Novel bladder preservation therapy for locally invasive bladder cancer: Combined therapy using balloon-occluded arterial infusion of anticancer agent and hemodialysis with concurrent radiation

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Abstract. We investigated the effect of balloon-occluded arterial infusion (BOAI) of anticancer agent (cisplatin/gemcitabine), used concomitantly with hemodialysis, which delivers an extremely high concentration of anticancer agent to the site of a tumor without systemic adverse effects, along with concurrent radiation (referred to as the OMC-regimen) in patients with advanced bladder cancer. One hundred and ninety-two patients were assigned to receive either the OMC-regimen (n=96) or total cystectomy (n=96). Patients in the OMC-regimen group who failed to achieve CR underwent cystectomy, or secondary BOAI with an increased amount of CDDP or gemcitabine (1600 mg). The OMC-regimen allowed >89% (69/77) of patients with locally invasive tumors to achieve CR [>70% (70/96) of all patients including those with T4 and N(+) disease]. Most (68/69) of the CR patients were still alive with no evidence of recurrence after a mean follow-up of 161 (range 12-805) weeks. The 5- and 15-year overall survival rates were 91.5 and 81.3% (vs. 59.8% and 40.1% for cystectomy, P<0.0001), respectively. No patients suffered Grade III or more severe toxicities. In contrast, at 5 and 15 years after surgery in the total cystectomy group, about 50 and 60% of patients had suffered disease progression or had died, respectively. The OMC-regimen, a new bladder-preservation strategy for patients with locally invasive bladder cancer, can be curative not only in patients for whom cystectomy is indicated, but also in patients whose condition is not amenable to curative treatment and for whom merely palliative therapy would otherwise seem the only option.

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Abbreviations: ANC, absolute neutrophil count; BOAI, balloon-occluded arterial infusion; CIS, carcinoma *in situ*; CTCAE, common terminology criteria for adverse events; DSA, digital subtraction angiography; ECOG, Eastern Cooperative Oncology Group; HD, hemodialysis; Qu, quartile; RTOG, radiation therapy oncology group; TURBT, transurethral resection of bladder tumor; UC, urothelial carcinoma

Key words: balloon-occluded arterial infusion, hemodialysis, OMC-regimen, invasive bladder cancer

Introduction

Radical cystectomy has long been the standard method of treatment for patients with locally invasive bladder cancer. However, this inevitably reduces the quality of life of the patients to some degree. Moreover, more than 40% of all patients with invasive bladder cancer die within 5 years (1-8). Trimodality therapy consisting of radical transurethral resection, chemotherapy and radiation therapy has been attempted as an alternative approach for patients who require cystectomy. Data from multiple institutional and cooperative group studies have shown that this approach is safe and effective, yielding a complete response (CR) in more than 60% of cases (9-15). However, prospective protocols conducted by the Radiation Therapy Oncology Group (RTOG) demonstrated a survival rate similar to that for radical cystectomy; none of the protocols achieved a 5-year survival rate of more than 60% (9-13). A highly effective, but non- or only minimally invasive therapy that conserves the bladder is therefore needed.

Accordingly, we conducted the present study to investigate the effect of combined therapy [referred to hereafter as the OMC (Osaka Medical College) regimen] involving balloon-occluded arterial infusion (BOAI) of an anticancer agent and concurrent hemodialysis (HD), which allows the anticancer agent to accumulate at a high concentration at the site of a tumor but ensures that the systemic concentration remains low after the agent has passed through the tumor, followed by radiation therapy. We found that more than 90% of patients (70/77) with locally advanced urothelial bladder cancer who were treated in this way achieved CR, of whom 97% (68/70) did not develop recurrent disease or metastasis within a mean follow-up period of 164 weeks [range, 11-805 weeks; 1st to

3rd quartile (Qu) = 66 to 195] after completion of therapy. Herein we describe this novel approach and its outcomes to date in comparison with total cystectomy at our institution.

Patients and methods

Eligibility criteria. Eligible patients had histologically confirmed stage T2, T3 or T4 muscle-invasive bladder cancer without distant metastasis. However, patients with pelvic lymph node metastasis, diagnosed by imaging studies, were also eligible. Imaging studies, including chest computed tomography (CT) scan, abdominal/pelvic magnetic resonance imaging (MRI) and CT scan, and bone scintigraphy were performed before the start of therapy. All patients who received the OMC regimen had an absolute neutrophil count (ANC) of 1,500/μl, platelet count 100,000/μl, creatinine 3.0 mg/dl, a bilirubin level 3 times the institutional upper limit of the normal range, an AST level 4 times the institutional upper limit of the normal range, an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2, and no prior radiotherapy or systemic therapy for bladder cancer. The study was reviewed and approved by the institutional review board of Osaka Medical College. Patients were informed of the investigational nature of the study and provided written informed consent before study enrollment.

Study design and treatment. Before study entry, patients underwent complete transurethral resection of the bladder tumor (TURBT) at our institution to establish the diagnosis. We primarily recommended total cystectomy when surgery was feasible. However, the OMC regimen was offered as another treatment option whenever total cystectomy was not feasible because of advanced age, performance status, or other reasons. Patients were assigned to receive the OMC regimen at 4-5 weeks after TURBT to allow adequate healing.

Assessability, toxicity, and response criteria. Pretreatment evaluation included a complete history and physical examination, performance status assessment, complete differential blood cell count, electrolytes, blood urea nitrogen, serum creatinine, liver function parameters, and appropriate imaging studies to assess the extent of disease. During treatment, patients were seen weekly at our department, when their weight was recorded and toxicity was monitored using the National Cancer Institute's Common Terminology Criteria for adverse events v4.0 (CTCAE). At 6 weeks, patients underwent repeat transurethral resection of the site of the original tumor, ultrasound-guided whole-layer biopsy, and urine cytology, as well as MRI and CT scan of the pelvis, and were evaluated for their response to this therapy. CR was defined as complete disappearance of all measurable and evaluable disease. Duration of response was defined as the period from documentation of the response until evidence of disease recurrence. Survival was the period from study entry until patient death. Patients who achieved CR were observed using our follow-up protocol. However, any evidence of residual tumor in the bladder was deemed as treatment failure, and such patients were primarily advised to undergo total cystectomy when possible, but otherwise to undergo secondary BOAI with a higher dosage of cisplatin or gemcitabine (1600 mg), as a salvage therapy. Patients who were found to have only a superficial amount of remaining tumor underwent intravesical injection of bacillus Calmette Guerin (BCG).

Follow-up. All patients were followed-up on the basis of monthly urine cytology, together with cystoscopy, biopsy and imaging studies, every three months for 2 years, including chest CT scan, abdominal/pelvic MRI and CT scan, and bone scintigraphy, and then at 6-month intervals thereafter.

Statistical analyses. Simple as well as multiple regression analyses were conducted to evaluate the significance of the following variables as risk factors of treatment failure: T-stage, tumor pathology (UC vs. non-UC), patient performance status, sex, age, and amount of CDDP administered. Differences at $P<0.05$ were considered to be statistically significant. The life table probabilities of overall survival and progression-free survival were determined using Kaplan-Meier analysis and log-rank test. Cox proportional hazards regression analysis was conducted to assess the associations of each factor, including T-stage, tumor pathology (UC vs. non-UC), patient performance status, sex, age, and amount of CDDP administered. Differences at $P<0.05$ were considered to be statistically significant.

