicin, cisplatin; NAC = neoadjuvant chemotherapy; RC = radical cystectomy; UC = urothelial carcinoma.

Table 1

Cohort characteristics, operative data, and pathologic outcomes

NAC regimen*	MVAC (*n* = 183)	GC (*n* = 602)	Other NAC (*n* = 144)
Age, yr, median (IQR)	62 (57–69)	65 (57–71)	65 (57–72)
Male, *n* (%)	145 (79.2)	472 (78.4)	117 (81.3)
Smoking history, *n* (%)	124 (67.8)	289 (48)	53 (36.8)
History of pelvis irradiation, *n* (%)	12 (6.6)	34 (5.6)	13 (9)
Clinical T stage, *n* (%)			
T2	91 (49.7)	418 (69.4)	94 (65.3)
T3	54 (29.5)	143 (23.7)	32 (22.2)
T4a	32 (17.5)	39 (6.5)	18 (12.5)
Tx	6 (3.3)	2 (0.3)	
Primary pathology TURBT, *n* (%)			
Urothelial cancer	162 (88.5)	543 (90.2)	131 (91)
Urothelial cancer with squamous differentiation	17 (9.3)	46 (7.6)	13 (9)
Urothelial cancer with glandular differentiation	4 (2.2)	13 (2.2)	–
Associated CIS, *n* (%)			
Yes	35 (19.1)	109 (18.1)	22 (15.3)
No	138 (75.4)	462 (76.7)	108 (75)
Unavailable data	10 (5.5)	31 (5.1)	14 (9.7)
Cycles, *n* (%)			
3	66 (46.1)	322 (53.5)	84 (58.3)
4	94 (51.4)	258 (42.9)	47 (32.6)
>4	23 (12.5)	22 (3.7)	13 (9.1)
Time between TURBT and NAC**, wk, median (IQR)	5 (2–8)	5 (4–8)	6 (4–9)
Time between NAC** and RC, wk, median (IQR)	14 (11–17)	17 (14–20)	17 (13–22)
Time between TURBT and RC, wk, median (IQR)	20 (16–26)	23 (19–29)	24 (19–31)
Extent of LND, *n* (%)			
Standard	60 (32.8)	186 (30.9)	36 (25)
Extended	103 (56.3)	310 (51.5)	81 (56.3)
None	3 (1.6)	14 (2.3)	5 (3.5)
Data unavailable	17 (9.3)	92 (15.3)	22 (15.3)
Type of urinary diversion, *n* (%)			
Ileal conduit	82 (44.8)	292 (48.5)	102 (70.8)
Orthotopic neobaldder	53 (29)	139 (23.1)	32 (22.2)

NAC regimen*	MVAC (*n* = 183)	GC (*n* = 602)	Other NAC (*n* = 144)
Continent cutaneous reservoir	8 (4.4)	33 (4.4)	6 (4.2)
Data unavailable	40 (21.9)	132 (21.9)	4 (2.8)
Pathologic outcome, *n* (%)			
pT0N0	45 (24.5)	144 (23.9)	22 (15.3)
≤pT1N0	82 (44.8)	263 (43.7)	36 (25)
Nodes removed, median (IQR)			
Extended LND	27 (17–41)	20 (13–29)	15 (9–21)
Standard LND	18 (11–25)	14 (9–20)	10 (5–15)
Positive nodes, median (range)	0 (0–23)	0 (0–50)	0 (0–15)
Positive surgical margins, no. (%)	14 (7.7)	31 (5.1)	19 (13.2)
Associated CIS, no. (%)	62 (33.9)	193 (32.1)	45 (31.3)

CIS = carcinoma in situ; GC = gemcitabine and cisplatin; IQR = interquartile range; LND = lymph node dissection; MVAC = methotrexate, vinblastine, doxorubicin, cisplatin; NAC = neoadjuvant chemotherapy; RC = radical cystectomy; TURBT = transurethral resection of bladder tumor.

*NAC regimen in six patients was unknown.

