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Case Report

Intrascrotal Dedifferentiated Leiomyosarcoma Originating from Dartos Muscle

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A 46-year-old man, who had visited our hospital complaining of a small intrascrotal nodule ten years ago, returned to us because of the rapid growth of the nodule. Computed tomography revealed a heterogeneously enhanced intrascrotal tumor of approximately 4×3 cm. The tumor and the right testis were excised with the adhered right scrotal skin. The pathological diagnosis was pleomorphic leiomyosarcoma with dedifferentiation originating from the dartos muscle. Urological dedifferentiated leiomyosarcomas are rarely reported and the clinical features are mostly unknown. This is the first report to describe the dedifferentiated leiomyosarcoma of the dartos muscle.

1. Introduction

Dedifferentiation is a well-recognized process in several bone and soft tissue tumors, including liposarcoma, chondrosarcoma, periosteal osteosarcoma, chordoma, and solitary fibrous tumor [1]. However, dedifferentiation of leiomyosarcomas is very rare. Herein we report a case of dedifferentiated leiomyosarcoma originating from dartos muscle.

2. Case Presentation

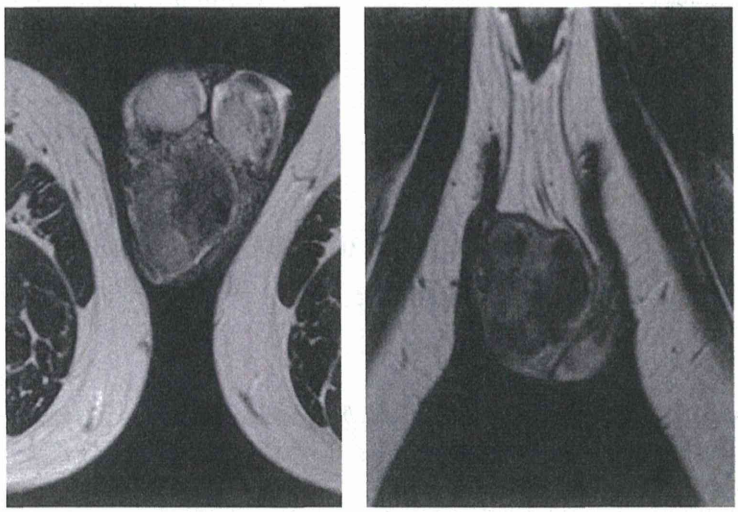
In 2004, a 46-year-old man visited our hospital with a complaint of a small intrascrotal nodule and was placed under observation. In January 2014, he noticed rapid growth of the nodule and visited us again. Physical examination showed a mass in the scrotum near the right testis. Blood tests yielded no specific results. Contrast-enhanced computed tomography revealed a heterogeneously enhanced tumor of approximately 4 × 3 cm. Magnetic resonance imagingshowed a heterogeneous signal in T2 weighted image and early contrast enhancement and washout (Figure 1). There was no evidence of metastasis. Under clinical diagnosis of a malignant intrascrotal tumor, we excised the scrotal tumor with the adhered skin and the right testis. The tumor was yellow in color and 4.7 cm in the maximum diameter. It was located beneath the scrotal skin, apart from the spermatic cord or testis (Figure 2).

Microscopically, the tumor consisted of two different components: leiomyosarcoma and malignant fibrous histiocytoma-like dedifferentiated sarcoma (Figure 3). Immunohistochemistry detected dedifferentiated components of leiomyosarcoma, which were characterized by lack of staining with muscle markers except for caldesmon (Figure 4, Table 1). The pathological diagnosis was pleomorphic leiomyosarcoma with dedifferentiation originating from the dartos muscle of the right scrotum. Immunohistochemical stains for MDM2 and CDK4 were negative; therefore, we excluded dedifferentiated liposarcoma with myogenic differentiation. Although the surgical margin of specimen was negative, there were multiple tumor invasions to peripheral veins. The dermis was invaded, but the epidermis was intact.

The patient had no evidence of recurrence at six months after the operation.