Results

Patient characteristics. Between 1988 and 2009, 96 (67 males and 29 females) were treated with the OMC regimen, and 96 (80 males and 16 females) underwent radical cystectomy. The characteristics of the patients in these two treatment groups are shown in Table I. For preoperative clinical staging, we used a simplified form of the 2002 TNM classification to stage bladder tumors as Tis, T1, T2, T3, and T4 (16). To make a valid comparison, preoperative clinical staging and not the pathologic stage after cystectomy was used to compare the two treatment groups, thus avoiding stage migration that may occur after pathologic staging (17). The distribution of clinical stage and histological grade is shown in Table I.

Treatment details

i) OMC-regimen group. Patients assigned to the OMC-regimen group underwent complete transurethral resection of the bladder tumor (TURBT) at our institution to establish the diagnosis. They were then scheduled to receive the OMC regimen 4-5 weeks after TURBT to allow adequate healing. We administered 100, 200, or 300 mg of cisplatin as a single bolus according to the criteria described in Table II.

For the intra-arterial infusion procedure, we used an intra-arterial catheter equipped with two occlusion balloons (size: 6 Fr., M6F-28-70-TBSB4-ST, Clinical Supply, Tokyo, Japan). The catheter was introduced into the posterior trunk of the internal iliac artery through the femoral arterial approach, and after the distal balloon had passed through the furcation of the anterior trunk of the internal iliac artery, both the distal and proximal balloons were inflated and immobilized, so that the anterior trunk of the internal iliac artery, which lies upstream of the target vessels (the vesical arteries) was isolated between the balloons. At this time, using digital

Table I. Characteristics of patients in the two groups.

Characteristic	OMC regimen	Total cystectomy	P-value
Age median (range years)	72 (38-98)	65 (44-79)	<0.0001
Sex			
Male (%)	67 (69.8%)	80 (83.3%)	0.0286
Female (%)	29 (30.2%)	16 (16.7%)	
Clinical stage			
T-stage			
Cis	0 (0%)	4 (4.2%)	N.S.
T2	32 (33.3%)	49 (51.0%)	0.0135
T3	48 (50.0%)	43 (44.8%)	N.S.
T4	16 (16.7%)	0 (0%)	
N-stage			
N0	86 (89.6%)	96 (100%)	
N1	10 (10.4%)	0 (0%)	
Tumor histology			
UC			
G2	10 (10.4%)	32 (33.3%)	0.0002
G3	78 (82.3%)	55 (57.3%)	0.0004
Others			N.S.
Adenocarcinoma	6 (5.2%)	1 (1.0%)	N.S.
Squamous cell carcinoma	1 (1.05%)	8 (8.3%)	N.S.
Choriocarcinoma	1 (1.05%)	0 (0%)	N.S.
ECOG performance status			
0	37 (38.5%)	64 (66.7%)	0.0001
1	41 (42.7%)	24 (25.0%)	0.0102
2	18 (18.8%)	8 (8.3%)	0.0395

Table II. Criteria for the administration of cisplatin.

In the initially enrolled 22 patients	
100 mg	Renal function (sCr ≥1.3) or age (≥75 years)
200 mg	Renal function (sCr <1.3) with [age (60-74 years) and T-stage (T2 or T3)]
300 mg	Renal function (sCr <1.3) with [age (<60 years) or T-stage: T4]
In the latest 74 patients	
100 mg	All patients

subtraction angiography (DSA), it was confirmed that the injected agent did not enter the superior gluteal artery and that there was no back-flow into the internal iliac artery, while the tumor was markedly stained due to active flow of injected contrast medium into the urinary bladder. Fig. 1 illustrates the extracorporeal circuit used in the treatment, and Fig. 2 presents DSA images of the bilateral common iliac arteries before (Fig. 2A) and after (Fig. 2B) balloon occlusion. Various amounts of cisplatin (100, 200, or 300 mg) were locally infused through the catheter over a 1-h period (Table I). Simultaneously, HD was performed via two double-lumen catheters (size: 12 Fr., Argyle®, Tyco Healthcare, Tokyo, Japan) placed in the bilateral common iliac veins for 2 h after the start of arterial infusion. The catheters were connected to a hollow-fiber dialyzer (APS150, Asahi, Tokyo, Japan) with a membrane area of 1.0-1.5 m^2 according to the weight of each patient. The blood flow rate was 180-250 ml/min and the hemodialysis-fluid flow rate was 500 ml/min.

Radiation therapy was administered to the whole pelvis using a CT-planned three-dimensional conformal technique to a total of 60.4 Gy: 50.4 Gy (1.8 Gy/day x 28 days) followed by 10 Gy (2 Gy/day x 5 days) of local irradiation to the bladder. Patients were treated with the bladder empty. The planned target volume for the bladder included the gross target volume (bladder plus any extravesical tumor) with a 1-cm expansion. At 6 weeks, patients underwent repeat transurethral resection of the site of the original tumor, ultrasound-guided whole-layer biopsy, and urine cytology, as well as MRI and CT scan of the pelvis, and the response to this therapy was then evaluated.

ii) Radical cystectomy group. Among the 96 patients in the radical cystectomy group, 32 underwent ileal conduit formation, 35 underwent uretero-cutaneostomy, 25 underwent continent urinary diversion with ileal-neobladder formation (Hartmann's method), and the remaining 4 underwent uretero-sigmoidostomy performed at the time of radical cystectomy. Standard pelvic lymphadenectomy was performed in 81 patients, 5 patients underwent iliac sampling, and 10 patients were not studied in sufficient detail to allow assessment of the level of lymph node dissection. As not all of the histology reports mentioned the number of lymph nodes examined, it was not possible to precisely evaluate the extent of dissection. There were no significant differences in cause-specific or overall survival between the patients who underwent nodal dissection and the patients who did not. Urethrectomy was performed in 10 patients at the time of radical cystectomy because of the presence of extensive carcinoma *in situ* or multifocal bladder tumors.

Response to the OMC regimen. Table III summarizes the treatment response, duration of response, and patient characteristics, including T stage, N stage, tumor histology (UC vs. non-UC), patient performance status, sex, age, and amount of CDDP administered. Overall, 73 of the 96 patients (76.0%, 95% CI, 66.3-84.2%) achieved a complete response as defined by the absence of persistent disease revealed by cystoscopy, biopsy, and urine cytology after therapy (Table III). More than 95% (70/73) of patients with CR were able to retain their urinary bladder with no evidence of recurrent disease or distant metastasis within a mean follow-up period of 161 weeks (range, 12-805 weeks; 1st to 3rd Qu = 63-193 weeks) from the completion of therapy. Most of the patients

