Retrospective Analysis of the Efficacy of Two Cycles of M-VAC Neoadjuvant Chemotherapy Followed by Radical Cystectomy for Muscle-invasive Bladder Cancer

YASUHIDE KITAGAWA, KOUJI IZUMI, SOTARO MIWA, YOSHIFUMI KADONO, HIROYUKI KONAKA, ATSUSHI MIZOKAMI and MIKIO NAMIKI

Department of Integrative Cancer Therapy and Urology, Kanazawa University Graduate School of Medical Science, Kanazawa, Japan

Abstract. *Background: Neoadjuvant chemotherapy before radical cystectomy for muscle-invasive bladder cancer is a commonly used treatment modality. However, in terms of chemotherapeutic regimens and the number of cycles of neoadjuvant chemotherapy, there is yet no international consensus, as various studies indicate the efficacy of several platinum-based combination chemotherapeutic regimens. We determined the efficacy of two cycles of neoadjuvant chemotherapy with methotrexate, vinblastine, adriamycin, and cisplatin followed by radical cystectomy. Patients and Methods: The study population included patients with clinical stage T2 – T4a, N0, M0 bladder cancer who underwent radical cystectomy. Clinical courses were compared between 27 patients treated with two cycles of M-VAC neoadjuvant chemotherapy and 25 treated with cystectomy alone. Results: The incidence of pT0 was 25.9% in the group treated with neoadjuvant chemotherapy. The probabilities of disease-free and cause-specific survival were significantly higher in patients treated with, than without neoadjuvant chemotherapy. On univariate Cox proportional hazards regression analysis for the patients treated with neoadjuvant chemotherapy, pathological stage and the pathological findings of venous involvement were significant prognostic factors. Conclusion: The results of this retrospective study demonstrated the clinical effectiveness of two cycles of neoadjuvant M-VAC chemotherapy for muscle-invasive bladder cancer.*

Correspondence to: Yasuhide Kitagawa, MD, Ph.D, Department of Integrative Cancer Therapy and Urology, Kanazawa University Graduate School of Medical Science, Takaramachi 13-1, Kanazawa, Ishikawa, Japan. Tel: +81 762652393, Fax: +81 762226726, e-mail: yasukita@med.kanazawa-u.ac.jp

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Bladder cancer is the second most common malignancy of the genitourinary tract, with an estimated 70,530 new cases and 14,680 deaths in the USA in 2010 (1). The disease has a high recurrence rate and metastatic potential, with an estimated 5-year survival rate after cystectomy of 27-67%, depending on the pathological stage of the patients presenting with muscle-invasive disease (2). The natural history of muscle-invasive bladder cancer (MIBC) dictates aggressive management with both local and systemic therapy. Neoadjuvant chemotherapy before radical cystectomy for MIBC is a commonly used treatment supported by level 1 evidence demonstrating a survival benefit compared to radical cystectomy alone. The Southwest Oncology Group reported a better clinical outcome in patients undergoing neoadjuvant M-VAC [methotrexate (MTX), vinblastine (VLB), adriamycin (ADR), and cisplatin (CDDP)] chemotherapy in a phase-3 randomized trial (SWOG 8710) in 2003 (3) and several subsequent meta-analyses yielded evidence supporting the use of neoadjuvant platinum-based combination chemotherapy (4-6). The European Association of Urology issued a grade A recommendation that neoadjuvant cisplatin-containing combination chemotherapy should be offered in MIBC, irrespective of further treatment (7).

There is as yet no international consensus regarding chemotherapeutic regimens or the number of cycles of neoadjuvant chemotherapy, as various studies have indicated the efficacy of several platinum-based combination chemotherapies, such as M-VAC, CMV (cisplatin, methotrexate and vinblastine), and GC (gemcitabine and cisplatin) (3-6). A randomized trial of SWOG 8710 indicated that three cycles of M-VAC chemotherapy was a reasonable form of neoadjuvant chemotherapy (3). However, it is possible that many cycles of chemotherapy would lead to poor clinical outcome due to excessive delay in performing radical cystectomy (8). As one of the advantages of neoadjuvant chemotherapy is the expectation of a pathological response

with major prognostic significance (3, 9), the delay of cystectomy in patients who do not respond to chemotherapeutic treatment represents a severe clinical problem (8, 10, 11). To avoid excessive delay in definitive surgery, we performed two cycles of neoadjuvant M-VAC chemotherapy followed by radical cystectomy. In the present study, we retrospectively analyzed the pathological findings and clinical outcomes of the patients, and defined the efficacy of two cycles of neoadjuvant M-VAC chemotherapy.

