Original Article

Efficient Delivery of Radical Cystectomy After Neoadjuvant Chemotherapy for Muscle-Invasive Bladder Cancer

A Multidisciplinary Approach

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BACKGROUND: Cystectomy delay >90 days after a diagnosis of muscle-invasive bladder cancer (MIBC) adversely affects pathologic stage and survival outcomes in patients who undergo primary surgery. After neoadjuvant chemotherapy (NAC), the impact of the timing of cystectomy delivery on these outcomes is uncertain. Poor communication between urologic and medical oncologists can result in cystectomy delay after systemic treatment. The authors of this report hypothesized that a delay in cystectomy delivery after NAC is associated with adverse survival outcomes. **METHODS:** An eligible cohort of 153 patients with MIBC received NAC and underwent radical cystectomy between 1990 and 2007. At the authors' institution, the genitourinary team strives to schedule patients for surgery at the time of initial evaluation or after their first chemotherapy cycle. Clinicopathologic characteristics, including timing of cystectomy, chemotherapy delivery, vital status, and reasons for excessive surgical delay, were analyzed retrospectively using an institutional database. A Cox proportional regression model was used to test the association between the timing of cystectomy delivery and survival. **RESULTS:** The median follow-up for all patients was 3.6 years. The median time to cystectomy was 16.6 weeks and 6.9 weeks from the first and last day of NAC, respectively. In multivariate analyses, the timing of cystectomy delivery from the termination of NAC did not significantly alter the risk of survival. The most common reason for cystectomy delivery beyond 10 weeks (28 patients; 18%) was procedural scheduling. **CONCLUSIONS:** Cystectomy delivery within 10 weeks after NAC did not compromise patient survival and, thus, provided a reasonable window for patient recovery and surgical intervention. ***Cancer*** **2012;118:44-53.** © *2011 American Cancer Society.*

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Historically, radical cystectomy has been the standard treatment for muscle-invasive bladder cancer (MIBC).[1,2] Multiple studies have suggested that a delay in undergoing cystectomy is associated with adverse outcomes.[3-9] Specifically, a cystectomy delay >3 months after a diagnosis of MIBC has been associated with local tumor progression[3] and worsened progression-free survival,[6] cancer-specific survival (CSS),[5] and overall survival (OS).[5]

More recently, randomized trials and a meta-analysis have demonstrated a survival advantage for cisplatin-based neoadjuvant chemotherapy (NAC) followed by radical cystectomy compared with cystectomy alone for the treatment of MIBC.[10,11] Outside of a clinical trial, the timing of cystectomy delivery after NAC can vary considerably, and a median delay of 7 months after a diagnosis of MIBC has been reported by some large academic centers.[12] The impact of cystectomy delay after NAC on survival currently is uncertain. Previous studies demonstrating adverse outcomes with cystectomy delay did not include patients who received NAC.[3-5] A theoretical possibility of adverse outcomes exists for patients who experience excessive cystectomy delay because of complications from NAC.[13] However, delays also may result from the administrative coordination of scheduling preparatory appointments, restaging evaluations, secondary opinions, and

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the actual surgical procedure. A lack of communication between the urologist and medical oncologist can occur during a 3-month course of systemic therapy, particularly when both practice in different institutions.

In this study, we analyzed the impact of the timing of cystectomy delivery after NAC on survival in patients with MIBC in a collaborative, multidisciplinary cancer program at an academic tertiary care center. We specifically sought to define a range of cystectomy delivery that would compromise CSS or OS. We hypothesized that a substantial delay in cystectomy delivery would result in adverse survival outcomes.

MATERIALS AND METHODS

Patient Cohort

We retrospectively analyzed data from an institutional review board-approved institutional database. Between January 1990 and December 2007, 1012 consecutive patients underwent radical cystectomy for high-risk bladder cancer at the University of Michigan, including 621 patients (61%) who had MIBC or clinical evidence of extravesical tumor without metastatic disease. Of these 621 patients, 166 (27%) received NAC without subsequent adjuvant chemotherapy. From this cohort, 13 patients were excluded from the current analysis, including 9 patients who had had pure nonurothelial histology, 2 patients who had a history of upper urinary tract cancer, 1 patient who withheld consent, and 1 patient who was lost to follow-up. The remaining 153 patients formed our study cohort.