3. Discussion

Soft tissue sarcomas are a heterogeneous group of nonosseous tumors that arise from the embryonic mesoderm [2]. In this group of tumors, genitourinary (GU) sarcoma is relatively



(a) (b)

FIGURE 1: MRI T2 transverse (a) and coronal (b) images show a mass in the right paratesticular region.

FIGURE 2: Macroscopic finding. The mass is separated from the testis and epididymis.

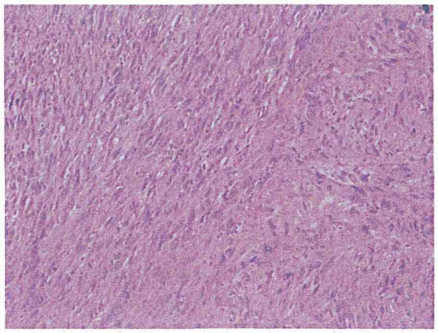


FIGURE 3: Microscopic finding. Spindle shaped leiomyosarcoma cells (right side) and what appeared to be MFH with a high mitotic rate (left side). Hematoxylin and eosin stain ×20 (upper).

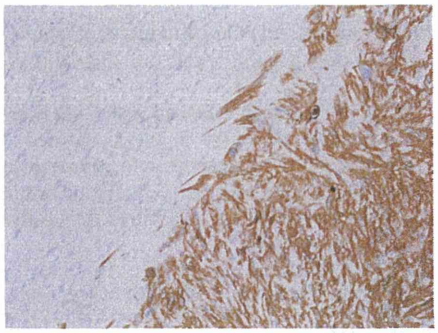


FIGURE 4: Leiomyosarcoma (right) is stained by antibody against calponin but dedifferentiated leiomyosarcoma (left) is not. ×20 (lower).

rare. It is estimated that approximately 10,000 new patients are yearly diagnosed with soft tissue sarcomas in the USA [3], of which GU tract sarcomas consist of 2.1% only [4]. Dotan et al. reported that among 131 GU tract sarcomas the most common histological type was leiomyosarcoma (19%) [2]. Coleman et al. reported that the spermatic cord was the most common site of GU sarcomas (30%) [5]. Of 24 cases of leiomyosarcoma of paratesticular region, only one case was reported to have the origin in the dartos muscle [6]. Our case is the first report of dedifferentiated leiomyosarcoma originating from the dartos muscle.

Chen et al. reported that dedifferentiated leiomyosarcoma was seen in 1.4% of all leiomyosarcomas consulted from 1991 to 2007 [1]. In their report, these dedifferentiated leiomyosarcomas lacked the characteristic immunohistochemical staining of differentiated leiomyosarcoma for muscle-specific actin, smooth muscle actin, desmin, and CD34 [1]. Our case showed the similar features; that is, the differentiated component showed to be strongly positive for muscle markers, but the dedifferentiated component was negative (Table 1).

As for grading systems of sarcomas, the French Federation of Cancer Centers Sarcoma Group grading system

Table 1: Immunostaining of our case.

	Smooth muscle sarcomatoid	Malignant fibrous histiocytoma-like tumor
Vimentin	++	++
α-Smooth muscle actin	++	−
Desmin	++	−
Muscle-specific actin	++	−
Calponin	++	−
Caldesmon	++	+
CD99	Focal+	+
CDK4	−	−
MDM2	−	−
S100	−	−
CD34	−	−
AE1/AE3	−	−
CAM5.2	−	−
MIB-1 index	5%	50%

has been shown to be reproducible among pathologists and correlate with the clinical outcome [7, 8]. In this French system, mitotic activity and the amount of tumor necrosis are scored individually, and these scores are summed up to give a final score of the sarcoma grade [7]. Following this grading system, the score of differentiation of our case was three, the score of necrosis one, and the score of mitotic activity three. The total score was seven, and our case was rated as grade 3.