Patients and Methods

A retrospective review of the patient database of Kanazawa University Hospital (Kanazawa, Japan) identified 69 patients with clinical stage T2-T4a, N0, M0 bladder cancer who underwent radical cystectomy from March 1997 to December 2010. There was no treatment protocol for neoadjuvant chemotherapy before 2004 in our institution, and after 2004, patients with this disease stage who accepted radical cystectomy received two 28-day cycles of M-VAC neoadjuvant chemotherapy followed by radical cystectomy. Patients who underwent nephrectomy before cystectomy (2 cases), those for whom the follow-up after cystectomy was too short (5 cases), and those who received other neoadjuvant chemotherapy regimens (10 cases) were excluded from this retrospective study. Consequently, 25 patients with radical cystectomy-alone and 27 patients with two cycles of M-VAC neoadjuvant chemotherapy were eligible for the study. Clinical staging was determined in accordance with the unified tumor node metastasis (TNM) criteria based on the results of computed tomography (CT), magnetic resonance imaging (MRI), and bone scan (12). Preoperative pathological diagnosis and tumor grading were determined by transurethral resection (TUR) before initiation of any treatment.

Two 28-day cycles of M-VAC neoadjuvant chemotherapy were administered, as follows: methotrexate (30 mg/m^2 body surface area) on days 1, 15, and 22; vinblastine (3 mg/m^2) on days 2, 15, and 22; and doxorubicin (30 mg/m^2) and cisplatin (70 mg/m^2) on day 2. The doses were adjusted if toxicity occurred. Second TUR was not performed after chemotherapy. Pelvic CT was performed before radical cystectomy; however, clinical response of neoadjuvant chemotherapy could not be evaluated due to the modification of TUR. There were no cases in which cystectomy was not performed based on the results of imaging after neoadjuvant chemotherapy.

All patients underwent radical cystectomy and bilateral pelvic lymphadenectomy. Various urinary diversions were performed, including the creation of ileal conduits, orthotopic reservoirs (ileal neobladder), and cutaneous ureterostomy. In terms of pathological analysis, whole-mount paraffin sections of the specimens were routinely used, and pathological staging was performed in accordance with the unified TNM criteria (12). Pathological changes after neoadjuvant chemotherapy were determined in accordance with the Japanese General Rules for Clinical and Pathological Studies of Bladder Cancer (13). Assessment of the pathological effect of neoadjuvant chemotherapy was based on the presence and assessment of nuclear pyknosis, nuclear karyolysis, and cytoplasmic vacuolization, and grading of the pathological effect on the amount of cancer cells with these features. That is, pathological effect grade 0 (Ef 0) was assigned to cases with none of these features, and pathological effect grade 3 (Ef 3) to cases with almost all cancer cells. Cases with neoadjuvant chemotherapy pathologically-free of cancer were defined as pT0, Ef 3, and pathological Grade 0 (G0) in this study. Some cases showed heterogeneous findings, and those with cancer cells positive for these features accounting for less than half of all cancer cells were considered Ef 1, while those with more than half of their cancer cells positive for such features were rated as Ef 2. Pathological effect in cases without neoadjuvant treatment was defined as "not analyzed" (Ef NA) in this study.

The date of surgery was used as the start of the observation for the study. Patients were evaluated postoperatively by routine chest and abdominal CT every 3-6 months to screen for metastatic disease. Bone scintigraphy and head CT were performed where indicated. Patients' medical records were reviewed and the status of each patient was assessed by their visits to the outpatient clinic. As only one patient died of other causes in this study, disease-free survival (DFS) and cause-specific survival (CSS) from the start of the observation were used as end-points, while overall survival (OS) was not used.

This analysis was performed in accordance with the principles of the Declaration of Helsinki, and all patients provided written informed consent with guarantees of confidentiality. All statistical assessments were performed and Figures were prepared using commercially available software (SPSS Statistics; IBM, Armonk, NY; and Prism; GraphPad Software, San Diego, CA), and $p<0.05$ indicated statistical significance. Comparisons between two groups were performed by unpaired *t*-test or Fisher's exact test. DFS and CSS were analyzed with univariate Cox proportional hazards regression models based on the pathological findings of the surgical specimens. In terms of the pathological treatment effect and pathological stage, DFS and CSS were examined by Kaplan–Meier analysis, and the significance of differences was analyzed by the log-rank test. In analyses of probabilities of survival, patients without evidence of progression and/or death were censored at the time of last follow-up.