Study Variables

Clinicopathologic parameters that were evaluated included age, sex, Eastern Cooperative Oncology Group (ECOG) performance status,[14] American Society of Anesthesiologists (ASA) score,[15] American Joint Committee on Cancer TNM staging before NAC (clinical stage) and after cystectomy (pathologic stage),[16] histology and lymphovascular invasion (LVI) at cystectomy, site of chemotherapy delivery (University of Michigan or other facility), chemotherapeutic regimen, and dates of initiation and termination of systemic treatment. Pathologically, organ-confined bladder cancer was defined as lymph node-negative (N0) disease with Ta, tumor in situ (Tis), T1, or T2 tumors. Extravesical disease was defined as pathologic T3 or T4 tumors or T_{any} tumors with lymph node invasion (N+).

Clinical staging before NAC was based on histologic evaluation at the time a patient underwent transurethral resection of bladder tumor, examination under anesthesia, and a metastatic survey, including plain radiograph or computerized tomography (CT) studies of the chest and axial imaging of the abdomen and pelvis with CT or magnetic resonance imaging. Bone scans were performed for bulky tumors, bone-related symptoms, or elevated alkaline phosphatase levels. Standard postoperative surveillance was performed.[17]

Determinants for a substantial delay in undergoing cystectomy ($\geq$10 weeks after treatment termination) were gleaned from the patient record. Reasons for delay were identified as patient factors (adverse health status from toxicity or comorbidities, patient preference, multiple opinions) or physician/institution factors (extended NAC on or off protocol, scheduling delay).

Chemotherapeutic Regimen

The 3 most commonly used NAC regimens were combined paclitaxel, carboplatin, and gemcitibine (PCG)[18] (paclitaxel 175 mg/m^2 on Day 1, carboplatin at an area under curve of 5 on Day 1, and gemcitabine 800 mg/m^2 on Days 1 and 8 every 21 days for 3 cycles); combined gemcitibine and cisplatin (GC)[19,20] (gemcitabine 1000 mg/m^2 on Days 1, 8, and 15 and cisplatin 70 mg/m^2 on Day 2 with cycles repeated every 28 days for 3 cycles); and combined methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC)[10] (methotrexate 30 mg/m^2 on Days 1, 15, and 22; vinblastine 3 mg/m^2 on Days 2, 15, and 22; doxorubicin 30 mg/m^2 on Day 2; and cisplatin 70 mg/m^2 on Day 2 repeated every 28 days for 3 cycles). Thus, most patients would be expected to receive NAC for 9 to 12 weeks. The "miscellaneous" group included regimens other than PCG, MVAC, or GC.

Statistical Analysis

The interval from the first and last day of NAC to radical cystectomy was used to calculate the time to cystectomy delivery from the initiation and termination of NAC, respectively. CSS was defined as the time from cystectomy to the time of death from bladder cancer, and OS was defined as the time from cystectomy to the time of death from any cause. Patients were censored at the date of last follow-up if they were alive or had died from causes unrelated to bladder cancer (CSS) or if they were alive (OS).

Log-rank tests were used to assess the unadjusted difference in survival probability among patient groups stratified by clinical parameters. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated using Cox proportional hazards regression for this difference and for

multivariate analyses. By using a process of forward selection of covariates, a step-wise Cox regression analysis was used to generate multivariate models to determine the odds of CSS and OS. Of the 11 variables that were considered for model selection, 8 variables for CSS and 9 variables for OS met criteria for inclusion based on their univariate significance ($P < .5$) or their clinical relevance with univariate P values $< .3$. Kaplan-Meier estimates were used to create survival plots. Comparisons of timing of cystectomy delivery by NAC regimen were performed using the Wilcoxon rank-sum test or the Kruskal-Wallis test. Comparisons of survival between NAC populations (miscellaneous vs all others) were performed using the log-rank test.

To identify correlations between the timing of cystectomy delivery and survival, all possible delay points were examined serially from the initiation and termination of NAC in weekly increments. Each assessment divided the cohort into 2 subsets (those with cystectomy delivery greater than the cutoff point and those with cystectomy delivery less than or equal to the cutoff point). Log-rank analyses then were used to detect any possible difference in survival between the 2 subsets. A relevant cutoff point was defined as one that resulted in a statistically significant survival difference between the 2 subsets measured at that cutoff point and consistently at subsequent cutoff points. The 5% significance level was applied to all tests and models. Analyses were performed using the SAS statistical software package (SAS Institute, Inc., Cary, NC).

