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Trends in the Use of Chemotherapy before and after Radical Cystectomy in Patients with Muscle-invasive Bladder Cancer in Korea

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We investigated trends in perioperative chemotherapy use, and determined factors associated with neoadjuvant chemotherapy (NAC) and adjuvant chemotherapy (AC) use in Korean patients with muscle- invasive bladder cancer (MIBC). We recruited 1,324 patients who had MIBC without nodal invasion or metastases and had undergone radical cystectomies (RC) between 2003 and 2013. The study's cut-off time for AC was three months after surgery, and the study's timespan was divided into three periods based on NAC use, namely, 2003-2005, 2006-2009, and 2010-2013. Complete remission was defined as histologically confirmed T0N0M0 after RC. NAC and AC were administered to 7.3% and 18.1% of the patients, respectively. The median time interval between completing NAC and undergoing RC was 32 days and the mean number of cycles was 3.2. The median time interval between RC and AC was 43 days and the mean number of cycles was 4.1. Gemcitabine and cisplatin were most frequently used in combination for NAC (49.0%) and AC (74.9%). NAC use increased significantly from 4.6% between 2003 and 2005 to 8.4% between 2010 and 2013 ($P < 0.05$), but AC use did not increase. Only 1.9% of patients received NAC and AC. Complete remission after NAC was achieved in 12 patients (12.5%). Multivariable modeling revealed that an advanced age, the earliest time period analyzed, and clinical tumor stage ≤ cT2 bladder cancer were negatively associated with NAC use ($P < 0.05$). While NAC use has slowly increased over time, it remains an underutilized therapeutic approach in Korean clinical practice.

Keywords: Urinary Bladder Neoplasms; Neoadjuvant Therapy; Adjuvant; Chemotherapy; Cystectomy

INTRODUCTION

Reports from annual surveys of bladder cancer (BC) estimate that about 380,000 patients worldwide are newly diagnosed with BC each year, and that there are about 150,000 BC-related deaths each year, which verifies that BC is one of the top 10 cancers worldwide (1, 2). Between 25% and 30% of newly diagnosed patients have muscle invasive BC (MIBC) (3, 4), and the standard treatment for MIBC is radical cystectomy (RC) with urinary diversion and lymph node (LN) dissection (5).

Despite improvements in surgical and medical treatments, the five-year overall survival rates for organ-confined LN-negative disease (pathologic tumor stage > pT2), extravesical disease, and LN metastasis after RC are estimated at 80%, 40%-50%, and 15%-35%, respectively; hence, the five-year overall survival rates have barely improved. These poor survival rates for MIBC are thought to be associated with understaging accompanied by micrometastasis at the time of RC, because postoperative distant recurrences occur more frequently than postoperative local recurrences (20%-50% vs. 5%-15% of cases). These findings suggest that perioperative systemic therapy has the potential to improve survival outcomes for those patients with understaged BC accompanied by micrometastasis (6).

In 2003, the Southwest Oncology Group (SWOG)-8710 randomized controlled trial demonstrated improved survival and pathologic down-staging in association with the use of neoadjuvant chemotherapy (NAC) administered before RC in patients with MIBC (7), and the results from subsequent meta-analyses

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have also suggested significant benefits associated with NAC (8, 9). However, the adoption of NAC for MIBC has been slow and inconsistent among oncologists, and only 1%-12% of MIBC patients receive NAC (6, 7, 10-13). Several explanations have been proposed for the slow uptake of the use of NAC for MIBC, including the significant toxicities of the chemotherapeutic agents, the higher proportions of older MIBC patients with multiple comorbidities, poor renal function, and poor performance statuses. Additionally, the slow uptake of the use of NAC for MIBC may be associated with patients being from lower social strata, for example, those from minority races, those on lower incomes, those without insurance, and patients who were treated at low-volume hospital centers.