The optimum local and systemic treatment for these tumors remains controversial, but there is a general consensus that all paratesticular sarcomas in adults should be managed with complete resection, including high ligation of the spermatic cord [7]. Prognosis of GU sarcomas depends on tumor size, grade, stage, histologic type, and lymph node involvement [9–13]. Froehner et al. indicated the tumor size over 5 cm as an important prognostic factor [14]. Of 14 patients of paratesticular leiomyosarcoma, four (29%) had local recurrences and one had metastases [6]. Galosi et al. recommended adjuvant radiation after radical surgery for the high rate of local recurrences [15]. Chen et al. reported a worse prognosis of dedifferentiated sarcomas compared with differentiated sarcomas; of 13 dedifferentiated leiomyosarcomas, metastasis occurred in five (38%) and local recurrence in five (38%) [1]. Close follow-up is needed because of a high frequency of recurrence and metastasis of dedifferentiated leiomyosarcoma.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Original Study

Adjuvant Chemotherapy Is Possibly Beneficial for Locally Advanced or Node-Positive Bladder Cancer

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Abstract

The role of adjuvant chemotherapy (AC) after radical cystectomy (RC) for bladder cancer remains controversial. In this retrospective study, we showed that cisplatin-based AC improves survival in locally advanced or node-positive bladder cancer, especially in node-positive cases. On multivariate analyses, AC was an independent predictive factor for both recurrence-free survival (RFS) and cancer-specific survival (CSS), along with surgical margin status and lymphovascular invasion.

Background: This study aimed to evaluate the outcomes of cisplatin-based adjuvant chemotherapy (AC) after radical cystectomy (RC) in non–organ-confined bladder cancer. **Methods:** Sixty-one patients who did not receive neoadjuvant chemotherapy (NAC) underwent RC for locally advanced (pT3-4) or node-positive (pN1-3) bladder cancer, or both, between 1990 and 2012. Of these patients, 39 (64%) received cisplatin-based AC after RC (AC group) and the remaining 22 patients (36%) did not (non-AC group). Cancer-specific survival (CSS) and recurrence-free survival (RFS) were compared between the groups. **Results:** The AC group was significantly younger ($P = .004$), but no significant differences were noted between the groups for pT stage, pN stage, nuclear grade, renal function, and salvage chemotherapy rates after recurrence. During a follow-up of 29 months (median), 40 patients (67%) experienced recurrence/metastasis and 34 (56%) died of recurrent bladder cancer. The AC group showed better RFS than the non-AC group, but the difference was not statistically significant (median survival time [MST], 23.7 vs. 11.4 months, respectively; $P = .154$). CSS was significantly better for the AC group than for the non-AC group (MST, 57.4 vs. 17.9 months, respectively; $P = .008$). On multivariate analysis, AC was an independent predictive factor for both RFS (hazard ratio [HR], 0.325; $P = .005$) and CSS (HR, 0.186; $P < .001$), along with surgical margin status and lymphovascular invasion (LVI). In a subgroup analysis of 31 node-positive cases, the AC group had a significantly better CSS compared with the non-AC group ($P = .029$). Analysis of node-negative cases (n = 30) yielded no significant benefit for AC. **Conclusion:** Our observations suggest that postoperative cisplatin-based AC improves survival in locally advanced or node-positive bladder cancer, especially in node-positive cases.

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Keywords: Adjuvant chemotherapy, Clinical outcome, Muscle-invasive bladder cancer, Urinary bladder cancer, Urothelial carcinoma

Introduction

Urinary bladder cancer is the second most common cancer of the genitourinary system.[1] An estimated 386,300 new cases and 150,200 deaths from bladder cancer occurred in 2008 worldwide.[1] Radical cystectomy (RC) with pelvic lymph node dissection is a standard treatment for muscle-invasive and high-risk non–muscle-invasive bladder cancer.[2] Despite the advances in surgical technique

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and patient selection, the risk of disease recurrence remains high; the 5-year recurrence-free survival (RFS) and overall survival (OS) after RC are reportedly 48% to 70% and 57% to 60%, respectively.[3-5] Once patients experience recurrence after RC, their median survival time (MST) is approximately 15 months,[6] and even shorter if they do not undergo salvage chemotherapy.[7]