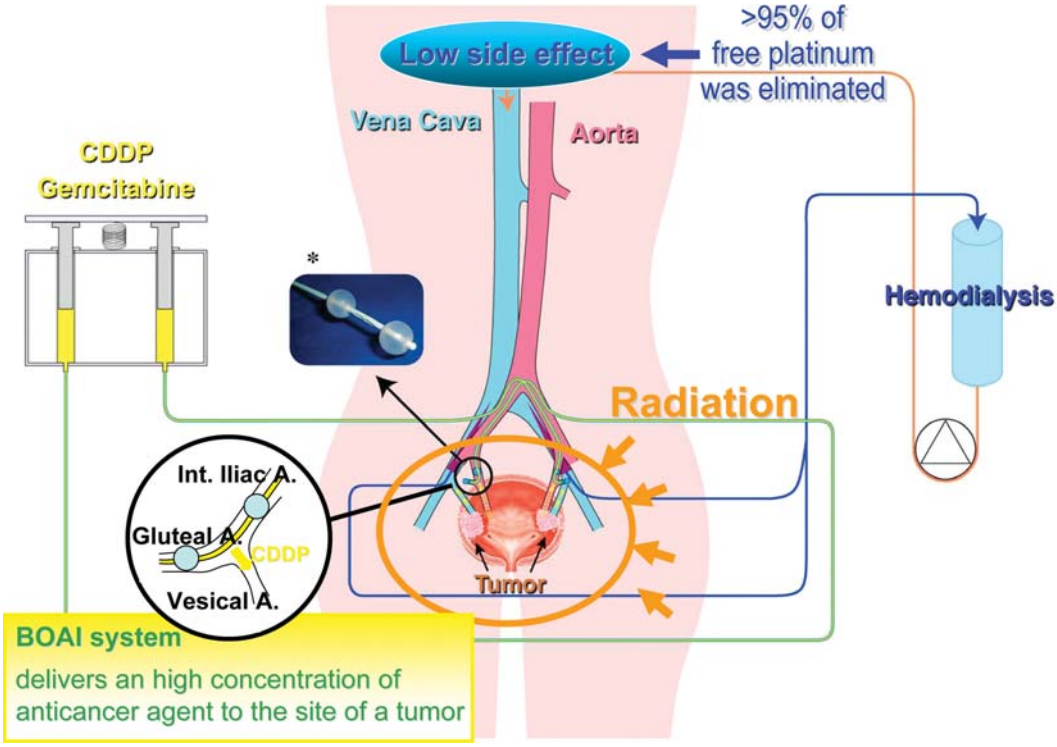

Figure 1. Schema of the OMC regimen (HD-BOAI-CDDP/gemcitabine with radiation). The extracorporeal circuit allowed balloon-occluded intra-arterial infusion of CDDP/gemcitabine concurrent with HD. Through the femoral arterial approach, an intra-arterial catheter equipped with two occlusion balloons was introduced into the posterior trunk of the internal iliac artery on each side. Both the distal and proximal balloons were inflated and immobilized at a position allowing the vesical arteries to be isolated between the balloons. After confirming by angiography that the catheter was in the right position, various amounts of cisplatin (100, 200, or 300 mg), or gemcitabine (1600 mg) were infused through the side holes of the catheter between the inflated balloons over a 1-h period. Simultaneously, HD was performed via double-lumen catheters placed in the bilateral common iliac vein for 2 h after the start of arterial infusion. The panel marked with an asterisk shows a picture of the intra-arterial catheter (M6F-28-70-TBSB4-ST, clinical supply), which is made of polyethylene, 6 French in size, and equipped with two occlusion balloons separated by a distance of 40 mm. It has side holes between the balloons enabling injection of contrast medium or anticancer agent.

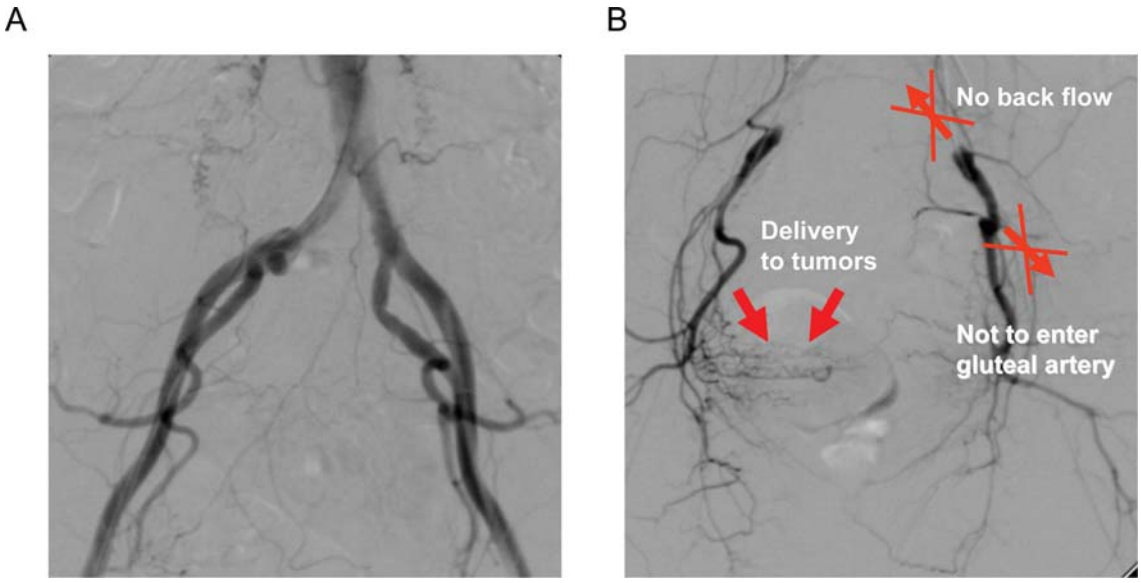

Figure 2. Bilateral common iliac arteriography before (A) and after (B) balloon occlusion. We ensured that contrast medium did not enter the superior gluteal artery and that there was no back-flow into the internal iliac artery. We also also confirmed that the anticancer agent was delivered to the urinary bladder, especially to the tumor site.

who achieved CR had locally invasive tumors (stage T2 or T3 node-negative; 71 of 73 patients, 97.3%, 95% CI, 90.5-99.7%) and UC histologically (72 of 73 patients, 98.6%, 95% CI, 92.6-99.9%). Indeed, only 6 of 77 patients (4.4%) with locally invasive tumors failed to achieve CR, while only 3 patients with stage T4 tumors achieved CR, only 1 patient

Table III. Response at 3 months after treatment, and current outcome.

	CR			PR			SD			PD		
	No.	%	95% CI	No..	%	95% CI	No..	%	95% CI	No..	%	95% CI
Total no. of patients	73	76.0	58.1-81.8	5	5.21	1.71 -11.7	8	8.33	3.67 -15.8	10	10.4	5.11 -18.3
Duration of response												
Mean, range		154, 8-802 weeks			45, 12-69 weeks			55, 15-237 weeks			0	
1st, 3rd QU		58, 189 weeks			27, 68 weeks			19, 42 weeks			0	
Recurrence	3	4.11	0.86-11.5	0	0	0-52.2	7	87.5	47.3-99.7			
Death	4	5.48	1.51-13.4	0	0	0-52.2	5	62.5	24.5-91.5	9	90.0	55.4-99.7
Age (mean, range)		70, 38-85 years			72, 62-78 years			79, 68-98 years			71, 55-81 years	
Sex												
Male	53	72.6	60.9-82.4	2	40.0	5.27-85.3	5	62.5	24.5-91.5	7	70.0	34.8-93.3
Female	20	27.4	17.6-39.1	3	60.0	14.7-94.7	3	37.5	8.52-75.5	3	30.0	6.67-65.2
	No.	%	95% CI	No.	%	95% CI	No.	%	95% CI	No.	%	95% CI
Categories												
2	31	42.5	31.0-54.6	1	0	0.50-71.6	0	0	0-36.9	0	0	0-30.8
T stage												
3	40	53.8	42.7-66.5	3	0	14.7-94.7	2	25.0	3.67-71.0	3	30.0	6.67-65.2
4	2	2.7	0.33-9.55	1	100	0.50-71.6	6	75.0	29.0-96.3	7	70.0	34.8-93.3
N stage												
N (-)	72	98.6	92.6-100	5	100	47.8-100	4	50.0	15.7-84.2	5	50.0	18.7-81.3
N (+)	1	1.4	0.03-7.40	0	0	0-52.2	4	50.0	15.7-84.2	5	50.0	18.7-81.3
Histology												
UC	72	98.6	92.6-100	5	100	47.8-100	5	62.5	24.5-91.5	6	60.0	26.2-87.8
Non-UC	1	1.4	0.03-7.40	0	0	0-52.2	3	37.5	8.52-75.5	4	40.0	12.2-73.8
PS												
0	32	43.8	32.2-55.9	1	20	0.50-71.6	1	12.5	0.32-52.7	3	30.0	6.67-65.2
1	30	41.1	29.7-53.2	2	40	5.27-85.3	6	75.0	29.0-96.3	3	30.0	6.67-65.2
2	11	15.1	9.80-35.3	2	40	5.27-85.3	1	12.5	0.32-52.7	4	40.0	12.2-73.8
CDDP												
100	65	89.0	67.3-91.8	5	100	47.8-100	5	62.5	24.5-91.51	7	70.0	34.8-93.3
200	4	5.5	2.53-21.7	0	0	0-52.2	1	12.5	0.32-52.7	1	10.0	0.25-44.5
300	4	5.5	2.53-21.7	0	0	0-52.2	2	25.0	3.19-65.1	2	20.0	2.52-55.6
Gemcitabine	1	1.4	0.06-12.0	2	40	5.27-85.3	2	25.0	3.19-65.1	1	10.0	0.25-44.5