In Korea, BC has been ranked the eleventh most common cancer and the ninth most common cancer affecting men (14). However, there is no information available about perioperative chemotherapy in Korean patients with MIBC who have undergone RC, and no reports have been published that describe the use of NAC before RC for MIBC in Korea. Therefore, this study used data from 2003 to 2013 that was retrieved from the cancer registries at five tertiary centers in Korea to investigate trends in the use of perioperative chemotherapy before and after RC, to search for general information about perioperative chemotherapy, including NAC, and to determine the reasons underlying the low utilization of NAC in Korean patients with MIBC.

MATERIALS AND METHODS

A total of 1,324 patients with clinical tumor stage ≥ T2 (cT2-4a N0M0) BC who underwent RC at the five participating Korean tertiary institutions between 2003 and 2013 were retrospectively recruited for this study after data-sharing agreements were approved. Based on information retrieved from the National Health Insurance Cooperation database, the enrolled patients comprised 39.4% (1,259/3,163) of the total number of patients who underwent RC in Korea during the time period investigated in this study, which included patients who did not have MIBC.

In addition to the patients' clinicopathologic data, we gathered information about the chemotherapeutic agents used, the number of chemotherapy cycles undertaken, and the time intervals between chemotherapy and RC. The study's cut-off time for AC was three months after surgery, and the study's time frame was divided into three time periods, namely, 2003-2005, 2006-2009, and 2010-2013, to ensure there was a delineation between 2006 and 2010, and to capture information relating to significantly different rates of NAC use ($P < 0.05$) (Fig. 1).

All of the patients with bladder masses underwent diagnostic transurethral resections of the bladder (TURB) to confirm the presence of MIBC, and those who did not have sufficient tissue to confirm the presence of MIBC underwent diagnostic TURB repeatedly during the course of 1 week. Patients with pure urothelial cell carcinomas or with BC of mixed histologic profiles involving squamous cell and/or glandular differentiation were included in this analysis. Patients with any other histologic variants were excluded from the analysis. Other exclusion criteria included non-MIBC, any MIBC with clinical LN positivity and/or distant metastases, and non-urothelial cell carcinomas, patients who had undergone salvage and palliative cystectomies, and those with no medical follow-up data after RC. A pathologic complete response following NAC was defined as pT0N0M0 without any visible cancer cells in RC specimens. Hospital pathologists from each institution assessed the specimens histopathologically using the World Health Organization's grading system (15) and the American Joint Committee on Cancer tumor-node-metastasis cancer staging system (16).

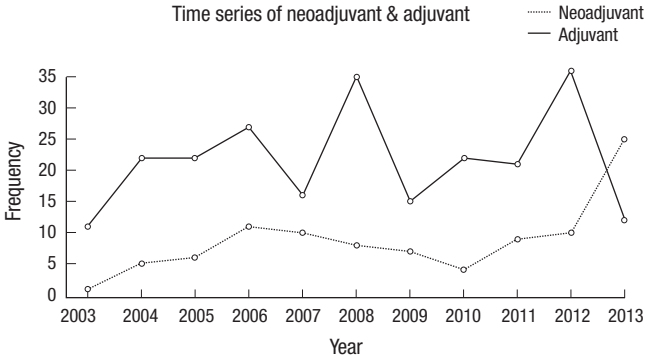

Fig. 1. Changes in neoadjuvant chemotherapy and adjuvant chemotherapy in patients with muscle invasive bladder cancer between 2003 and 2013.

Statistical analysis

The clinical characteristics of the patients were analyzed with the patients grouped as "All patients", "RC only patients", "NAC and RC patients", and "RC and AC patients", and the data were expressed as numbers and percentages (Table 1). The Chi-squared test and Fisher's exact test were used to compare the clinical characteristics of the patients who received NAC with those who did not receive NAC, and to compare the clinical characteristics of the patients who received AC with those who did not receive AC.