Postoperative cisplatin-based systemic chemotherapy has been used to prevent recurrence.[8] Although 2 previous randomized controlled trials (RCTs) showed a survival benefit for presurgical chemotherapy (neoadjuvant chemotherapy [NAC]),[9,10] it has not been widely adopted in practice.[8] In contrast, postoperative systemic chemotherapy (adjuvant chemotherapy [AC]) has been used more often; David et al reported that in stage III bladder cancer, NAC and AC are applied in 1.4% and 10.4% of cases, respectively.[11] A recent meta-analysis of 9 RCTs including 945 participants revealed a statistically significant benefit of AC on OS in muscle-invasive bladder cancer (hazard ratio [HR], 0.77; 95% confidence interval, 0.59-0.99; $P = .049$).[12] However, most RCTs failed to prove the benefit of AC, and the optimal targets of AC have never been identified.[13-15]

In our institution, 3 cycles of cisplatin-based AC have been offered to patients with non–organ-confined bladder cancer (pT3-4

Table 1 Clinicopathologic Characteristics of the Patients

Variable	AC After RC	RC Alone	*P* Value
No. of Patients	39	22	
Male/Female	34/5	21/1	.404
Age, Median (IQR)	62 (58-69)	72 (63-79)	.004
BMI, Median (IQR)	22.5 (21.4-25.3)	21.4 (18.8-23.4)	.024
Form of Urinary Diversion			.023
Ileal conduit (%)	24 (61.5)	12 (54.5)	
Ileal neobladder (%)	12 (30.8)	4 (18.2)	
Continent reservoir (%)	2 (5.1)	0 (0.0)	
Ureterocutaneostomy (%)	1 (2.6)	6 (27.3)	
Estimated Blood Loss, Median (IQR) (mL)	1620 (1215-2290)	1550 (1240-2280)	.781
Allogeneic Blood Transfusion (%)	11 (28.2)	13 (59.1)	.029
Postoperative GFR <60 mL/min (%)	16 (41.0)	9 (40.9)	.993
Postoperative Complications of Clavien-Dindo Classification Grade 3	2 (5.1)	6 (27.3)	.038
Performance Status			
≤1	36	16	.089
2	3	6	
pT Stage (%)			
<pT2	3 (7.7)	0 (0.0)	.256
pT2	2 (5.1)	3 (13.6)	
pT3	23 (59.0)	16 (72.7)	
pT4	11 (28.2)	3 (13.6)	
Nuclear Grade (%)			
Grade 1/Grade 2	4 (10.3)	3 (13.6)	.746
Grade 3	33 (84.6)	19 (86.4)	
pN (%)			
pN0	18 (46.2)	12 (54.5)	.621
pN1	9 (23.1)	6 (27.3)	
pN2	10 (25.6)	4 (18.2)	
pN3	2 (5.1)	0 (.0)	
Lymph Nodes Removed, Median (IQR)	17 (10-25)	14 (9-24)	.373
Metastatic Lymph Nodes, Median (IQR)	1 (0-2)	0 (0-1)	.739
Lymphovascular Invasion (%)	36 (92.3)	15 (68.2)	.015
Positive Surgical Margins (%)	5 (12.8)	2 (9.1)	.661
Cisplatin-Based AC			
MVAC/GC (%)	28 (71.8)/11 (28.2)		
Median AC cycles (IQR)	3 (2-3)/3 (3-3)		

Abbreviations: AC = adjuvant chemotherapy; BMI = body mass index; GC = gemcitabine and cisplatin; GFR = glomerular filtration rate; IQR = interquartile range; MVAC = methotrexate, vinblastine, doxorubicin, and cisplatin; RC = radical cystectomy.

or pN1-3, or both). In this study, the outcomes were compared between patients with non–organ-confined bladder cancer receiving AC and those not receiving AC, and the predictors of survival benefit were analyzed.

Patients and Methods

This study was approved by our institutional review board (No. 3124). We reviewed medical records of all patients undergoing RC with curative intent at our institution from 1990 to 2012 and collected data for locally advanced (pT3-4) or node-positive (pN1-3) disease, or both, for the present study. Patients who received NAC or perioperative radiotherapy or those with early recurrence or mortality (within 8 weeks after RC) were excluded. It has been our policy to recommend 3 cycles of AC for patients with non–organ-confined bladder cancer, although not all patients choose to receive treatment.