Results

Urothelial carcinoma was confirmed histologically in all 52 patients. The characteristics of the patients with or without two cycles of neoadjuvant M-VAC chemotherapy are presented in Table I. Patients undergoing neoadjuvant M-VAC chemotherapy were significantly younger than those without chemotherapy. There were no significant differences in preoperative findings, including Eastern Cooperative Oncology Group (ECOG) performance status and the types of urinary diversions, between the two groups. Among the patients treated with M-VAC neoadjuvant chemotherapy, 15 patients (55.6%) showed neutropenia as an adverse event of grade 3 or 4 according to the National Cancer Institute Common Terminology Criteria (CTCAE), which was improved by granulocyte colony-stimulating factor. Several patients complained of nausea and appetite loss, as well as of grade 3 adverse events during chemotherapy, but the symptoms were not severe and improved with conservative treatment. The doses of drugs were adjusted if toxicity occurred, and relative dose intensities (DI) are shown in Table II. In most cases, dose adjustments were performed on days 15 and 22 without

Table I. *Patients' characteristics.*

Neoadjuvant chemotherapy	None	M-VAC	*p*-Value
Patient No.	25	27	
Mean age (year)	71.1	64.3	0.0026
Gender			
Male	20	25	0.2407
Female	5	2	
ECOG performance status			
0	21	24	0.6983
1	4	3	
Primary or Recurrent tumor			
Primary	20	24	0.4583
Recurrent	5	3	
Clinical stage			
cT2	16	18	0.8804
cT3	4	6	
cT4a	5	3	
Grade of TUR specimen			
G2	9	9	0.9285
G3	16	18	
Hydronephrosis at diagnosis			
Absent	19	19	0.8852
Present	6	8	
Urinary diversion			
Ileal conduit	11	11	0.9745
Ileal neobladder	11	14	
Cutaneous ureterostomy	3	2	

Table II. *Relative dose intensity of 2 cycles of M-VAC neoadjuvant chemotherapy.*

DI (mg/m^2/week)	MTX	VLB	ADR	CDDP
Planned	22.5	2.25	7.5	17.5
Received	17.74	1.76	7.40	17.12
Relative DI (%)	78.8	78.2	98.7	97.8

DI: Dose intensity.

administration of methotrexate and vinblastine. The median duration between diagnosis of muscle invasion and cystectomy was 91 days (range: 63-111 days).

The pathological and postoperative characteristics of the groups according to the performance of neoadjuvant M-VAC chemotherapy are presented in Table III. The patients with pT0 were defined as the group with neoadjuvant M-VAC chemotherapy and the incidence of pT0 was 25.9%. However, the difference in pathological stage between the two groups was not statistically significant (p=0.2972). Pathological grade tended to be lower in cases with than without neoadjuvant chemotherapy; however, the difference was not significant (p=0.0527). In terms of pathological N stage, concomitant carcinoma *in situ* (CIS), and venous involvement, were pathological findings which seemed not to be affected by neoadjuvant M-VAC chemotherapy. Adjuvant chemotherapy was given to 9 patients according to the pathological findings, and the performance rates were not different between the two groups. Out of these 9 patients, 8 had pathological lymph node metastases and one patient was diagnosed with pathological T4. Seven patients underwent M-VAC adjuvant chemotherapy. One patient without neoadjuvant chemotherapy underwent pelvic radiation therapy, and one with neoadjuvant chemotherapy underwent adjuvant chemotherapy with gemcitabine and carboplatin. The mean postoperative follow-up period was 41.2 months (range: 4-170 months), and the difference between the two groups was not statistically significant.

Table III. *Pathological and postoperative characteristics of study population.*

Neoadjuvant chemotherapy	None	M-VAC	*p*-Value
Patient No.	25	27	
Pathological T stage			
pT0	0	7	0.2972
≤pT1	9	7	
pT2	7	6	
pT3	6	5	
pT4	3	2	
Pathological N stage			
pN0	19	23	0.6259
pN+	6	4	
Pathological Grade			
G0	0	7	0.0527
G2	5	6	
G3	20	14	
Concomitant CIS			
Absent	20	22	0.8284
Present	5	5	
Venous involvement			
Absent	17	20	0.8597
Present	8	7	
Adjuvant chemotherapy			
Absent	21	22	0.8990
Present	4	5	
Mean follow-up period (months)	38.5	42.6	0.6801