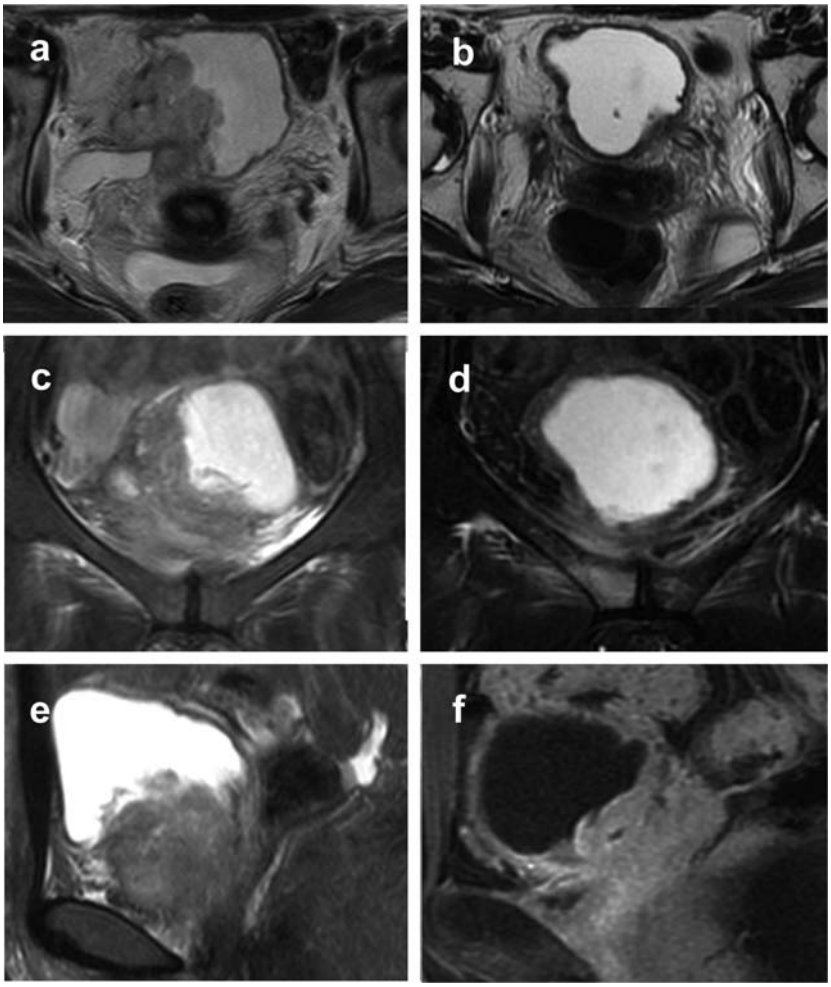

Figure 3. MRI before (a-c) and after (d-f) the treatment. The horizontal (a), coronal (b) and sagittal (c) MRI slices reveal that bulky tumors occupy more than half of the bladder cavity, and that the tumors invade the abdominal wall, indicating stage T4. In contrast, all imaging studies (d, horizontal; e, coronal; and f, sagittal slices) confirm complete disappearance of the tumors, and that the mucosa and muscle layer are intact, at 10 weeks after completion of the therapy.

Table IV. Risk factors for treatment failure in the OMC-regimen group.

		Univariate		Multivariate	
	Category	Odds ratio	P-value	Odds ratio	P-value
T-stage	T4 vs. T2-3	55.22	<0.0001	47.310	0.0005
N-stage	N(+) vs. N(-)	46.285	0.0005	87.670	0.0044
Histology	Non-UC vs. UC	31.50	0.0018	7.565	0.0291
Performance status	2 vs. 0 or 1	2.466	0.1043	0.967	0.9693
Sex	Male vs. female	0.587	0.2880	0.317	0.1644
Age	Cont. variable	1.045	0.1084	1.141	0.1348
Amount of CDDP	Cont. variable	1.006	0.0896	0.994	0.5886

Cont. variable, continuous variable.

with lymph node metastasis achieved CR, and only 1 patient with a histologically confirmed non-UC tumor achieved CR. Fig. 3 shows horizontal, coronal and sagittal MRI images obtained before and after treatment.

In contrast to the high CR induction ratio in patients with locally invasive UC tumors, most patients with lymph node involvement (9 of 10 patients; 90%, 95% CI, 55.4-99.7%), stage T4 tumors (13 of 16 patients; 26.8%, 95% CI, 14.2-

Table V. Postoperative clinical course and risk factors for disease recurrence in the cystectomy group.

Characteristic	NED	Recurrence	P-value
Age median (range years)	64 (44-79)	67 (45-76)	N.S.
Sex			
Male (%)	51 (85.0%)	29 (80.6%)	N.S.
Female (%)	9 (15.0%)	7 (19.4%)	N.S.
ECOG performance status			
0	45 (75.0%)	19 (52.8%)	N.S.
1	12 (20.0%)	12 (33.3%)	N.S.
2	3 (5.0%)	5 (13.9%)	N.S.
Chemotherapy			
Neoadjuvant	1 (1.7%)	4 (11.1%)	N.S.
Adjuvant	20 (33.3%)	16 (44.4%)	N.S.
None	39 (65.0%)	16 (44.4%)	N.S.
Clinical stage			
CisN0M0	4 (6.7%)	0 (0%)	N.S.
T2N0M0	38 (63.3%)	11 (30.6%)	0.0024
T3N0M0	18 (30.0%)	25 (69.4%)	0.0003
Pathological stage			
T-stage			
Tis	5 (8.3%)	1 (2.8%)	N.S.
pT1	12 (20.0%)	2 (5.6%)	N.S.
pT2	23 (38.3%)	9 (25.0%)	N.S.
pT3	19 (31.7%)	16 (44.4%)	N.S.
pT4	1 (1.7%)	8 (22.2%)	0.0092
N-stage			
pN(-)	52 (86.7%)	20 (72.2%)	N.S.
pN(+)	8 (13.3%)	10 (27.8%)	N.S.
Tumor histology			
UC			
G2	24 (40.0%)	8 (22.2%)	N.S.
G3	30 (50.0%)	25 (69.4%)	N.S.
Others			N.S.
Adenocarcinoma	1 (1.7%)	0 (0%)	N.S.
Squamous cell carcinoma	5 (8.3%)	3 (8.3%)	N.S.

42.9%), and/or tumors besides UC (1 patient with SCC, 1 patient with choriocarcinoma, and 5 patients with adenocarcinoma) failed to achieve CR after the treatment. Table IV shows the results of simple and multiple regression analysis of risk factors for treatment failure, the independent variables being T stage, N stage, histology, age, sex, PS, and amount of CDDP. Stage T4, lymph node involvement, and histological type (non-UC) were independent statistically significant risk factors for treatment failure by simple or multiple logistic analysis (Table IV).