Cystectomy specimens were restaged based on the 2009 Union for International Cancer Control TNM system.[16] Glomerular filtration rate was evaluated by the revised formula for Japanese participants,[17] and body surface area was evaluated by the formula of Du Bois.[18]

Until 2008, the AC protocol had been MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin), and thereafter GC (gemcitabine and cisplatin) was used. Three cycles of AC were offered, but some patients failed to complete the protocol because of poor tolerance, and a few underwent 4 courses at the physician's discretion. The dose of chemotherapeutic agents was reduced by 25% to 50% in cases of impaired renal function or severe adverse events, or both, in the previous courses.

Follow-up comprised physical examination, serum biochemical profile, urine cytologic analysis, chest radiography or computed tomography, and abdominopelvic computed tomography. Bone scintigraphy was performed when clinically indicated.

Clinicopathologic characteristics were compared between the 2 groups using the χ^2 test or the Mann-Whitney U test. RFS and CSS from the date of surgery were calculated using the Kaplan-Meier method, and the difference was tested with a log-rank test. Multivariate analyses were carried out using a Cox proportional hazards regression model. StatView-J 5.0 (SAS Institute, Inc, Cary, NC) was used. P values less than .05 were considered significant.

Results

Of the 187 patients undergoing RC, 64 were identified as having non–organ-confined bladder cancer. Three patients were excluded from the analysis because of early recurrence (n = 2) and postoperative mortality (n = 1). Of the remaining 61 patients, 39 (64%) received AC after RC (AC group), and 22 (36%) did not (non-AC group) because they declined AC treatment (n = 10), had a protracted recovery after RC (n = 5), or had insufficient renal function (n = 3), comorbidities (n = 2), or advanced age (n = 2). AC was initiated between 6 and 10 weeks after RC and was completed in 28 patients (72%).

Clinicopathologic characteristics of the patients are shown in Table 1. The median age was 64 years (interquartile range [IQR], 59-75 years), and the median follow-up period was 29 months (IQR, 17-59 months). The patients receiving AC were significantly younger (P = .004) and had a higher body mass index (BMI) (P = .024) and a lower perioperative blood transfusion rate (P = .029). Two (5.1%) patients in the AC group (ileus and postoperative bleeding) and 6 (27.3%) in the non-AC group (ileus in 4, intestinal fistula in 1, and lymphocele in 1) had postoperative complications of grade 3 or more according to the Clavien-Dindo classification (P = .038).[19] There were no significant differences in pT stage, pN stage, nuclear grade, and renal function between the 2 groups (Table 1).

During follow-up at a median of 29 months, 25 of 39 (64%) patients in the AC group and 15 of 22 (68%) patients in the non-AC group ultimately experienced recurrence/metastasis. Salvage systemic chemotherapy was administered in 68% (17 of 25) and 47% (7 of 15) of the AC and non-AC groups, respectively (P = .205). Nineteen (49%) patients in the AC group and 15 (68%) patients in the non-AC group died of recurrent bladder cancer.

RFS was better for the AC group, but the difference was not statistically significant (MST, 23.7 vs. 11.4 months; P = .154)

Figure 1 **(A) Recurrence-Free Survival (RFS). The AC Group Showed Better RFS Than Did the Non-AC Group, but the Difference Was Not Statistically Significant (Median Survival Time [MST] 23.7 vs. 11.4 Months, Respectively; P = .154). (B) Cancer-Specific Survival (CSS) of Patients Having Adjuvant Chemotherapy (AC) After Radical Cystectomy (RC) (AC Group) and Those Having RC Alone (Non-AC Group). CSS Was Significantly Better for the AC Group Than for the Non-AC Group (MST, 57.4 vs. 17.9 Months, Respectively; P = .008)**