RESULTS

Patient Demographics and Clinicopathologic Parameters

Table 1 summarizes the cohort demographics of the 153 eligible patients. The mean age (64 years) and sex distribution (73% men) were similar to other retrospective series and randomized trials of patients with MIBC undergoing cystectomy.[10,21] The median follow-up was 3.6 years from cystectomy. The ECOG performance status before surgery was 0 in 94% of patients, reflecting their suitability for cystectomy. In total, 76% of patients received NAC at our home institution.

Patients typically received carboplatin-containing (n = 107; 69.5%) or cisplatin-containing (n = 40; 26.1%) regimens, and only 6 patients (3.9%) did not receive platinum-based therapy. Overall, 99 patients (64.7%) received PCG, and 32 patients (21%) received MVAC or GC, reflecting commitment to institutional and national clinical trials,[18,22] provider preference, or compromised renal function. A fourth "miscellaneous" group consisted of 22 patients (14%) who received an NAC regimen other than PCG, MVAC, or GC. Compared with patients who received PCG, MVAC, or GC, patients who received a miscellaneous regimen did not differ significantly in age ($P = .72$), ECOG performance status ($P = .49$), or ASA score ($P = .63$). Fourteen of those 22 patients (64%) were treated at our institution, and 16 (73%) received a platinum drug as part of their treatment regimen.

At the time of cystectomy, the ASA score largely was 2 (51%) or 3 (46%), which demonstrated the presence of a significant number of coexisting comorbidities within this well performing population. A pathologic complete response to NAC (pT0) was observed in 24% of the cohort, and another 12% demonstrated non-MIBC (NMIBC) and no lymph node metastases. One hundred forty-four of 153 patients (94%) underwent pelvic lymphadenectomy, and 23% of patients had lymph node invasion. LVI status was available in 147 (96%) patients. We observed evidence of LVI in 27% of tumors, a rate that was lower than the rates reported in cystectomy-alone series.[21,23]

Timing of Cystectomy Delivery

The median time to cystectomy delivery from the *initiation* of NAC was 16.6 weeks (range, 6.3-195.6 weeks; 25th and 75th percentiles, 13.9 weeks and 21.6 weeks, respectively). The median time to cystectomy delivery from the *termination* of NAC was 6.9 weeks (range, 1.7-179.6 weeks; 25th and 75th percentiles, 5.3 weeks and 9.1 weeks, respectively). Pertinent variables were explored to discern a potential association with cystectomy delivery (Table 2). Advanced age (≥70 years), regimen type, chemotherapy site, and advanced clinical stage did not have an impact on the timing of cystectomy delivery. Patients who had LVI, extravesical disease, or an incomplete treatment response did not have a longer time to cystectomy compared with patients who did not have LVI, patients who had organ-confined tumor, or patients who achieved a complete pathologic response, respectively.

The association between survival and the timing of cystectomy delivery from the termination of NAC is summarized in Table 3 over Weeks 4 through 12. An analysis of all evaluable time points at weekly intervals revealed no difference in CSS or OS between those patients who were treated at points longer than the delivery interval

Table 1. Cohort Demographics and Clinicopathologic Parameters for the Entire Cohort (n=152)

Parameter	No. of Patients (%)
Age: Mean±SE, y	64.26±0.86
Sex	
Women	41 (27)
Men	112 (73)
NAC regimen	
MVAC	12 (8)
GC	20 (13)
PCG	99 (65)
Miscellaneous	22 (14)
NAC site	
UM Hospital	117 (76)
Outside hospital	36 (24)
Clinical stage[a]	
T2N0M0	59 (39)
T3N0M0	57 (37)
T4N0M0	22 (14)
N+	15 (10)
T1N+M0	2 (1)
T2N+M0	4 (3)
T3N+M0	6 (4)
T4N+M0	3 (2)
ECOG performance status at cystectomy	
0	144 (94)
1	9 (6)
ASA score at cystectomy[b]	
1	4 (3)
2	77 (51)
3	70 (46)
4	1 (1)
Histology at cystectomy	
Urothelial	112 (73)
Mixed urothelial-small cell	2 (1)
Mixed urothelial-squamous cell	3 (2)
NA[c]	36 (23)
Lymphovascular invasion at cystectomy[d]	
Present	39 (27)
Absent	108 (73)
Pathologic stage	
Tumor classification	
T0	36 (24)
Ta	2 (2)
Tis	14 (10)
T1	6 (4)
T2	23 (15)
T3	51 (33)
T4	21 (14)
Lymph node status	
N0	109 (71)
N+	35 (23)
TaN+	1 (1)
TisN+	2 (1)
T1N+	1 (1)
T2N+	2 (1)
T3N+	19 (12)
T4N+	10 (7)
Nx	9 (6)
Overall pathologic stage	
Organ confined	75 (49)
Extravesical	78 (51)
Marital status	
Married	115 (75)
Not married	38 (25)
Year of surgery	
2001-2009	129 (84)
1990-2000	24 (16)