Effect of salvage therapy for remaining cancer. Two patients who were found to have only a superficial remaining tumor underwent intravesical injection of BCG. One patient achieved CR with no evidence of recurrent disease or distant metastasis after a follow-up period of 80 weeks. The other, however, suffered disease progression, necessitating total cystectomy. We basically recommended total cystectomy as a salvage therapy for patients with any remaining invasive tumor without lymph node involvement. However, most patients were ineligible for this option because of age, performance status or presence of other disease, such as myocardial infarction and liver dysfunction. These patients received secondary BOAI with gemcitabine (1600 mg), which can also be eliminated by HD, as a salvage therapy, or requested no further treatment. Six patients received secondary BOAI with gemcitabine; one of them achieved CR and 2 achieved PR with no evidence of recurrent disease or distant metastasis at the 1-year follow-up point, while other 3 patients showed progressive disease or disease recurrence after a period of stable disease.

Postoperative clinical course after radical cystectomy. Overall, 36 of the 96 patients (37.5%, 95% CI, 27.8-50.0%) were found to have disease recurrence, of whom >90% (34/36, 94%, 95% CI, 81.3-99.3%) subsequently died. Table V shows the influence of various factors, including age, sex, PS, and chemotherapy (neoadjuvant or adjuvant) before and after surgery, pretreatment clinical T stage, pathological T stage, N stage, and histology on disease recurrence. Table VI shows the results of simple and multiple regression analysis for each factor. Clinical stage T3 (vs. T2), pathological stage pT4 (vs. pT1-3), as well as pathological stage pT4 or pN(+) (vs. others) were independent statistically significant risk factors for disease recurrence by simple logistic analysis. Moreover, clinical stage T3 (vs. T2) and pathological stage pT4 (vs. pT1-3) were independent statistically significant risk factors for disease recurrence by multiple logistic analysis.

Comparison of survival between the two groups

i) Overall survival. Overall survival was significantly improved in the OMC-regimen group, with 5- and 15-year survival rates of 76.3 and 65.4%, respectively (vs. 59.8% and 40.1% in the cystectomy group, log-rank test, P<0.0475, Fig. 4A). Fig. 4B shows the Kaplan-Meier curves used for comparison of overall survival among the two OMC-regimen subgroups (OMC-confined, comprising patients with organ-confined disease, and OMC-T4-N+, comprising patients with stage T4 or N+ disease) and the cystectomy group. As can be seen, the 5- and 15-year survival rates were even better, at 91.5 and 81.3%, respectively (P<0.0001 vs. cystectomy group), when the results were compared under the same conditions by matching of the clinical stage, and excluding patients with stage T4 tumors and/or lymph node metastasis from the OMC-regimen group.

ii) Progresion-free survival. The progression-free survival ratio was significantly better in the OMC-regimen group than in the

Table VI. Risk factors for disease recurrence in the cystectomy group.

		Univariate		Multivariate	
	Category	Odds ratio	P-value	Odds ratio	P-value
Age	Cont. variable	1.016	0.5454	0.995	0.8971
Sex	Male vs. female	1.368	0.5725	1.059	0.9343
Performance status	2 vs. 0-1	3.065	0.1425	5.431	0.0623
Chemotherapy	(+) vs. (-)	2.321	0.0507	1.651	0.3349
Clinical T-stage	T3 vs. T2	5.303	0.0003	3.948	0.0128
Pathol T-stage	pT4 vs. pT1-3	16.857	0.0092	10.798	0.0356
Pathol N-stage	N(+) vs. N(-)	2.500	0.0848	1.327	0.6527
Pathol TN-stage	T4 or N(+) vs. others	4.048	0.0047		
Histology	Non-UC vs. UC	0.818	0.7865	0.823	0.8116

Cont. variable, continuous variable.

cystectomy group, the 5- and 15-year survival rates being 81.3 and 69.7% vs. 52.6 and 40.4%, respectively; log-rank test, P=0.0021, Fig. 4C). After completion of the OMC regimen, almost 80% of the patients (74 of 96 patients; 77.0%, 95%CI, 67.4-85.0%) survived without disease progression and were followed-up, showing a mean survival of 158 weeks (range 12-805 weeks, 1st to 3rd Qu = 61-193 weeks). Fig. 4D shows the Kaplan-Meier curves used for comparison of progression-free survival among the two OMC-regimen subgroups (OMC-confined and OMC-T4-N+), and the cystectomy group. The progression-free 10-, and 15-year survival rates were 89.3 and 79.4% in patients with organ-confined disease, respectively, compared with 5-year survival rate of 16% in patients with T4 tumors or lymph node metastasis.

Predictors of overall survival and progression-free survival selected using univariate and multivariate analyses in the two groups

i) OMC-regimen group. We investigated the significance of each factor, including pretreatment T-stage, lymph node involvement, tumor pathology (UC vs. non-UC), patient performance status, sex, age, and amount of CDDP administered as a predictor of progression-free survival and overall survival using the Cox regression model. As shown in Table VII, univariate Cox regression analysis selected stage T4, lymph node metastasis, and tumor pathology (non-UC) as significant factors affecting both disease progression and overall survival. Moreover, multivariate Cox regression analysis selected stage T4 and lymph node metastasis as significant factors affecting both disease progression and overall survival. Fig. 5 shows the Kaplan-Meier curves for overall survival and progression-free survival of patients at each clinical stage (A and B) and for each histological type (C and D), respectively. Both overall survival and progression-free survival were significantly better for patients with organ-confined disease than for patients with T4 disease or lymph node metastasis. In addition, both were better for patients with histologically confirmed UC tumors than for patients with non-UC tumors.

ii) Radical cystectomy group. We investigated the significance of each factor, including pretreatment clinical T-stage, pathological T-stage (pT1-2 vs. pT3-4), pathological N stage, pathological TN stage (pT4 or lymph node involvement vs. others), tumor pathology (UC vs. non-UC), patient performance status, sex, age, and chemotherapy as a predictor of progression-free survival and overall survival using the Cox regression model (Table VIII). As shown in Table VIII, univariate Cox regression analyses selected pretreatment clinical T-stage (T3 vs. T2), pathological T-stage (pT4 vs. others), pathological T-stage (pT3-4 vs. others), and lymph node metastasis as significant factors affecting both overall and progression-free survival. Moreover, multivariate Cox regression analysis selected clinical T-stage (T3 vs. T2) as a significant factor affecting both overall and progression-free survival. Fig. 6 shows the Kaplan-Meier curves for overall survival and progression-free survival of patients who underwent total cystectomy at each clinical stage (A and B) and pathological stage (C and D), respectively.

Survival comparison between groups at each clinical stage. Fig. 7 shows the Kaplan-Meier curves for overall survival and progression-free survival of patients at each clinical stage (T2, A and B; T3, C and D) in both groups. For stage T3, both overall and progression-free survival were significantly better in the OMC-regimen group than in the cystectomy group.