Multivariable analysis was performed to examine chronological changes in NAC and AC after adjusting for all of the clinical characteristics listed in Table 1. All of the variables described in Table 1 were included in the multivariable logistic regression model, and their odds ratios and *P* values were calculated. In addition, backward selection at a significance level of 0.05 was performed using all of the variables within the multivariable model (Table 2) until no variables with *P* values > 0.05 existed. Table 3 shows the variables with *P* values < 0.05 in the multivariable logistic model. All of the statistical analyses were performed using Stata software version 11.1 (StataCorp, College Station, TX, USA). All *P* values were two-sided, and *P* values < 0.05 were considered statistically significant.

Table 1. Analysis of patient characteristics

Characteristics	All patients, n (%)	RC only, n (%)	NAC and RC, n (%)	*P* value*	RC and AC, n (%)	*P* value†
No. subjects	1,324 (100)	1,014 (76.59)	96 (7.25)		239 (18.05)	
Age				0.043		0.110
-49	116 (8.76)	81 (69.83)	11 (9.48)		26 (22.41)	
50-59	269 (20.32)	195 (72.49)	29 (10.78)		55 (20.45)	
60-69	491 (37.08)	374 (76.17)	29 (5.91)		92 (18.74)	
70-	448 (33.84)	364 (81.25)	27 (6.03)		66 (14.73)	
Gender				0.146		0.530
Male	1141 (86.18)	874 (76.6)	78 (6.84)		209 (18.32)	
Female	183 (13.82)	140 (76.5)	18 (9.84)		30 (16.39)	
Study period				0.131		0.195
2003-2005	264 (19.94)	199 (75.38)	12 (4.55)		55 (20.83)	
2006-2009	491 (37.08)	377 (76.78)	36 (7.33)		93 (18.94)	
2010-2013	569 (42.98)	438 (76.98)	48 (8.44)		91 (15.99)	
Name of hospital				< 0.001		< 0.001
NCC	101 (7.63)	41 (40.59)	23 (22.77)		53 (52.48)	
SMC	386 (29.15)	346 (89.64)	9 (2.33)		32 (8.29)	
AMC	492 (37.16)	384 (78.05)	30 (6.1)		81 (16.46)	
SNUH	295 (22.28)	204 (69.15)	29 (9.83)		67 (22.71)	
KUMC	50 (3.78)	39 (78)	5 (10)		6 (12)	
Clinical stage				0.476		0.013
≤ cT2	722 (54.53)	575 (79.64)	49 (6.79)		113 (15.65)	
≥ cT3	602 (45.47)	439 (72.92)	47 (7.81)		126 (20.93)	
Pathologic stage				0.779		< 0.001
≤ pT2	630 (47.58)	550 (87.3)	47 (7.46)		38 (6.03)	
≥ pT3	694 (52.42)	464 (66.86)	49 (7.06)		201 (28.96)	
pNstage§				0.005		< 0.001
Node positive	376 (29.40)	211 (56.12)	39 (10.37)		141 (37.5)	
Node negative	917 (69.26)	777 (84.73)	54 (5.89)		95 (10.36)	
Type of urinary diversion				0.967‡		0.192‡
Ileal conduit	800 (60.42)	615 (76.88)	59 (7.38)		143 (17.88)	
Orthotopic neobladder	510 (38.52)	386 (75.69)	36 (7.06)		96 (18.82)	
Others	14 (1.06)	13 (92.86)	1 (7.14)		0 (0.00)	

**P* value of Chi-square test for NAC and RC group; †*P* value of Chi-square test for RC and AC group; ‡Fisher's exact test; §Missing 31 (pNstage = Nx). NCC, National Cancer Center; SNUH, Seoul National University Hospital; SMC, Samsung Medical Center; AMC, Asan Medical Center; KUMC, Korean University Medical Center.

Ethics statement

This study was approved by the ethics committees and the institutional review boards at each hospital (IRB No. NCC- 2014-0117) that participated in the study, and the requirement for the patients to provide consent was waived.