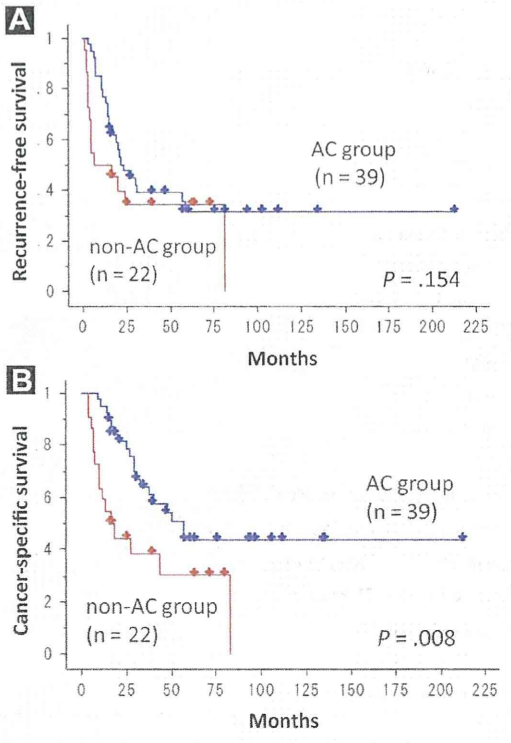


Table 2 Univariate and Multivariate Cox Regression Analysis of Recurrence-Free Survival

Variable	Referent	Univariate			Multivariate		
		HR	95% CI	*P* Value	HR	95% CI	*P* Value
Age, years		0.997	0.937-1.028	.825	0.984	0.946-1.022	.403
Female Sex	Male	0.593	0.182-1.934	.386			
Performance Status 2	≤1	1.416	0.592-3.386	.434	1.324	0.496-3.534	.576
BMI		0.945	0.842-1.060	.334	0.901	0.779-1.043	.165
GFR ≥60 mL/min	<60	0.986	0.520-1.870	.965			
Transfusion Yes	No	1.567	0.836-2.932	.161	1.691	0.851-3.360	.134
Complication Grade 3	No	0.914	0.324-2.577	.865			
≥pT3	≤pT2	1.134	0.443-2.902	.793			
Grade 3	Grade 1/2	1.560	0.551-4.405	.403			
LVI Positive	Negative	2.198	0.781-6.172	.136	7.366	2.037-26.64	.002
≥pN1	pN0	1.582	0.846-2.959	.151			
Metastatic LNs		1.084	1.010-1.164	.026			
Removed LNs		0.991	0.968-1.015	.461			
Positive Surgical Margin	Negative	2.725	1.180-6.289	.019	3.204	1.314-7.816	.011
AC	Non-AC	0.630	0.331-1.198	.159	0.325	0.147-0.717	.005

Abbreviations: AC = adjuvant chemotherapy; BMI = body mass index; CI = confidence interval; GFR = glomerular filtration rate; HR = hazard ratio; LVI = lymphovascular invasion; LNs = lymph nodes.

(Figure 1A). By multivariate analysis, AC was an independent predictive factor for RFS (HR, 0.325; $P = .005$), along with surgical margin status and lymphovascular invasion (LVI) (Table 2).

CSS was significantly longer in the AC group (MST, 57.4 vs. 17.9 months; $P = .008$) (Figure 1B). Negative surgical margins ($P = .041$) and administration of AC ($P = .011$) were factors associated with CSS by univariate analyses. By multivariate analysis, AC was significantly associated with better CSS (HR, 0.186; $P < .001$), along with negative surgical margins, negative LVI, and increased body mass index (BMI) (Table 3).

Node-positive and node-negative cases were also evaluated separately. As shown in Figure 2A, of 31 patients with pTanypN+ disease, 21 (68%) who received AC had significantly better CSS compared with 10 (32%) who were not given AC ($P = .029$). In contrast, in patients with pT3-4pN0 disease (n = 30), AC was not associated with any survival benefit ($P = .103$) (Figure 2B).