Abbreviations: ASA, American Society of Anesthesiologists physical status scale; ECOG, Eastern Cooperative Oncology Group; GC, gemcitabine and cisplatin; MVAC, methotrexate, vinblastine, doxorubicin, and cisplatin; NA, not applicable; NAC, neoadjuvant chemotherapy; PCG, paclitaxel, carboplatin, and gemcitabine; SE, standard error; Tis, tumor in situ; UM, University of Michigan.

[a] Reflects the clinical stage before NAC.

[b] The ASA score was unknown in 1 patient.

[c] Reflects a pathologic complete response.

[d] Lymphovascular invasion status was not available for 7 patients.

compared with those who were treated at points less than or equal to the delivery interval. Log-rank analyses of delivery time points <4 weeks and >12 weeks included subsets of ≤10% patients and, thus, were interpreted with caution. A similar analysis of all evaluable time periods (13-27 weeks) from the initiation of NAC to cystectomy delivery also revealed no survival difference between patients who were treated at points longer than the delivery interval compared with those who were treated at points less than or equal to the delivery interval (data not shown).

Cystectomy delivery occurred in 28 patients (18%) ≥10 weeks after the termination of NAC, reflecting the population closest to the upper quintile with surgical delay. The most common factor contributing to a prolonged time to surgery was "scheduling issues," which were observed in 11 patients (39%), including 7 patients who were treated outside of our home institution. Adverse health status because of patient comorbidity or toxicity from NAC occurred in 3 patients (11%) and 4 patients (14%), respectively. Elective delays in surgery related to patient preference/multiple opinions (2 patients; 7%), cystectomy refusal (6 patients; 21%), unknown factors (1 patient; 4%), or a combination of factors (1 patient; 4%) occurred much less frequently.

Table 2. Timing of Radical Cystectomy Delivery From the Last Day of Neoadjuvant Chemotherapy Stratified by Clinicopathologic Parameters

Variable	No. of Patients (%)	Timing of Radical Cystectomy Delivery After NAC, wk		P^a
		Mean±SE	Median	
Age, y				
<70	97 (65)	8.90±1.81	7.14	.09
≥70	52 (35)	12.69±2.80	6.71	
NAC regimen				
MVAC	10 (8)	8.53±1.43	6.64	.67
GC	20 (13)	6.99±0.88	6.36	
PCG	99 (66)	11.43±2.28	7.14	
Miscellaneous	20 (13)	8.29±0.91	6.50	
NAC site				
UM Hospital	114 (77)	10.84±1.99	6.86	.99
Outside hospital	35 (23)	8.19±0.76	6.14	
Clinical tumor classification[b]				
≤T2	63 (42)	13.54±3.53	6.71	.66
≥T3	86 (58)	7.79±0.49	6.93	
Lymphovascular invasion at cystectomy				
Present	38 (27)	6.91±0.41	6.50	.46
Absent	107 (73)	11.40±2.12	6.86	
Pathologic stage				
Organ confined	75 (50)	8.42±0.64	7.00	.40
Extravesical	74 (50)	12.04±3.01	6.71	
Response to NAC				
Complete response: pT0	36 (24)	13.23±4.93	6.21	.39
Incomplete response: Non-pT0	113 (76)	9.26±1.28	6.86	
Marital status				
Married	113 (76)	10.14±1.98	6.71	.22
Not married	36 (24)	10.46±1.28	7.43	
Year of surgery				
2001-2009	129 (87)	10.54±1.76	6.71	.73
1990-2000	20 (13)	8.17±0.92	7.07	

Abbreviations: GC, gemcitabine and cisplatin; MVAC, methotrexate, vinblastine, doxorubicin, and cisplatin; NAC, neoadjuvant chemotherapy; PCG, paclitaxel, carboplatin, and gemcitabine; SE, standard error; UM, University of Michigan.

[a] Based on the median time to cystectomy delivery.

[b] Reflects the clinical stage before NAC.