RESULTS

Table 1 presents the patients' demographic and clinicopathologic data. The mean ± standard deviation (SD) age of the study population was 64.4 ± 10.0 yr, and the study population comprised 1,141 (86.2%) men and 183 (13.8%) women with BC. Within the study population, 7.3% (96/1,324) received NAC and 18.1% (239/1,324) received AC.

The utilization of NAC increased significantly from 4.6% between 2003 and 2005 to 8.4% between 2010 and 2013 ($P = 0.019$). The utilization of AC did not show any significant changes, with decreases from 20.8% to 16.0% during the three study periods (Fig. 1). The median time interval between completing NAC and undergoing RC was 32 days (range, 9-369 days), and the mean (± SD) number of NAC cycles was 3.2 (±1.8) cycles. The median time interval between AC and RC was 43 days (range, 7-100 days), and the mean (± SD) number of AC cycles was 4.1 (±1.7) cycles. The most frequently used combination of NAC and AC agents was gemcitabine and cisplatin, which was used in 49.0% of NAC and 74.9% of AC recipients, followed by a combination of gemcitabine and carboplatin, which was used in 20.8% of NAC and 14.2% of AC recipients (data not shown). Of the 96 patients who received NAC, five patients delayed undergoing RC by more than three months after completing their NAC treatment, and, of these, three patients were apprehensive about undergoing RC, one patient developed sepsis, and one patient had irregular follow-up assessments. Twelve patients (12.5%) achieved complete remission after NAC.

The multivariable analysis, which evaluated the use of perioperative chemotherapy, showed that particular variables in the NAC model, including age ($P = 0.002$), the study period analyzed ($P = 0.019$), the institution ($P < 0.001$), and the clinical tumor stage ($P = 0.007$), and that particular variables in the AC model, including age ($P < 0.001$), the institution ($P < 0.001$), the pathologic tumor stage ($P < 0.001$), and the presence of any LN metastases ($P < 0.001$), were significantly associated with the

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Table 2. Univariable analysis of covariates associated with delivery of perioperative chemotherapy

Characteristics	Neoadjuvant chemotherapy			Adjuvant chemotherapy*		
	Proportion NC	Univariate analysis		Proportion AC	Univariate analysis	
		OR (95% CI)	*P* value		OR (95% CI)	*P* value
No. of subjects (%)	96 (7.25)			236 (18.25)		
Age			0.002			< 0.001
-50	11 (9.5)	2.84 (1.262, 6.394)	0.104	26 (22.4)	3.311 (1.75, 6.266)	0.019
50-59	29 (10.8)	2.977 (1.6, 5.536)	0.012	55 (20.5)	2.335 (1.407, 3.877)	0.374
60-69	29 (5.9)	1.357 (0.756, 2.435)	0.098	92 (18.7)	2.168 (1.402, 3.355)	0.609
†70-	27 (6.0)			66 (14.7)		
Gender			0.337			0.056
Male	78 (6.84)	0.75 (0.417, 1.35)	0.337	209 (18.3)	1.654 (0.985, 2.777)	0.056
†Female	18 (9.84)			30 (16.4)		
Study period			0.024			0.853
2003-2005	12 (4.6)	0.39 (0.198, 0.767)	0.011	55 (20.8)	1.082 (0.683, 1.713)	0.905
2006-2009	36 (7.3)	0.809 (0.505, 1.297)	0.296	93 (18.9)	1.112 (0.762, 1.621)	0.709
†2010-2013	48 (8.4)			91 (16.0)		
Name of hospital			< 0.001			< 0.001
NCC	23 (22.8)	4.354 (1.471, 12.887)	< 0.001	53 (52.5)	7.616 (2.656, 21.838)	< 0.001
SMC	9 (2.3)	0.18 (0.057, 0.572)	< 0.001	32 (8.3)	0.278 (0.1, 0.77)	< 0.001
AMC	30 (6.1)	0.657 (0.234, 1.847)	0.141	81 (16.5)	0.815 (0.303, 2.197)	0.021
SNUH	29 (9.8)	1.172 (0.422, 3.257)	0.213	67 (22.7)	1.557 (0.58, 4.178)	0.159
KUMC	5 (10)			6 (12)		
Clinical stage			0.012			0.181
≤ cT2	49 (6.8)			113 (15.7)		
≥ cT3	47 (7.8)	1.810 (1.141, 2.872)	0.012	126 (20.9)	1.289 (0.889, 1.869)	0.181
Pathologic stage						< 0.001
†≤ pT2				38 (6.0)		
≥ pT3				201 (29.0)	5.650 (3.679, 8.678)	< 0.001
pNstage						< 0.001
Node positive				141 (37.5)	4.299 (3.028, 6.102)	< 0.001
†Node negative				95 (10.4)		
Type of urinary diversion			0.726			0.085
Ileal conduit & others	60 (14.5)	1.098 (0.65, 1.856)	0.726	143 (17.9)	0.704 (0.472, 1.05)	0.085
†Orthotopic neobladder	36 (7.1)			96 (18.8)		