Toxicity. The most significant outcome of the OMC regimen was that its related toxicities were markedly less severe than those reported for other protocols, as shown in Table IX. None of the patients suffered Grade III or more severe toxicities. Some patients experienced Grade I blood/bone marrow toxicity [8 patients, 8.33%; 95% confidence interval (CI), 3.67-15.8%], gastrointestinal toxicity (49 patients, 35.5%; 95%CI, 40.6-61.4%) or neuropathy (4 patients, 4.17%; 95%CI, 1.15-10.3%). The duration of blood/bone marrow toxicity, including granulocytopenia and anemia, was relatively short:

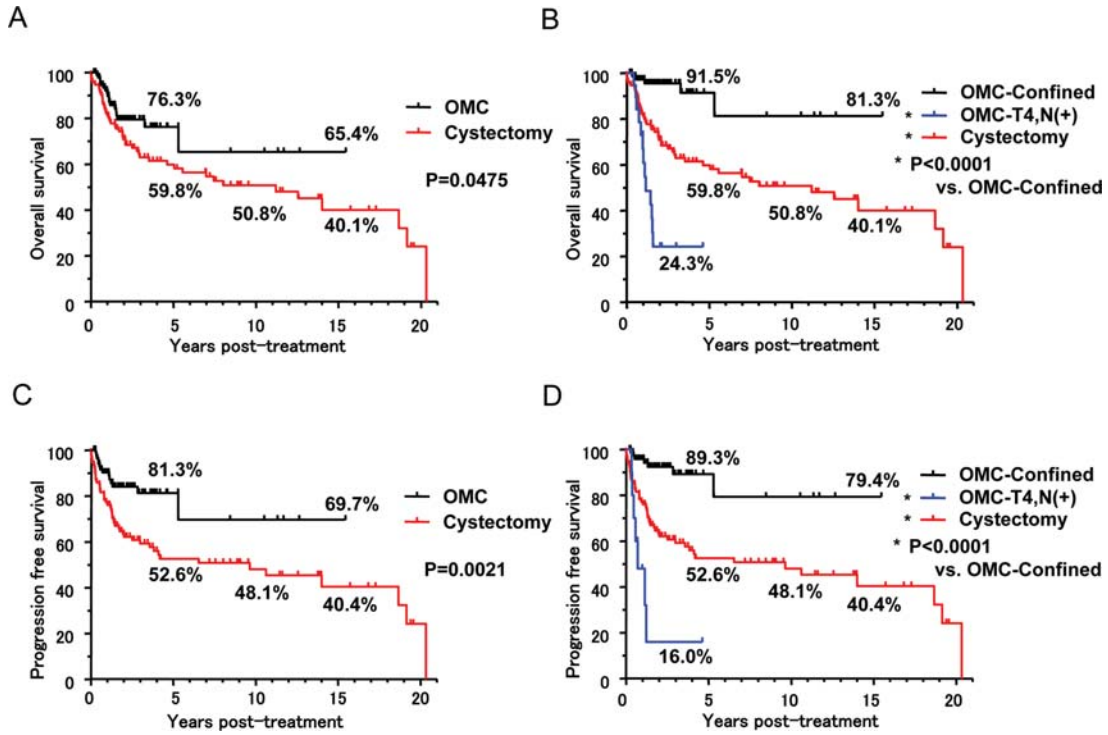

Figure 4. Kaplan-Meier curves for overall survival (A and B) and progression-free survival (C and D) in each group. (A) Comparison of overall survival between the OMC-regimen and cystectomy groups. (B) Comparison of overall survival among the two OMC-regimen subgroups (OMC-confined and OMC-T4-N+, and the cystectomy group. The OMC-confined group comprised patients with organ-confined disease, and the OMC-T4-N+ group comprised patients with stage T4 or N(+) disease. The 5- and 15-year overall survival rates were 91.5 and 81.3%, respectively (P<0.0001 vs. cystectomy group) the results were compared under the same conditions by matching of the clinical stage, excluding patients with stage T4 tumors and/or lymph node metastasis from the OMC-regimen group. (C) Comparison of progression-free survival between the OMC-regimen and cystectomy groups. (D) Comparison of progression-free survival among the OMC-confined and OMC-T4,N+ subgroups and the cystectomy group, respectively.

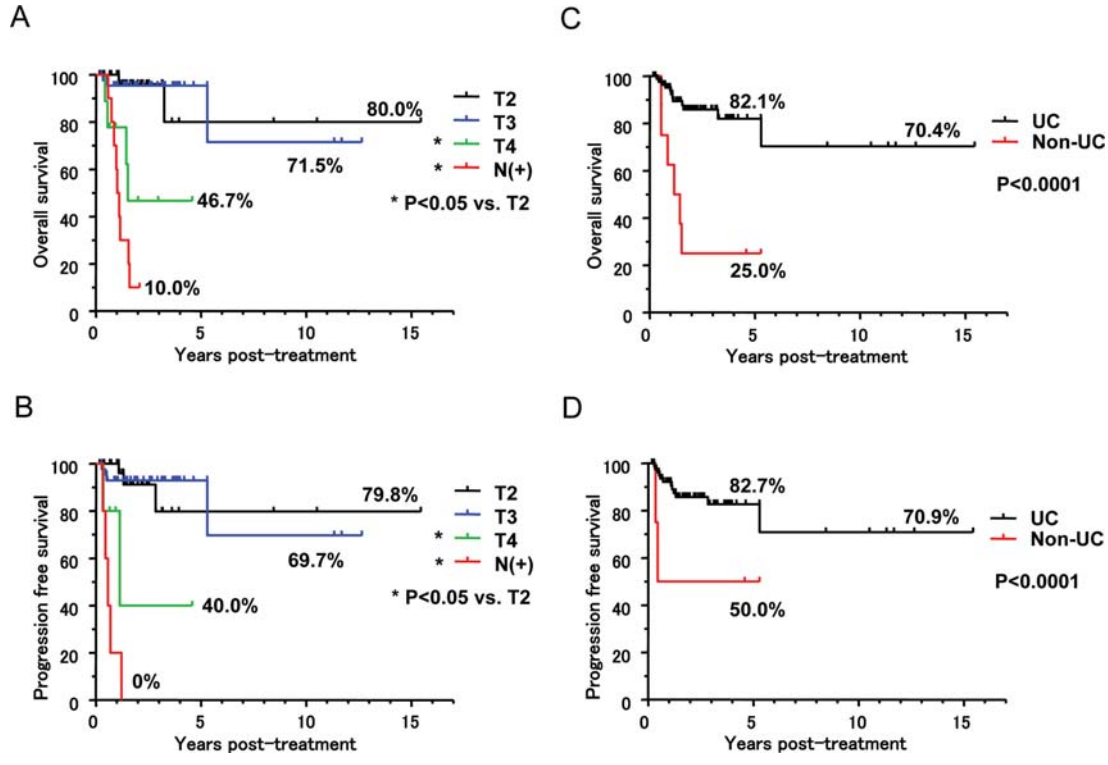

Figure 5. Kaplan-Meier curves for overall survival and progression-free survival of patients treated with the OMC regimen at each clinical stage (A and B) and for each histological type (C and D), respectively. Both overall survival and progression-free survival were significantly better for patients with organ-confined disease than for patients with T4 disease or with lymph node metastasis; both were also better for patients with histologically proven UC tumors than for patients with non-UC tumors.

Table VII. Predictors of survival (PFS, OS) in the OMC-regimen group evaluated by univariate (a) and multivariate Cox regression analyses.

a, Univariate Cox regression analysis

		PFS		OS	
	Category	Hazard ratio	P-value	Hazard ratio	P-value
T-stage	T4 vs. T2-3	13.33	<0.0001	14.08	<0.0001
N-stage	N(+) vs. N(-)	10.53	<0.0001	14.49	<0.0001
Pathology	Non-UC vs. UC	6.185	0.0008	7.092	<0.0001
Performance status	2 vs. 0-1	1.767	0.2357	2.577	0.0624
Sex	Male vs. female	1.276	0.5786	1.020	0.9691
Age	Cont. variable	1.012	0.5985	1.038	0.1834
Amount of CDDP	Cont. variable	1.003	0.2661	1.004	0.1511

b, Multivariate Cox regression analysis

		PFS		OS	
	Category	Hazard ratio	P-value	Hazard ratio	P-value
T-stage	T4 vs. T2-3	8.475	0.0008	6.803	0.0124
N-stage	N(+) vs. N(-)	4.237	0.0169	7.576	0.0052
Pathology	Non-UC vs. UC	1.284	0.7211	1.287	0.7576
Performance status	2 vs. 0-1	1.164	0.8006	1.118	0.8879
Sex	Male vs. female	1.300	0.6090	1.070	0.9113
Age	Cont. variable	1.023	0.3039	1.037	0.1885
Amount of CDDP	Cont. variable	2.088	0.1841	1.353	0.6223

Cont. variable, continuous variable.