Out of the 52 patient total population, 20 died of bladder cancer and 1 died of other causes. Recurrence of bladder cancer occurred in 23 patients; 12 patients had local recurrence and 11 had distant metastases, including lymph node metastases. DFS and CSS rates in terms of performance of neoadjuvant M-VAC chemotherapy are shown in Figure 1. The probabilities of DFS and CSS at 5 years were 72.4% and 79.7% for those treated with neoadjuvant M-VAC chemotherapy and 37.8% and 41.4% for those treated without neoadjuvant M-VAC chemotherapy, respectively (Figure 1A and B). The differences in DFS and CSS between

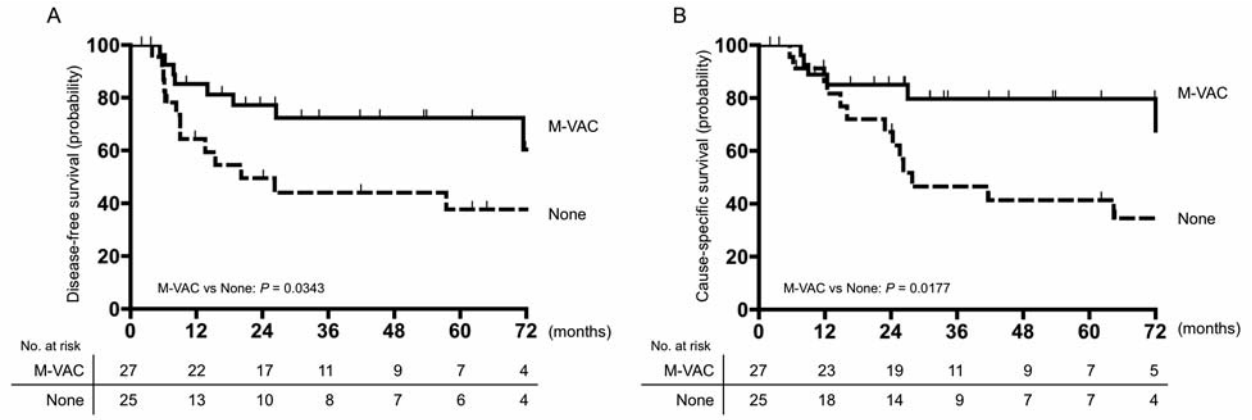

Figure 1. *Kaplan–Meier curves showing disease-free survival (A) and cancer-specific survival (B) of patients treated with M-VAC neoadjuvant chemotherapy and cystectomy alone.*

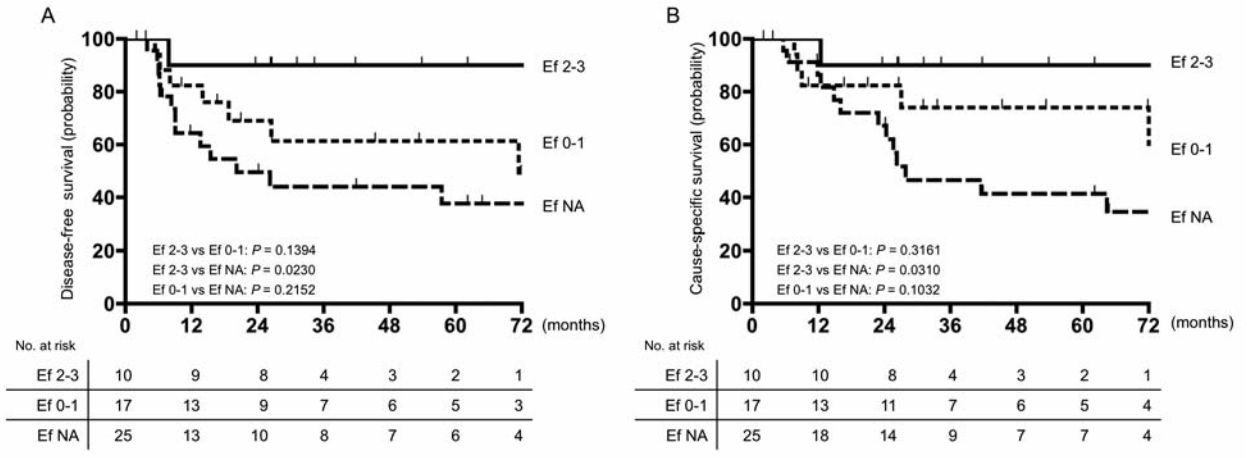

Figure 2. *Kaplan–Meier curves showing disease-free survival (A) and cancer-specific survival (B) stratified by the pathological treatment effect for patients with M-VAC neoadjuvant chemotherapy (Ef 2-3 and Ef 0-1) and cystectomy alone (EF NA).*