Variables Impacting OS

The median OS was 2.6 years, and the 2-year and 5-year survival rates were 57% and 38%, respectively. At the time of the current report, the median CSS had not been reached, and the 2-year and 5-year CSS rates were 60% and 52%, respectively. In total, 2 patients (1.3%) died in the perioperative period within 30 days of cystectomy. Table 4 summarizes the association between the study variables and CSS. Pathologic stage, LVI, NAC regimen, and year of surgery year were all associated with CSS in univariate analysis. Table 5 summarizes the association between study variables and OS. Pathologic stage, LVI, NAC regimen, and ASA score were associated with OS in univariate analysis. Although the type of chemotherapy regimen was associated statistically with CSS and OS in univariate analyses, there certainly were analytic limitations because of the small numbers of patients receiving specific regimens, particularly in the MVAC group. Secondary analyses attributed the survival difference to the superiority of established regimens (GC and PCG) over the

Table 3. Patient Survival Stratified by Cystectomy Delivery After Termination of Neoadjuvant Chemotherapy (n=149)[a]

	No. of Patients		Cancer-Specific Survival		Overall Survival	
Weeks to Cystectomy	≤Delivery Time Point	>Delivery Time Point	HR (95% CI)	Log-Rank *P*	HR (95% CI)	Log-Rank *P*
4	15	134	1.24 (0.53-2.88)	.62	1.77 (0.77-4.09)	.17
5	32	117	0.86 (0.48-1.53)	.60	0.99 (0.58-1.67)	.96
6	55	94	0.80 (0.49-1.32)	.38	1.08 (0.69-1.69)	.74
7	81	68	0.86 (0.52-1.41)	.54	1.05 (0.68-1.62)	.83
8	103	46	1.07 (0.63-1.84)	.80	1.21 (0.76-1.91)	.42
9	111	38	1.29 (0.74-2.24)	.38	1.38 (0.86-2.22)	.19
10	121	28	1.22 (0.65-2.28)	.54	1.50 (0.90-2.52)	.12
11	127	22	1.01 (0.48-2.12)	.98	1.35 (0.74-2.44)	.32
12	131	18	0.66 (0.27-1.65)	.37	1.10 (0.57-2.13)	.78

Abbreviations: CI, confidence interval; HR, hazard ratio.
[a] Data on the end date for chemotherapy were unavailable for 4 patients.

"miscellaneous" group with respective HRs of 0.24 (95% CI, 0.10-0.61) and 0.45 (95% CI, 0.27-0.77). Multivariate models (Tables 4 and 5) demonstrated that pathologic stage and year of surgery were the strongest predictors of CSS, whereas pathologic stage was the strongest predictor of OS. The timing of cystectomy delivery after NAC as a continuous variable did not have an impact on CSS (HR, 0.97; 95% CI, 0.92-1.03; $P = .32$) or OS (HR, 0.97; 95% CI, 0.93-1.01; $P = .24$).

Optimal survival was observed among the patients who achieved a complete pathologic response (pT0), with 2-year and 5-year OS rates of 80% and 63%, respectively (Fig. 1); whereas the collective population with residual disease had 2-year and 5-year OS rates of 49% and 29%, respectively. Patients who had residual nonmuscle-invasive disease had more favorable survival rates compared with patients who had residual muscle-invasive and extravesical disease ($P = .02$) (Fig. 2). The 2-year and 5-year OS rates were 68% and 53%, respectively, for patients with lymph node negative NMIBC and 44% and 24%, respectively, for the combined population of patients with muscle-invasive and extravesical disease. There was no significant difference in the survival of patients with pT0N0 disease and those with pathologic NMIBC ($P = .33$).

DISCUSSION

The current data demonstrate the feasibility of efficient delivery of cystectomy after NAC for MIBC in a multidisciplinary group practice. The median time to cystectomy from the termination of NAC was <7 weeks, and 80% of the study cohort underwent cystectomy by 10 weeks. Age did not have an impact on the timing of surgery. Patients aged >70 years (34% of the cohort) underwent cystectomy at a median of 6.7 weeks after the completion of treatment and enjoyed an OS similar to that of younger patients (aged <70 years). Systemic treatment at an outside institution did not delay cystectomy delivery or compromise survival. Furthermore, the timing of cystectomy delivery did not appear to contribute to local disease progression, in that patients with higher pathologic stage tumors had a time to cystectomy similar to that of patients with organ-confined disease. Likewise, an incomplete pathologic response could not be attributed to prolonged time to cystectomy delivery. Despite the use of multiple regimens in this study group, the timing of cystectomy delivery after NAC across the various therapies was similar, with a median that ranged from 6.4 weeks to 7.1 weeks.