Discussion

The role of adjunct chemotherapy with RC in the treatment of muscle-invasive bladder cancer remains controversial.[8] At our

Table 3 Univariate and Multivariate Cox Regression Analysis of CSS

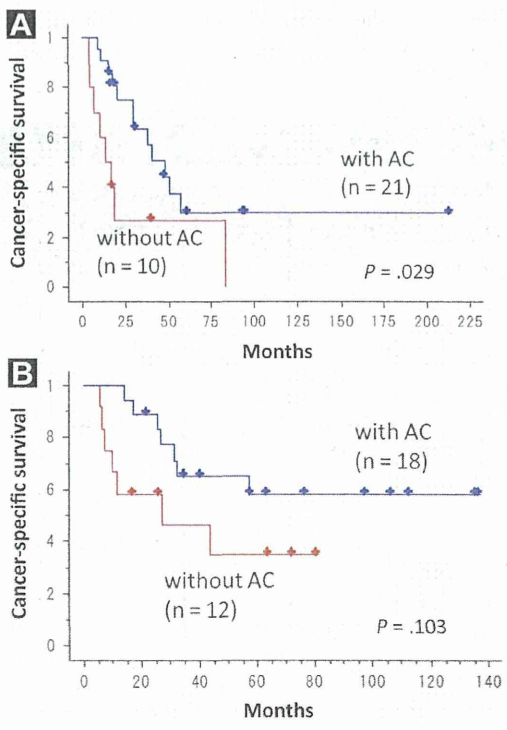
Variable	Referent	Univariate			Multivariate		
		HR	95% CI	*P* Value	HR	95% CI	*P* Value
Age, years		1.012	0.978-1.046	.494	1.003	0.961-1.047	.884
Female Sex	Male	0.521	0.124-2.185	.373			
Performance Status 2	≤1	1.072	0.377-3.053	.896	0.604	0.184-1.985	.406
BMI		0.892	0.783-1.018	.089	0.822	0.690-0.980	.029
GFR ≥60 mL/min	<60	0.870	0.438-1.730	.692			
Transfusion Yes	No	1.782	0.902-3.521	.096	1.972	0.908-4.282	.086
Compllicatioin Grade 3	No	0.919	0.278-3.033	.889			
≥pT3	≤pT2	0.882	0.341-2.284	.796			
Grade 3	Grade1/2	2.976	0.707-12.50	.137			
LVI Positive	Negative	2.146	0.654-7.042	.208	18.31	4.089-81.99	<.001
≥pN1	pN0	1.692	0.852-3.356	.133			
Metastatic LNs		1.055	0.983-1.133	.139			
Removed LNs		0.991	0.966-1.016	.472			
Positive Surgical Margin	Negative	2.538	1.037-6.211	.041	2.733	1.065-7.015	.037
AC	Non-AC	0.411	0.207-0.814	.011	0.186	0.081-0.430	<.001

Abbreviations: AC = adjuvant chemotherapy; BMI = body mass index; CI = confidence interval; GFR = glomerular filtration rate; HR = hazard ratio; LNs = lymph nodes; LVI = lymphovascular invasion.

institution, all patients with locally advanced or node-positive bladder cancer (pT3-4 or N+, or both) are offered 3 courses of cisplatin-based AC, although approximately one third decline treatment. In this study, comparing the prognoses of those receiving AC (AC group) and those not receiving AC (non-AC group), we found a significant survival advantage for the AC group. The advantage, represented as 57.4 versus 17.9 months in the MST of CSS ($P = .008$), remained significant after adjusting for possible confounding factors, and was even more evident for node-positive bladder cancer ($P = .029$).

The prognosis of patients undergoing RC clearly depends on the pathologic stage. Those with organ-confined disease (pT2 or less) have an acceptable 5-year OS of 75% to 83%, whereas the 5-year survival rate is reportedly 47% to 65% for patients with locally advanced disease (pT3-4) and 22% to 40% for patients with node-positive disease (pN1-3).[3-5] AC has been used to improve such an ominous prognosis for locally advanced or node-positive bladder cancer. Leow et al found favorable outcomes in patients with node-positive disease in their meta-analysis study of RCTs, suggesting that nodal involvement could be an indication for AC.[12] Svatek et al retrospectively analyzed their large cohort and found that bladder cancers of advanced T stage (≥ T3) with nodal involvement were most likely to benefit from AC.[20] Our results are consistent with their conclusions.