*Missing 31 (pNstage = Nx); †Bold font, rereference variable. NCC, National Cancer Center; SNUH, Seoul National University Hospital; SMC, Samsung Medical Center; AMC, Asan Medical Center; KUMC, Korean University Medical Center.

use of perioperative chemotherapy (Tables 2 and 3). However, sex (P = 0.064), the study period analyzed (P = 0.853), and the type of urinary diversion (P = 0.089) used were not significantly associated with the use of AC after RC (Table 3).

DISCUSSION

This study identified for the first time since the SWOG-8710 trial results, which were published in 2003, important trends in the use of perioperative chemotherapy, including NAC and in the use of AC after RC, in patients with MIBC in Korea. NAC use has slowly and significantly increased from 4.6% between 2003 and 2005 to 8.4% between 2010 and 2013 (P = 0.019), whereas AC use has not changed significantly, despite a decrease from 20.8% to 16.0% (P = 0.853).

This study is of further clinical significance because it is the first to demonstrate pathologic complete remission to NAC treatment in Korean MIBC patients after RC. However, some reports have suggested that the complete remission response achieved after NAC treatment might be affected by the quality of the TURB before and, particularly, after NAC (7, 17). Herr examined a population of patients with MIBC who received NAC and subsequently declined RC, and found that the completeness of the endoscopic resection was a factor that contributed to improve survival, which suggested a role for aggressive endoscopic resection (7). As this study had not fully evaluated the surgical complete remission rate among the cases with pathologic complete remission of NAC at RC specimens, it would be necessary in the future study to compare the complete remission rate affected by between TURB or NAC with a repeated TURB before RC.

While none of the previously published reports have addressed the use of NAC in patients with MIBC in Korea, investigators from four tertiary Korean hospitals have described clinical outcomes in relation to the use of AC after RC in patients with MIBC (18-21). Kwon et al. showed that of 338 cases who underwent RC, 153 (45.3%) patients with clinical stage ≥ T3 BC received AC between 1990 and 2012, and that combined therapy with gemcitabine and cisplatin was used more frequently than combinations of methotrexate (M), vinblastine (V), Adriamycin®

Table 3. Mutivariable analysis of covariates associated with delivery of perioperative chemotherapy (Backward selection at alpha = 0.10)