**From starting time of NAC.

Table 2

Correlation of clinical stage and final pathologic stage stratified by neoadjuvant chemotherapy regimen

	pT0N0 (pCR)	pTis/pTa/ pT1N0	≤pT1N0 (pPR)	pT2N0	pT3–4N0	pTany N1–3	pTx or Nx	Total
MVAC NAC, no. (%)								
cT2	23 (25.2)	21 (23.0)	44 (48.3)	13 (14.0)	12 (13.0)	19 (21.0)	3 (3.3)	91
cT3	16 (29.6)	8 (14.8)	24 (44.4)	11 (20.4)	10 (18.5)	9 (16.6)	0 (0.0)	54
cT4	5 (15.6)	7 (21.8)	12 (37.5)	2 (6.2)	7 (21.8)	10 (31.2)	1 (3.1)	32
cTx	1 (16.6)	1 (16.6)	2 (33.3)	1 (16.6)	1 (16.6)	2 (16.6)	–	6
Total	45 (24.5)	37 (20.2)	82 (44.8)	27 (14.7)	30 (16.4)	40 (21.8)	4 (2.1)	183
GC NAC, no. (%)								
cT2	114 (27.3)	84 (20.0)	198 (47.4)	65 (15.5)	71 (17.0)	74 (17.7)	10 (2.4)	418
cT3	22 (15.4)	30 (21.0)	52 (36.4)	21 (14.7)	39 (27.3)	30 (21.0)	1 (0.7)	143
cT4	6 (15.4)	5 (12.8)	11 (28.2)	4 (10.3)	14 (35.9)	10 (25.6)	–	39
cTx	2 (100)	–	2 (100)	–	–	–	–	2
Total	144 (23.9)	119 (19.7)	263 (43.7)	90 (15.0)	124 (20.6)	114 (18.9)	11 (1.8)	602
Other NAC, no. (%)								
cT2	12 (12.8)	11 (11.7)	23 (24.5)	21 (22.3)	18 (19.1)	31 (33.0)	31 (33.0)	94
cT3	3 (9.3)	2 (6.2)	5 (15.6)	4 (12.5)	10 (31.2)	11 (34.4)	11 (34.4)	32
cT4	7 (38.9)	1 (5.6)	8 (44.4)	1 (5.6)	7 (38.9)	2 (11.1)	2 (11.1)	18
cTx	–	–	–	–	–	–	–	–
Total	22 (15.3)	14 (9.7)	36 (25)	26 (18)	35 (24.3)	44 (30.6)	44 (30.6)	144

GC = gemcitabine and cisplatin; MVAC = methotrexate, vinblastine, doxorubicin, cisplatin; NAC = neoadjuvant chemotherapy; pCR = complete pathologic response; pPR = partial pathologic response.

Table 3

Multivariable analysis of factors predicting partial pathologic response (pT0N0)

Variable	Multivariable analysis	
	Coefficient (95% CI)	*p* value
Age, yr	1.00 (0.98–1.02)	0.69
Gender		
Female	1	
Male	1.18 (0.80–1.76)	0.39
T stage		
≤T2	1	
≥T3	0.67 (0.47–0.95)	0.02
Chemotherapy regimen		
MVAC	1	
GC	0.89 (0.61–1.34)	0.60
Other regimens	0.48 (0.27–0.87)	0.02

CI = confidence interval; GC = gemcitabine and cisplatin; MVAC = methotrexate, vinblastine, doxorubicin, cisplatin.

Table 4

Multivariable analysis of factors predicting partial pathologic response (≤pT1N0)

Variable	Multivariable analysis	
	Coefficient (95% CI)	*p* value
Age, yr	0.99 (0.98,1.01)	0.31
Gender		
Female	1	
Male	1.11 (0.80–1.54)	0.55
T stage		
≤T2	1	
≥T3	0.66 (0.49–0.88)	0.006
Chemotherapy regimen		
MVAC	1	
GC	0.88 (0.62–1.24)	0.46
Other regimens	0.35 (0.21–0.58)	<0.001

CI = confidence interval; GC = gemcitabine and cisplatin; MVAC = methotrexate, vinblastine, doxorubicin, cisplatin.