Figure 2 **(A) Cancer-Specific Survival (CSS) of Patients With Positive Nodes. Subgroup Analysis of 31 Node-Positive Cases: The AC Group (n = 21) had Significantly Better CSS Compared With the Non-AC Group (n = 10) (Median Survival Time [MST], 47.8 vs. 15.2 Months, Respectively; $P = .029$). (B) CSS of Patients With pT3-4 pN0. Analysis of Node-Negative Cases (n = 30) Yielded No Significant Benefit for AC**



One of the issues affecting AC is delayed commencement of chemotherapy because of protracted recovery after RC. In fact, patients who experienced grade 3 postoperative complications were less likely to undergo AC in our study. A large cohort study at Memorial Sloan-Kettering Cancer Center found that 298 of 1142 (26%) patients required readmission after RC and 347 (30%) may have skipped AC because of postoperative complications.[21] Furthermore, toxicity can make it difficult to complete multiple cycles of AC.[12] Of 102 candidates, 78%, 74%, and 62% of patients achieved 2, 3, and 4 cycles, respectively, mostly as a result of treatment-related toxic effects in the largest RCT of AC that had an intended 4 cycles per protocol.[15] In our study, 28 patients (72%) finished 3 cycles of AC.

Another important issue is the relative effectiveness of AC versus NAC, with the latter now strongly recommended, based on RCTs,[9,10] by the European Association of Urology guidelines[22] and the National Comprehensive Cancer Network guidelines.[23] Nevertheless, NAC has been less commonly adopted in practice than has AC[7,10,22]; 17% and 35% of patients received cisplatin-based NAC and AC, respectively, even in a high-volume tertiary referral center committed to multimodality therapy.[24] Underuse of NAC may result from concerns with overtreatment in overstaged patients or disease progression in unresponsive patients. Wosnitzer et al. observed no statistically significant difference in survival between patients receiving NAC and those receiving AC, stating that chemotherapy sequence relative to surgery appeared less important than the actual execution of perioperative chemotherapy.[25] Development of efficient predictors of therapeutic efficacy including molecular markers[26,27] would facilitate more rational use of chemotherapy.

Our study has several limitations. First, this is a retrospective study with a relatively small sample size. Although AC remained a statistically significant factor predictive of CSS even by multivariate analysis, different characteristics of the 2 groups, including age, postoperative complications, and salvage chemotherapy, might confound the study end points. Furthermore, other unexamined factors might affect the comparison. Second, the AC regimen was changed during the study period. MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin) was used through 2008, and GC (gemcitabine and cisplatin) replaced it in 2009. Different profiles of adverse events might have affected treatment decisions, although equivalent efficacies were shown in the locally advanced or metastatic setting for these 2 protocols.[6] Third, there was a transition of the surgical procedure during the study period. For example, the standard upper boundary of the lymph node dissection was the iliac bifurcation until 2004. Since 2005, more than 80% of the patients underwent lymph node dissection up to the aortic bifurcation. Despite such modification, our policy of AC for the management of non–organ-confined bladder cancer had not changed.

Conclusion

In summary, our results suggest that postoperative cisplatin-based AC gives patients a survival advantage in locally advanced or node-positive bladder cancer, especially in node-positive cases. Further clinical trials targeting such patients are warranted.

Adjuvant Chemotherapy in Bladder Cancer

Clinical Practice Points

- A survival benefit of presurgical chemotherapy (NAC) in the treatment strategy for muscle-invasive bladder cancer has been established by 2 previous RCTs. In contrast, the role of post-surgical chemotherapy (AC) remains to be determined.
- Although a recent meta-analysis of 9 RCTs revealed a statistically significant benefit of AC on overall survival in muscle-invasive bladder cancer, individual RCTs failed to prove the benefit of AC, and the optimal targets of AC have never been identified.
- In our retrospective study, postoperative cisplatin-based AC improved survival in locally advanced or node-positive bladder cancer, especially in node-positive cases. The survival benefit of AC was retained even after adjustment with other confounding factors on multivariate analysis.

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