Neoadjuvant chemotherapy			Adjuvant chemotherapy*		
Characteristics	Multivariate analysis		Characteristics	Multivariate analysis	
	OR (95% CI)	*P* value		OR (95% CI)	*P* value
No. of subject (%)	96 (7.25)			236 (18.25)	
Age		0.002	Age		< 0.001
-50	2.702 (1.235, 5.913)	0.114	-50	3.858 (2.087, 7.13)	0.017
50-59	2.81 (1.559, 5.064)	0.016	50-59	2.648 (1.624, 4.318)	0.362
60-69	1.321 (0.746, 2.337)	0.105	60-69	2.361 (1.542, 3.615)	0.626
†70-			†70-		
Study period		0.019	Gender		0.064
2003-2005	0.381 (0.194, 0.748)	0.008	Male	1.734 (1.041, 2.889)	0.064
2006-2009	0.807 (0.504, 1.292)	0.281	†Female		
†2010-2013					
Hospitals		< 0.001	Hospitals		< 0.001
NCC	4.446 (1.506, 13.12)	< 0.001	NCC	7.594 (2.669, 21.61)	< 0.001
SMC	0.18 (0.057, 0.57)	< 0.001	SMC	0.295 (0.106, 0.82)	< 0.001
AMC	0.629 (0.229, 1.732)	0.083	AMC	1 (0.377, 2.649)	0.038
SNUH	1.161 (0.419, 3.217)	0.217	SNUH	1.712 (0.64, 4.581)	0.17
KUMC			KUMC		
Clinical stage		0.007	Pathologic stage		< 0.001
†≤ cT2			†≤ pT2		
≥ cT3	1.865 (1.182, 2.943)	0.007	≥ pT3	5.857 (3.887, 8.824)	< 0.001
			pNstage		< 0.001
			Node positive	4.17 (2.953, 5.888)	< 0.001
			†Node negative		
			Type of urinary diversion		0.089
			Ileal conduit	0.709 (0.476, 1.055)	0.089
			Orthotopic neobladder		

*Missing 31 (pNstage = Nx); †rereference variable. NCC, National Cancer Center; SNUH, Seoul National University Hospital; SMC, Samsung Medical Center; AMC, Asan Medical Center; KUMC, Korean University Medical Center.

(A), and cisplatin (C) (MVAC) (20). Other Korean tertiary institutions have shown rates of AC use after RC of 55%-60% between 2001 and 2011, and that combinations of gemcitabine and cisplatin are mainly used because of their favorable safety and tolerability profiles in patients with clinical stage ≥ T3 BC (18, 19, 21). These rates of AC use are much higher than the rate of AC use in the current study (18.1%) and the rates of AC use reported from studies in countries other than Korea (20%-38%). These differences in the AC usage rates relate to the different stages of the disease that were present when the patients were enrolled to participate in the studies, because the patients in the previously reported studies included those with clinical stage > T3 BC. Therefore, no definitive reports have been published to date that have assessed perioperative chemotherapy in MIBC patients with clinical stage > T2 BC in Korea.

Since the investigators involved in the SWOG-8710 trial published their favorable results for NAC, the use of NAC has been described (6, 7). Compared with papers published since 2003 that describe rates of NAC use of between 12% and 20% in countries other than Korea, the rate of NAC use in this study (7.3%) was much lower. This underutilization of NAC can be explained in the context of the Korean medical system. Firstly, the policy associated with the national health insurance system in Korea has not supported the use of NAC in MIBC patients. This policy could be the most important reason underlying the reluctance of clinicians to use NAC in MIBC patients before RC. However, the national health insurance system covers AC use and clinicians should use AC after RC. Secondly, given that the observed complete response rate following NAC in this study was 12.5% after RC in MIBC patients, the complete response rate reported from the SWOG trial that reached 38% could be considered to be overestimated (7). Hence, uro-oncologists, particularly those in Korea, should expect more realistic and much lower efficacies with NAC in routine clinical practice. However, the discrepancies between the complete response rates might be explained by differences in the studies' inclusion criteria and the different chemotherapeutic regimens. Other randomized controlled trials have reported NAC response rates of between 20% and 30%, which are lower than the response rate reported from the SWOG trial (10). The low NAC response rate in the current study may be explained by differences between this study and the randomized controlled trials in relation to the enrolled patients' disease statuses and the response rates associated with more advanced disease. Thirdly, the relatively slow adoption of NAC use might be associated with the chemotherapeutic regimen used and its related toxicities. In this study, the most frequently

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used NAC regimen was a combination of gemcitabine and cisplatin (48.0%), which has a more favorable toxicity profile than the MVAC treatment regimen used in the SWOG trial (7). The second most commonly used NAC regimen was gemcitabine and carboplatin (20.8%). This substitution indicated that a considerable portion of the patients in this study already had problems in relation to renal function (data not shown).