The majority of our patients (65%) received neoadjuvant PCG in keeping with ongoing institutional and national clinical trials during the study period.[18,22] These trials certainly impacted general practice patterns at our institution, because several patients received this regimen off protocol. Consequently, only 21% of the cohort received a standard cisplatin-based regimen. Moreover, 14% received alternative regimens generally because of individual patient comorbidity. The resultant survival outcomes in this cohort may be a reflection of the predominant use of carboplatin instead of cisplatin-based regimens. The 2-year and 5-year survival rates of 57% and 38%, respectively, were lower than expected when considering the survival rates reported from randomized trials that used primarily cisplatin-based neoadjuvant combinations before local therapy. For example, data from the Advanced Bladder Cancer Meta-Analysis Collaborative comparing randomized NAC and cystectomy with cystectomy alone suggested 2-year and 5-year OS rates of

Table 4. Cancer-Specific Mortality Stratified by Clinicopathologic Parameters

Variable	No. (%)		Univariate Analysis		Multivariate Analysis	
	Cancer-Specific Deaths	Alive or Dead of Other Causes	HR [95% CI]	Log-Rank *P*	HR [95% CI]	*P*
Age, y[a]						
<70	44 (44)	56 (56)	1.02 [0.61-1.72]	.93	NA	NA
≥70	21 (40)	32 (60)				
NAC regimen						
MVAC	7 (58)	5 (42)	Reference	.01	Reference	.34
GC	5 (25)	15 (75)	0.40 [0.13-1.25]		0.84 [0.20-3.51]	
PCG	39 (39)	60 (60)	0.64 [0.29-1.44]		0.96 [0.32-2.87]	
Miscellaneous	14 (64)	8 (36)	1.50 [0.60-3.72]		1.85 [0.60-5.75]	
NAC site						
UM Hospital	47 (41)	69 (59)	0.72 [0.42-1.24]	.23	0.86 [0.46-1.61]	.64
Outside hospital	18 (49)	19 (51)				
Clinical tumor classification before NAC						
≤T2	22 (34)	43 (66)	1.56 [0.93-2.60]	.09	1.32 [0.71-2.46]	.38
≥T3	43 (49)	45 (51)				
ECOG performance status at cystectomy[a]						
0	61 (42)	83 (58)	0.87 [0.31-0.39]	.78	NA	NA
1	4 (44)	5 (56)				
ASA score at cystectomy						
1, 2	31 (38)	50 (62)	1.46 [0.89-2.38]	.13	1.50 [0.87-2.58]	.15
3, 4	34 (48)	37 (52)				
Lymphovascular invasion at cystectomy						
Present	27 (69)	12 (31)	2.94 [1.75-5]	<.0001	1.49 [0.79-2.86]	.21
Absent	33 (31)	75 (69)				
Pathologic stage						
Extravesical	50 (64)	28 (36)	4.55 [2.5-8.33]	<.0001	4.76 [2.27-10.0]	<.0001
Organ confined	15 (20)		60 (80)			
Marital status[a]						
Married	50 (43)	65 (57)	0.93 0.52-1.66]	.81	NA	NA
Not married	15 (39)	23 (61)				
Year of surgery						
1990-2000	15 (63)	9 (37)	1.92 [1.06-3.45]	.03	2.63 [1.10-6.25]	.03
2001-2009	50 (39)	79 (61)				
Cystectomy delivery from termination of NAC					0.97 [0.92-1.03]	.32

Abbreviations: ASA, American Society of Anesthesiologists physical status scale; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; GC, gemcitabine and cisplatin; HR, hazard ratio; MVAC, methotrexate, vinblastine, doxorubicin, and cisplatin; NA, not applicable; NAC, neoadjuvant chemotherapy; PCG, paclitaxel, carboplatin, and gemcitabine; UM, University of Michigan.

[a] Not included in multivariate analysis.

approximately 68% and 48%, respectively.[11] Patients who received alternative regimens in the miscellaneous category in our cohort had survival rates that were inferior to those achieved by patients who received either PCG or GC, although selection bias and case mix likely influenced this result.