Table 5

Cox regression model assessing factors predicting overall survival

Variable	Cox regression analysis	
	HR (95% CI)	*p* value
Age, yr	0.99 (0.98–1.01)	0.61
Time between NAC and RC	0.99 (0.98–1.01)	0.92
Gender		
Female	1	
Male	1.15 (0.76–1.76)	0.49
Chemotherapy regimen		
MVAC	1	
GC	1.25 (0.80–1.93)	0.33
Other regimens	1.64 (1.01–2.66)	0.04
Surgical margin		
Negative	1	
Positive	2.21(1.36–3.57)	0.001
Lymph node dissection		
None	1	
Standard	1.25 (0.36–3.34)	0.72
Extended	1.65 (0.49–5.59)	0.42
pPR (≤pT1N0)		
No	1	
Yes	0.25 (0.16–0.40)	<0.001

CI = confidence interval; GC = gemcitabine and cisplatin; HR = hazard ratio; MVAC = methotrexate, vinblastine, doxorubicin, cisplatin; NAC = neoadjuvant chemotherapy; pPR = partial pathologic response; RC = radical cystectomy.

Table 6

Comparison of patients from SWOG-8710 MVAC arm with the MVAC and GC subgroups in the present series

	SWOG-8710, MVAC (*n* = 153)	Current series, MVAC (*n* = 183)	Current series, GC (*n* = 602)
Age, yr, median (range)	63 (39–84)	62 (31–85)	65 (27–89)
Male, %	81	79.2	78.4
cT3–T4a, %	60.4	48.6	30.3
pT0N0, %	38 *	24.5	23.9
≤pT1N0, %	44	44.8	43.7
cT2 → pT0N0, %	39	25.2	27.3
cT3-4 → pT0N0, %	24	24.4	15.4
cT2 → ≤pT1N0, %	55	48.3	47.4
cT3-4 → ≤pT1N0, %	35	36.8	34.6

GC = gemcitabine and cisplatin; MVAC = methotrexate, vinblastine, doxorubicin, cisplatin.

* The SWOG-8710 study did not specifically report the nodal status of the patients with pT0 disease, but we have attributed all pT0 patients to pT0N0 in this table because only 17 patients in the entire cohort were pN1–3.

Table 7

Summary of comparative studies assessing complete pathologic response and partial pathologic response after different neoadjuvant chemotherapy regimens

Study	Year	Study design	Patients treated with Cx, no.	Patient characteristics	pCR	pPR
Dash et al [15]	2008	Retrospective, GC vs MVAC	42 vs 54	cT2–4N0M0	GC 26%, MVAC 28%	GC 36%, MVAC 35%
Kaneko et al [24]	2011	Retrospective, GC vs MVAC	22 vs 9	cT2–4N0–1M0	GC 50%, MVAC 22%,	GC 64%, MVAC 44%
Yeshchina et al [17]	2012	Retrospective, GC vs MVAC	16 vs 45	cT2–4N0–2M0	GC 25%, MVAC 31%	GC 50%, MVAC 44%
Pal et al [16]	2012	Retrospective, GC vs MVAC vs other	24 vs 22 vs 15	cT2–4N0M0	GC 25%, MVAC 22.5%	GC 58%, MVAC 50%
Fairey et al [14] *	2013	Retrospective, GC vs MVAC	58 vs 58	cT2–4N0M0	GC 21%, MVAC 10.3%	GC 35%, MVAC 22%
Meijer et al [25] *	2013	Retrospective series, GC and MVAC	125	cT2–4N0–2M0	26% for the entire series	Not reported

GC = gemcitabine/cisplatin; MVAC = methotrexate/vinblastine/doxorubicin/cisplatin; pCR = complete pathologic response; pPR = partial pathologic response.

* Subset of patients from this study that met our inclusion criteria is included in our series.