The multivariable logistic regression analysis identified significant associations between the use of NAC and age ($P = 0.002$), the study period analyzed ($P = 0.019$), the institution ($P < 0.001$), and the clinical tumor stage ($P = 0.007$), Patients aged < 60 yr received NAC significantly more frequently than patients aged ≥ 60 yr (hazard ratio [HR], 2.81; 95% confidence Interval [CI], 1.56-5.06; $P = 0.016$). Furthermore, patients who were treated between 2003 and 2005 (HR, 0.38; 95% CI, 0.19-0.75; $P = 0.008$) and those with clinical stage T2 BC (HR, 0.54; 95% CI, 0.34-0.85; $P = 0.007$) were less likely to receive NAC.

Similarly, patients aged < 50 yr (HR, 3.858; 95% CI, 2.087-7.130; $P = 0.017$) and who were managed at the National Cancer Center Hospital (HR, 7.594; 95% CI, 2.669-21.610; $P < 0.001$), had pathologic stage ≥ T3 BC (HR, 5.857; 95% CI, 3.887-8.824; $P < 0.001$), and who were LN positive (HR, 4.17; 95% CI 2.953-5.888; $P < 0.001$) were more likely to receive AC after RC than patients who were aged > 60 yr, were managed at the Samsung Medical Center or Asan Medical Center hospitals, had pathologic stage ≤ T2 BC, and were LN negative ($P < 0.05$). However, sex and the type of urinary diversion used did not significantly affect the use of AC after RC.

This study has some important limitations, which include its retrospective nature, the small number of patients that did not adequately represent all Korean BC patients, the lack of randomization, the lack of standardization of NAC and AC administration across the participating centers, the variability in the indications for NAC and AC, the different rates of NAC use among the hospitals, and the selection bias associated with the choice of chemotherapy regimen. Moreover, centralized radiologic evaluations and pathologic assessments were lacking, which represented additional potentially confounding factors. Furthermore, we did not assess the chemotherapeutic dose densities, dose adjustments, or drug-related toxicities. In addition, using the pathologic response as a primary end point meant that those patients who received NAC but did not undergo cystectomies because of disease progression or changes in their performance statuses, were not assessed in relation to their outcomes. Furthermore, data relating to some risk factors that were associated with the patients' baseline characteristics, including performance statuses, renal function, and laboratory data, were not collected. Despite these limitations, this study is the largest and the first to assess perioperative chemotherapy use in patients with MIBC and their pathologic responses to NAC, and it is representative of routine clinical experiences in Korea as opposed to the controlled environment that exists within clinical trials.

We have demonstrated some of the trends in perioperative chemotherapy use in Korean patients with MIBC for the first time since 2003, and we have shown that NAC remains underutilized despite a slow but significant increase in its use. Those patients who were aged > 60 yr, were treated between 2003 and 2009, and had BC at lower clinical stages, were less likely to be administered NAC. Further studies that analyze the different results generated by NAC and AC are recommended.

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DISCLOSURE

The authors have no conflicts of interest to disclose.

AUTHOR CONTRIBUTION

Manuscript conception and preparation: Ku JH, Kim HS, Jeon HK, Jung BC, Jeong IG, Kang SH, Hong B. Data collection and analysis: Chang SJ, Shin HC, Kim SH, Seo HK. Internal review for draft: Kim SH, Seo HK. Manuscript approval: All authors.

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