Pathologic staging at the time of cystectomy was a strong predictor of survival, and patients who had

Table 5. All-Cause Mortality Stratified by Clinicopathologic Parameters

	No. (%)		Univariate Analysis		Multivariate Analysis	
Variable	Dead	Alive	HR [95% CI]	Log-Rank *P*	HR [95% CI]	*P*
Age, y						
<70	54 (54)	46 (46)	0.75 [0.48-1.16]	.19	1.5 [0.9-2.57]	.12
≥70	33 (62)	20 (38)				
NAC regimen						
MVAC	8 (67)	4 (33)	Reference	.004	Reference	0.43
GC	6 (30)	14 (70)	0.47 [0.16-1.40]		0.75 [0.20-2.78]	
PCG	53 (54)	46 (46)	0.83 [0.39-1.76]		0.93 [0.33-2.56]	
Miscellaneous	20 (91)	2 (9)	1.73 [0.75-3.99]		1.51 [0.52-4.43]	
NAC site						
UM Hospital	63 (54)	53 (46)	0.70 [0.43-1.12]	.13	1.32 [0.76-2.25]	.34
Outside hospital	24 (65)	13 (35)				
Clinical tumor classification before NAC						
≤T2	32 (49)	33 (51)	0.73 [0.47-1.13]	.15	1.11 [0.65-1.9]	.7
≥T3	55 (63)	33 (37)				
ECOG performance status at cystectomy[a]						
0	83 (58)	61 (42)	1.19 [0.43-3.25]	.74	NA	NA
1	4 (44)	5 (56)				
ASA score at cystectomy						
1, 2	42 (52)	39 (48)	1.63 [1.05-2.5]	.03	0.63 [0.39-1.05]	.64
3, 4	45 (63)	26 (37)				
Lymphovascular invasion at cystectomy						
Absent	52 (48)	56 (52)	0.45 [0.28-0.71]	.0005	1.32 [0.74-2.36]	.34
Present	29 (74)	10 (26)				
Pathologic stage						
Organ confined	28 (37)	47 (63)	3.33 [2.04-5.26]	<.0001	3.0 [1.65-5.42]	.0003
Extravesical	59 (76)	19 (24)				
Marital status[a]						
Married	65 (57)	50 (43)	0.91 [0.56-1.48]	.71	NA	NA
Not married	22 (58)	16 (42)				
Year of surgery						
2001-2009	66 (51)	63 (49)	0.62 [0.36-1.05]	.07	2.17 [0.98-4.80]	.06
1990-2000	21 (87)	3 (13)				
Cystectomy delivery from termination of NAC					0.97 [0.93-1.01]	.24

Abbreviations: ASA, American Society of Anesthesiologists physical status scale; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; GC, gemcitabine and cisplatin; HR, hazard ratio; MVAC, methotrexate, vinblastine, doxorubicin, and cisplatin; NA, not available; NAC, neoadjuvant chemotherapy; PCG, paclitaxel, carboplatin, and gemcitabine; UM, University of Michigan.
[a] Not included in multivariate analysis.

extravesical tumors had nearly 5-fold and 3-fold increases in the risk of death from bladder cancer or from any cause, respectively, compared with patients who had organ-confined tumors. Surgery year was an independent predictor of CSS. Within the cohort, 24% had a complete pathologic response, and another 12% had residual NMIBC, and both were associated with superior survival outcomes compared with patients who had muscle-invasive or extravesical disease.[10] The frequency of pT0 after NAC varies in published series based on the regimen and study design

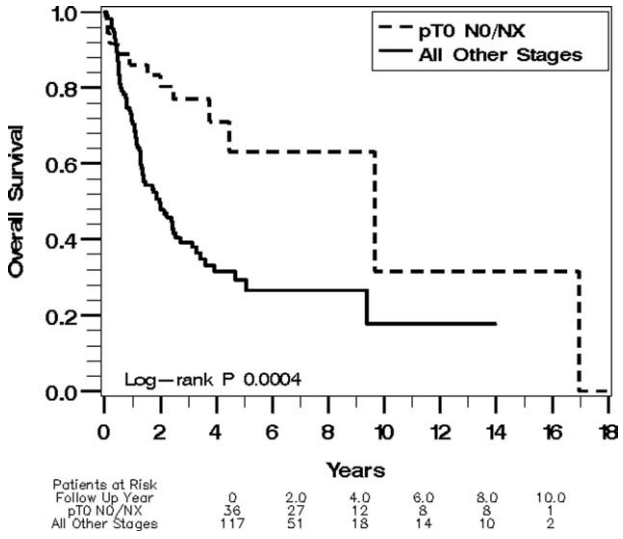

Figure 1. Overall survival stratified according to pathologic complete response (pT0) versus incomplete response.