Table VIII. Predictors of survival (PFS, OS) in the total cystectomy group evaluated by univariate (a) and multivariate (b) Cox regression analyses.

a, Univariate Cox regression analysis

		PFS		OS	
	Category	Hazard ratio	P-value	Hazard ratio	P-value
Clinical T-stage	T3 vs. Cis or T2	4.717	0.0005	2.994	0.0004
Pathol T-stage	pT4 vs. others	2.404	0.0002	3.115	0.0026
Pathol T-stage	pT3-4 vs. others	4.505	0.0012	2.725	0.0011
Pathol N-stage	N(+) vs. N(-)	2.653	0.0372	2.625	0.0041
Histology	Non-UC vs. UC	1.335	0.6381	1.229	0.6954
Performance status	0-1 vs. 2	1.222	0.7120	1.294	0.5899
Sex	Male vs. female	1.472	0.3210	1.535	0.2332
Age	Cont. variable	1.047	0.0	1.035	0.0752
Chemotherapy	(+) vs. (-)	1.304	0.4993	1.256	0.4546

b, Multivariate Cox regression analysis

		PFS		OS	
	Category	Hazard ratio	P-value	Hazard ratio	P-value
Clinical T-stage	T3 vs. Cis or T2	2.475	0.0091	2.128	0.0437
Pathol T-stage	pT4 vs. others	2.500	0.0338	1.767	0.2091
Pathol N-stage	N(+) vs. N(-)	1.733	0.1309	1.695	0.1539
Histology	Non-UC vs. UC	1.019	0.9728	1.504	0.4658
Performance status	2 vs. 0-1	1.038	0.9464	1.023	0.9693
Sex	Male vs. female	1.278	0.5625	1.279	0.5525
Age	Cont. Variable	1.015	0.5455	1.032	0.2180
Chemotherapy	(+) vs. (-)	1.162	0.6426	1.036	0.9213

Cont. variable, continuous variable.

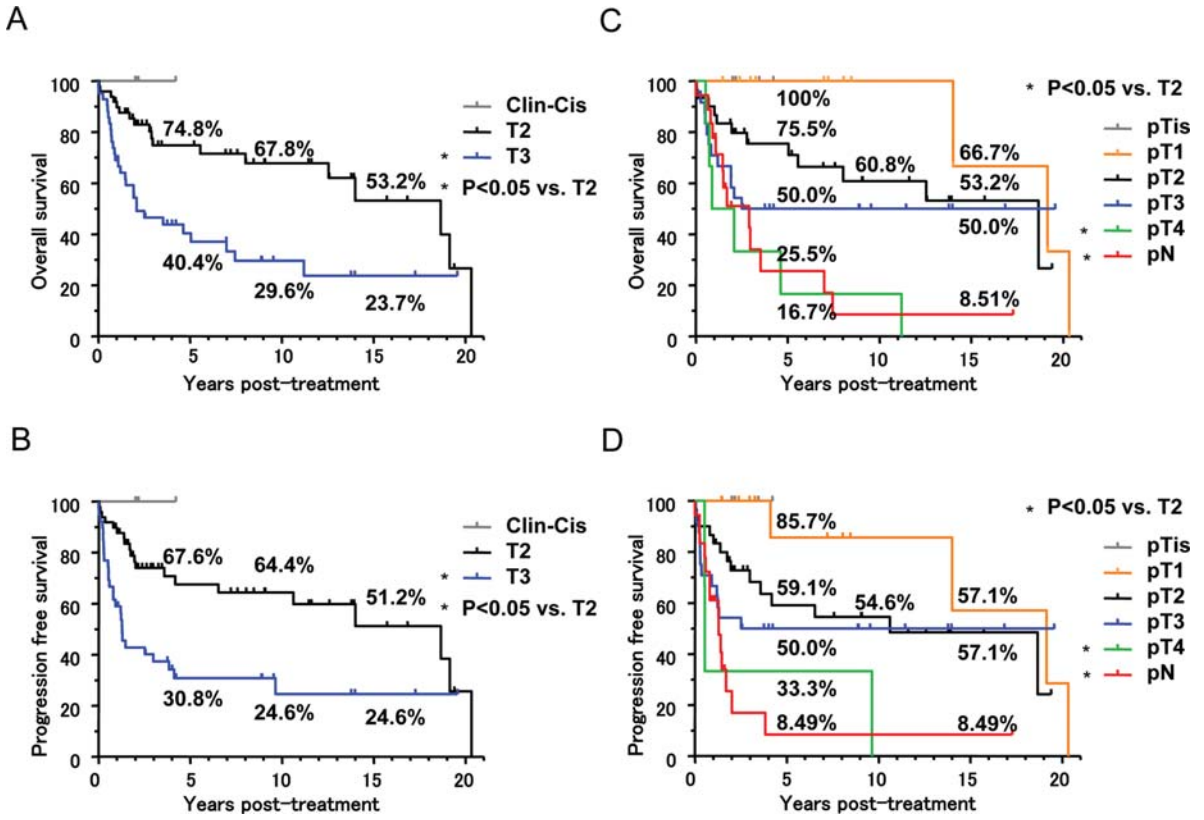

Figure 6. Kaplan-Meier curves for overall (A and C) and progression-free survival (B and D) of patients who underwent total cystectomy at each clinical stage, as well as for each pathological stage, respectively. Both overall and progression-free survival were significantly better for patients with T2 as compared to T3 tumors clinically; both were also better for patients with pathological stage pT2 than for patients with either pT3 or pN(+), respectively.