the two groups were statistically significant. Out of 27 patients with neoadjuvant chemotherapy, 10 were defined as pathological treatment Ef 2 and 3, and 17 as Ef 0 and 1 based on surgical specimens. DFS and CSS rates in terms of pathological treatment effect of the surgical specimens are shown in Figure 2. The probabilities of DFS and CSS of the cases with EF 2-3 were significantly higher than those of cases with Ef NA, *i.e.* cases without neoadjuvant M-VAC chemotherapy (Figure 2A and B).

Table IV shows the results of univariate Cox proportional hazards regression analysis of time-to-DFS and CSS for patients treated with neoadjuvant M-VAC chemotherapy based on pre-treatment and pathological factors. Pathological stage and pathological findings of venous involvement were significant predictors of DFS and CSS. Multivariate analysis was performed, but the results were unreliable due to the small number of variables (data not shown). DFS and CSS among the patients treated with neoadjuvant M-VAC chemotherapy by pathological stage are shown in Figure 3. The cases with pathological stage T2 or less had better prognosis than those with stage T3 or more and/or lymph node metastases on log-rank test (Figure 3A, B).

Discussion

Neoadjuvant cisplatin-based chemotherapy for patients with MIBC improved overall survival rate by 5% and decreased risk of death from bladder cancer by 14%-16% in several randomized clinical trials; these results support the efficacy of neoadjuvant chemotherapy followed by radical cystectomy

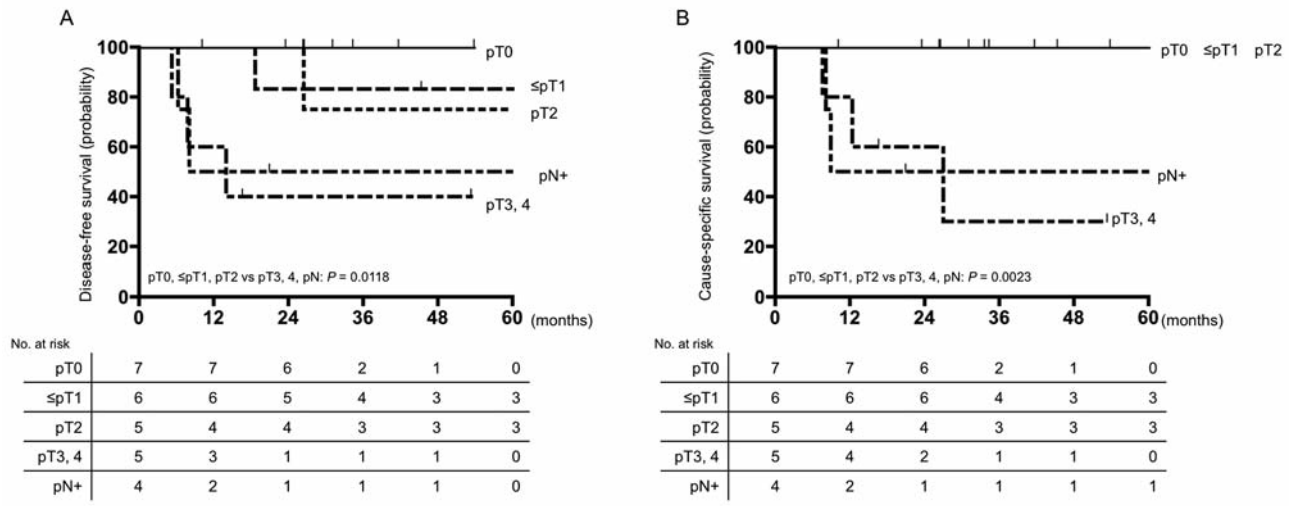

Figure 3. *Kaplan–Meier curves showing disease-free survival (A) and cancer-specific survival (B) stratified by the pathological stage for patients treated with M-VAC neoadjuvant chemotherapy.*

Table IV. *Univariate Cox proportional hazards regression analysis for time-to-disease-free and cause-specific survival for neoadjuvant cases.*