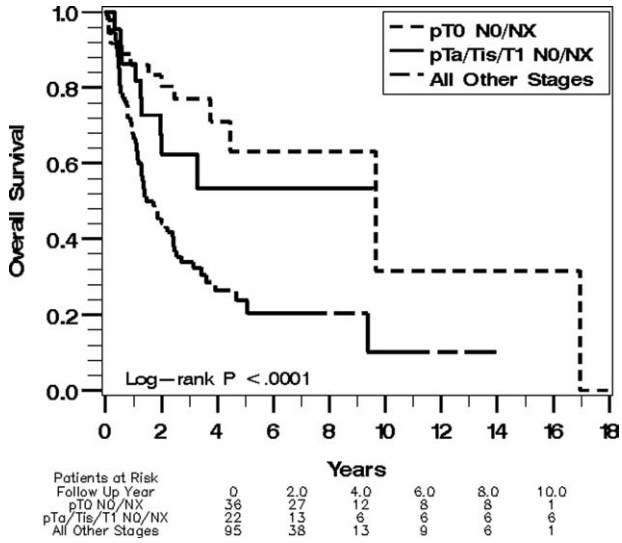

Figure 2. Overall survival stratified according to pathologic stage. pT indicates pathologic complete response; Tis, tumor in situ.

(7%-28% in single-center, retrospective studies using MVAC or GC[12,24]; 18% in a multicenter phase 2 study using PCG[22]; and 38% in a multicenter, cooperative group, randomized controlled trial using MVAC[10]). The pT0 rate of 24% in the current series is certainly a reflection of "real world" practice with the administration of different systemic regimens to a population of patients who had a variety of social circumstances and comorbidities. Although our population included high-performing patients, nearly 50% of the study cohort had substantial medical conditions, as evidenced by ASA scores of 3 or 4. Our inclusion of these patient categories reflects the aggressiveness with which our group delivers NAC. Finally, an important observation was the similar 2-year and 5-year survival of patients with pT0 and residual NMIBC, suggesting that a finding of Ta, Tis, or T1 at cystectomy is of great importance to this population. Consequently, the presence of pathologic NMIBC after NAC is a relevant endpoint that should be considered in NAC trials.

An assessment of the patterns of survival stratified by the timing of cystectomy suggested similar survival when cystectomy was delivered within 4 to 12 weeks after the termination of chemotherapy. Although we did not observe a survival disadvantage in the weeks before or after this time period, these analyses had small cohorts of patients; thus, the results must be interpreted with caution. The patient numbers in the analyses up to and including 10 weeks after NAC termination were more robust, permitting greater confidence in deeming this a safe window for cystectomy delivery after NAC. Although we strive to deliver cystectomy as expeditiously as possible after NAC, there is potential benefit in permitting some patients an additional 1 to 3 weeks to recover from systemic therapy. In that context, we can be more confident that a brief delay up to 10 weeks after NAC is unlikely to compromise CSS or OS. The data evaluating survival patterns from the initiation of chemotherapy resulted in similar conclusions.

Delays in surgery beyond 10 weeks after NAC termination certainly are possible because of complications from systemic treatment, patient indecision, and/or coordination of care between medical oncology and urology. Within our study population, the 28 patients (18%) who underwent cystectomy at or beyond 10 weeks generally had delays because of procedural scheduling. Adverse health status related to patient comorbidity or NAC toxicity also was an important cause of surgical delay, whereas delays caused by patient preference or multiple opinions were infrequent. It is worthwhile to note that scheduling issues occurred disproportionately in those who were receiving NAC outside of our institution, emphasizing the need for good communication and planning. Still, we did not observe a survival disadvantage for patients who were treated outside our facility; thus, treatment away from the home institution should not dissuade the use of NAC before cystectomy.

Although the findings from this study are interesting, they are limited by the retrospective nature of the study and because the data were compiled from a single center with potentially unique patient referral and practice patterns. We specifically identified patients who received

NAC and were able to undergo radical cystectomy, because our intent was to evaluate the timing of cystectomy delivery. Consequently, we did not collect data on patients who initiated NAC but did not undergo cystectomy because of either treatment-related toxicity or death, patient refusal, or disease progression.

In conclusion, concerns regarding the use of NAC have been attributed in part to apprehension over the timing of cystectomy delivery after systemic treatment. Our data demonstrate the feasibility of timely cystectomy when a neoadjuvant strategy is used to treat MIBC, even when therapies are administered at different institutions. It is noteworthy that, should unanticipated actions delay surgery, then cystectomy delivery up to a period of 10 weeks after the termination of NAC is unlikely to compromise patient survival. Active communication between treating physicians facilitates surgical scheduling and minimizes treatment delays and patient uncertainty.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

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