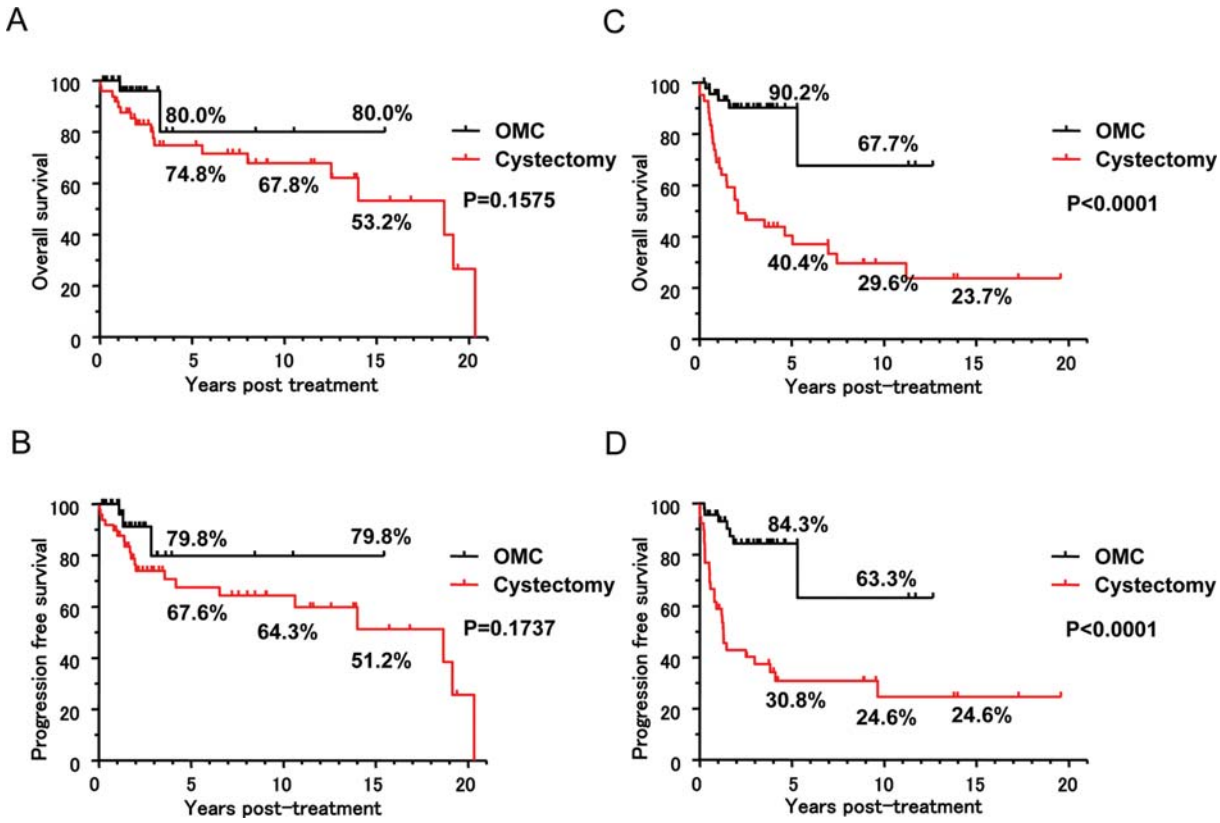

Figure 7. Kaplan-Meier curves for overall survival and progression-free survival of patients at each clinical stage (T2, A and B; T3, C and D) in both groups. Both overall and progression-free survival were significantly better for both stage T2 and T3 in the OMC-regimen group than in the cystectomy group.

Table IX. Toxicity.

	Grade			Duration		
	Grade 1	Grade 2	Grades 3-4	<3 days	3-7 days	>7 days
Toxicity	No. (%)	No. (%)	No. (%)	No.	No.	No.
Blood/bone marrow						
Total	8 (8.3)	0	0	0	7 (7.3)	1 (1.0)
Granulocytopenia	6 (6.3)	0	0	0	5 (5.2)	1 (1.0)
Anemia	8 (8.3)	0	0	0	7 (7.3)	1 (1.0)
Gastrointestinal						
Total	49 (51.0)	0	0	0	0	0
Anorexia	33 (34.4)	0	0	21 (21.9)	12 (12.5)	0
Constipation	16 (16.7)	0	0	9 (9.4)	7 (7.3)	0
Diarrhea	19 (19.8)	0	0	12 (12.5)	7 (7.3)	0
Nausea	29 (30.2)	0	0	23 (24.0)	6 (6.3)	0
Vomiting	10 (10.4)	0	0	7 (7.3)	3 (3.1)	0
Neuropathy	3 (3.1)	1 (1.0)	0	0	0	4 (4.2)

median duration was 6 days (range 5-9 days) for granulocytopenia, and 5 days (range 3-10 days) for anemia. No patients were treated with granulocyte colony-stimulating factor or transfusion of red blood cells. Gastrointestinal toxicity included anorexia in 33 patients (34.4%; 95%CI, 25.0-44.8%), constipation in 16 (16.7%; 95%CI, 9.84-25.6%), diarrhea in 19 (19.8%; 95%CI, 12.4-29.2%), nausea in 29 (29.0%; 95%CI, 21.2-40.4%), and vomiting in 10 (10.4%; 95%CI, 5.11-18.3%), but all symptoms disappeared within 4 days after intra-arterial infusion. Three patients experienced Grade I neuropathy in the peroneal nerve area (3.13%; 95%CI, 0.65-8.86%), and one had Grade II neuropathy (1.04%; 95%CI, 0.03-5.67%). With regard to renal function, four patients showed an increase of >20% in the peak level of serum creatinine, 7 days after intra-arterial infusion, but this returned to the previous level after 14 days in all patients. In other patients, however, we found no significant differences in the level of BUN or serum creatinine before and after intra-arterial infusion. There were no other adverse reactions such as genitourinary toxicity, radiation cystitis or life-threatening complications.

Discussion

BOAI allows delivery of an extremely high concentration of anticanacer agent to the bladder and surrounding pelvic region (18-20). In addition, severe hypoxia in the target region resulting from BOAI may play a role in the marked anti-tumor effect, as several basic studies have demonstrated that hypoxia greatly enhances the effectiveness of cisplatin (21,22). Enhanced radiosensitivity of the cancer cells due to the BOAI-induced high concentration of cisplatin may also contribute significantly to the good response achieved. Cisplatin is a well-known radiosensitizer, which facilitates cell death by inhibiting the repair of radiotherapy-induced DNA damage, and/or may damage genes known to be related to radiosensitivity, e.g., BRCA2, and hMLH1, thereby enhancing radiosensitivity and eventually triggering apoptosis (21-24). These factors would likely be responsible for the better outcome achieved with the OMC-regimen than with cystectomy.

The predictive factors selected on the basis of the present results should be useful for improving the efficacy of treatment and yielding more satisfactory outcomes. Clinical stage is one of the most important predictive factors of outcome for this therapy. More than 90% (70/77) of patients with locally invasive tumors achieved CR, of whom most (97%, 68/70) survived with a functional bladder and no evidence of recurrence, while most patients with stage T4 tumors and/or lymph node metastasis showed disappointing outcomes. Our results indicate that patients with organ-confined tumors are more promising candidates for this treatment. The histological type of the tumor, i.e. UC or non-UC, is another important determinant of treatment outcome. Of the 96 patients treated using the OMC-regimen, all but one (98.6%) who achieved CR had UC tumors, whereas the response was rated as PD or disease recurrence in other patients with non-UC tumors.

A significant reduction of systemic side effects is another advantage of the OMC-regimen. Cisplatin exerts its anti-tumor activity via the non-protein-bound form, which decreases rapidly after administration: its half-life is normally less than 60 min, decreasing to below the detection limit 4 h after administration (25,26). Accordingly, removal of non-protein-bound Pt immediately after administration of cisplatin, which markedly reduces systemic side effects, may be highly advantageous for patients undergoing selective intra-arterial infusion. In order to accomplish efficient drainage of cisplatin immediately after passage through the tumor, we performed HD via the bilateral common iliac veins. As the molecular

weight of protein-unbound cisplatin is approximately 300, similar to that of creatinine, HD is efficient for cisplatin elimination. Additionally, the anatomic structure and blood supply of the bladder may largely account for the efficient drainage of cisplatin achieved with this approach. As the urinary bladder is situated at the base of the pelvis, the relatively close circuit formed by the internal iliac artery, bladder, and common iliac veins may contribute to efficient drainage of the anticancer agent, thus increasing the elimination efficiency without influencing the systemic circulation. Indeed, we found that >95% of free Pt was efficiently eliminated by HD during BOAI of cisplatin (data not shown), thus providing optimal conditions for effective local accumulation of Pt in the tumor, with minimal systemic toxicity.

Considering the present findings overall, it seems relevant to evaluate the significance of this therapy and its indications. The OMC-regimen can be regarded as a curative therapy targeting mainly two patient groups: those for whom total cystectomy is indicated, or those for whom total cystectomy is not feasible because of age, performance status or other reasons and who are considered physically incapable of tolerating the chemotherapeutic regimens that are usually applied clinically. Thus it is noteworthy that this therapy will improve the feasibility of radical cure without the need for cystectomy in patients for whom such surgery would otherwise be necessary, and also facilitate potential cure in patients whose condition would normally rule out this likelihood and for whom, otherwise, merely palliative treatment would seem the only option.

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