		DFS		CSS	
Variable	Patient No.	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Age, years					
≤70	19	1	0.142	1	0.708
≥71	8	2. 86 (0.70-11.58)		1.38 (0.25-7.61)	
Status					
Primary tumor	24	1	0.678	1	0.538
Recurrent tumor	3	1.57 (0.19-13.21)		1.99 (0.22-17.88)	
Hydronephrosis					
Absent	19	1	0.158	1	0.081
Present	8	2.76 (0.67-11.35)		4.68 (0.83-26.48)	
Pathological stage					
pT0-pT2	18	1	0.016	1	0.015
pT3, 4, pN+	9	5.98 (1.39-25.85)		14.78 (1.71-128.10)	
Pathological Grade					
G0-2	13	1	0.067	1	0.159
G3	14	1.93 (0.96-3.90)		1.68 (0.82-3.47)	
Treatment effect					
Ef 2-3	10	1	0.175	1	0.338
Ef 0-1	17	4.30 (0.52-35.33)		2.88 (0.33-24.95)	
Concomitant CIS					
Absent	24	1	0.622	1	0.885
Present	3	1.50 (0.30-7.45)		0.85 (0.10-7.31)	
Venous involvement					
Absent	20	1 (reference)	0.006	1	0.019
Present	7	7.80 (1.82-33.35)		7.69 (1.40-42.20)	
Adjuvant chemotherapy					
Absent	22	1	0.356	1	0.247
Present	5	2.14 (0.43-10.78)		2.77 (0.49-15.54)	

(3-6). Nevertheless, the neoadjuvant approach has not been widely practiced, and a recent analysis of the National Cancer Data Base indicated that only 1.2% of patients with stage III bladder cancer received neoadjuvant chemotherapy (14). One of the reasons for the lack of acceptance of neoadjuvant chemotherapy was that delaying definitive

surgery in patients who do not respond to treatment raises concerns regarding compromise of curability (15). It has been demonstrated that a delay in radical cystectomy results in poorer pathological stage and diminished survival rate (10, 11), and a recent study suggested that an excessive delay (>120 days) in performing radical cystectomy may negate the survival benefit of neoadjuvant chemotherapy (8).

This study demonstrated that the probabilities of DFS and CSS for MIBC patients treated with two cycles of neoadjuvant M-VAC chemotherapy were higher than those for patients treated with radical cystectomy-alone. In terms of pathological efficacy, the incidence of pT0 was 25.9% in the present study, which was lower than in previous reports in patients undergoing 3 or 4 cycles of neoadjuvant M-VAC chemotherapy (28-38%) (3, 16). The differences may have been related to the number of cycles of neoadjuvant chemotherapy; however, the survival rates of patients with favorable pathological treatment effects, including pT0 cases, were significantly higher than those of patients without neoadjuvant chemotherapy. On the other hand, the survival rate of patients with incomplete pathological treatment effect was not inferior to that of patients without neoadjuvant chemotherapy. These results indicated that two cycles of neoadjuvant chemotherapy with M-VAC for MIBC may be a reasonable way to obtain the therapeutic benefit of neoadjuvant chemotherapy and avoid excessive delay in performing radical cystectomy.

In terms of prognostic factors for MIBC patients with neoadjuvant chemotherapy, we demonstrated that patients with pathological stage T2 or less and those without venous involvement had better clinical outcomes. Pathological T0 state, *i.e.* lack of viable cancer cells in surgical specimens, was thought to be the strongest pathological prognostic factor, and achieving the pT0 state may be one of the advantages of neoadjuvant chemotherapy (3, 4, 17). The results of the present study supported these suggestions, and added the possibility that pathological radicality (pT2 or less and no venous involvement) of cystectomy after neoadjuvant chemotherapy are important prognostic factors.

The present study had several limitations. The study design was retrospective, and the major issue of concern was the relatively small sample size. The patients were younger in the group treated with than without neoadjuvant chemotherapy, and this difference in patient characteristics between the two groups may have affected the clinical outcomes, especially CSS, because of the therapeutic options after disease recurrence. However, there was no difference in ECOG performance status of the patients between the two groups, and this characteristic may overcome the difference in age. To our knowledge, there have been no previous studies demonstrating the efficacy of two cycles of neoadjuvant chemotherapy with methotrexate, vinblastine, adriamycin, and cisplatin followed by radical cystectomy for muscle-invasive bladder cancer. We, therefore, showed that the probabilities of DFS and CSS were higher in patients with favorable pathological treatment effects of two cycles of M-VAC neoadjuvant chemotherapy. Although further studies are needed to define the optimal patient characteristics for this type of treatment, this neoadjuvant chemotherapy regimen is a therapeutic option for muscle-invasive bladder cancer.

Conflicts of Interest

None declared.

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