Tetramodal therapy using balloon-occluded arterial infusion of anticancer agents, the Azuma regimen, for lymph node-involved bladder cancer

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Received April 25, 2018; Accepted August 10, 2018

DOI: 10.3892/ijo.2018.4619

Abstract. Overall, >900 patients have been treated at Osaka Medical College (Takatsuki, Osaka, Japan) using the novel approach of balloon-occluded arterial infusion (BOAI) to deliver an extremely high concentration of the anticancer agents cisplatin (CDDP)/gemcitabine to the pelvis (referred to as the OMC-regimen), together with pelvic irradiation. In a previous study, overall survival (OS) rate was significantly higher in this treatment group compared with that in a control group receiving total cystectomy (79.6 vs. 49.6%, respectively, at 10 years). It was speculated that intensive treatment of the pelvic area may aid in preventing metastasis, and thus the present study focused on the effect of this therapy in patients with lymph node metastasis (LN^+). A total of 102 patients with advanced LN^+ bladder cancer received tetramodal therapy (termed the Azuma regimen), comprising radical transurethral resection of the bladder tumor, systemic chemotherapy, BOAI and pelvic irradiation. Patients who failed to achieve a complete response (CR) underwent secondary BOAI with an increased amount of CDDP and/or gemcitabine with/without hemodialysis. A CR was achieved in 57.8% (59/102) of patients in total, and in 78.8% (41/52) of patients with N1 and Tis-3 disease. Among the complete responders, 81.4% (48/59) of patients retained their bladders with no evidence of recurrence or metastasis within a mean follow-up period of 121 weeks. Stages N2-3 and T4 were determined as significant risk factors for treatment failure in addition to survival. Notably, the 10-year overall survival rates in N1, Tis-3, and N1 and Tis-3 were 67.6% (vs. 33.6% in N2-3; P=0.0003), 61.5% (vs. 37.9% in T4; P=0.0485) and 75.1% (vs. 35.5% in N2-3 or T4; P=0.0002), respectively. No patients suffered from grade IV toxicities. In conclusion, the Azuma regimen may be a feasible option for patients with LN^+ disease. The use of intensive treatment in the pelvic area may serve an important role in outcome improvement, and the prevention of metastasis may be its mechanism.

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Key words: balloon-occluded arterial infusion, tetramodal therapy, Azuma regimen, bladder cancer, lymph node metastasis, pelvic irradiation

Introduction

Lymph node metastasis (LN^+) is one of the strongest predictors of disease-specific mortality in patients with bladder cancer (1-4). Stein *et al* (1) demonstrated that the incidence of lymph node metastasis at the time of the surgery ranged from 5% in non-muscle invasive disease to 25% in pT2 disease, and 45% in pT3-4 disease. In addition, a number of studies reported a higher incidence of LN involvement (30-40%), including micrometastasis, in patients receiving extended LN dissection (5-8). These reports emphasize the importance of nodal involvement in prognosis prediction and nodal control in the treatment of patients with advanced bladder cancer.

We previously developed the OMC-regimen, a novel bladder preservation therapy involving balloon-occluded arterial infusion (BOAI) of an anticancer agent to concentrate it within the pelvis, and a total of >900 patients with advanced bladder cancer have now been treated at Osaka Medical College (Takatsuki, Osaka, Japan) using BOAI methods (OMC-regimen), together with pelvic irradiation with or without systemic chemotherapy. Although LN involvement is a significant risk factor for treatment failure and poor patient survival, the 5-year overall survival (OS) rate in all patients receiving the bladder preservation therapy, including those with T4-disease, was >50% (9), which is an improvement compared with the outcomes of other treatments, including systemic chemotherapy with or without total cystectomy.

We hypothesized that the intensive treatment of the pelvic area with high concentrations of anticancer agents, together with irradiation, may reduce cancer cell metastasis, thereby contributing to an improved outcome for the patient. The present retrospective study thus focused on the effect of this therapy on LN metastasis, investigating 102 patients with LN^+ disease who received the quadruple combination therapy (termed the Azuma regimen) comprising complete transurethral resection of the bladder tumor (TURBT), systemic chemotherapy with *cis*-diamminedichloridoplatinum(II) (CDDP) and gemcitabine, BOAI-CDDP/gemcitabine (OMC-regimen) and pelvic irradiation. The present study describes the outcomes and associated toxicity.

Materials and methods

Eligibility criteria. In Osaka Medical College, eligible patients (n=102) were diagnosed with bladder cancer plus intra-pelvic LN metastasis (stage N1, N2 or N3) without distant metastasis according to the Tumor-Node-Metastasis staging system (10). All patients had an absolute neutrophil count of >1,500/μl (normal range, 4,000-9,000/μl), a platelet count of >100,000/μl (normal range, 150-350x10^3/μl), a creatinine level of <3.0 mg/dl (normal range, 0.65-1.09 mg/dl), a bilirubin level three times the institutional upper limit of the normal range (0.2-1.0 mg/dl), an aspartate aminotransferase (AST) level four times the institutional upper limit of the normal range (10-40 U/l) and an Eastern Cooperative Oncology Group performance status of 0-2 (11). Imaging studies, including a chest computed tomography (CT) scan, abdominal/pelvic magnetic resonance imaging (MRI) and CT scan, and bone scintigram, were performed prior to the start of therapy. The study was reviewed and approved by the Osaka Medical College Ethics Committee (approval number OMC-0536). Patients were informed of the investigational nature of the study and provided written informed consent prior to study enrollment.

Study design and treatment. The present study retrospectively investigated the effect of the quadruple combination therapy termed the Azuma regimen, comprising radical TURBT, systemic chemotherapy with CDDP and/or gemcitabine, BOAI of CDDP/gemcitabine and pelvic irradiation, on patients with LN metastasis.

Radical TURBT. Patients received TURBT twice prior to the BOAI treatment. The tumors were resected as completely as possible.

BOAI treatment. For intra-arterial infusion, an intra-arterial catheter equipped with two occlusion balloons (size, 6 Fr; M6F-28-70-TBSB4-ST; Clinical Supply, Tokyo, Japan) was used. The treatment generally involved the administration of 100 mg cisplatin as a single bolus through the catheter over a 1-h period. In certain patients, hemodialysis was simultaneously performed via a double-lumen catheter (size, 12 Fr; Argyle®, Tyco Healthcare, Tokyo, Japan) placed in the vena cava for 2 h following the start of arterial infusion. Fig. 1 illustrates the extracorporeal circuit used in the treatment. The treatment using the BOAI method was termed the OMC-regimen.

Radiation therapy. The radiation therapy (total, 60 Gy) was administered to the whole pelvis using a CT-planned three-dimensional conformal technique: 50 Gy (2 Gy/day for 25 days) followed by 10 Gy (2 Gy/day for 5 days) of local irradiation to the bladder. The planned target volume for the bladder included the gross target volume (empty bladder plus any extravesical tumor) with a 1-cm expansion.

Systemic chemotherapy. One cycle of chemotherapy with CDDP and/or gemcitabine at the doses of 70 mg/m^2 CDDP (on day 2) and 1,000 mg/m^2 gemcitabine (on days 1, 8 and 15) were administered.

Evaluation of toxicity and response. Toxicity was monitored weekly, according to the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0 (12). At 6 weeks post-treatment, the response was evaluated by repeat transurethral resection and urine cytology, in addition to MRI of the pelvis and CT scans of the whole body. Patients who achieved a CR were observed using the follow-up protocol. Patients who did not achieve a CR were deemed treatment failures, and such patients were advised to undergo secondary BOAI with a higher dosage of cisplatin or gemcitabine (1,000 mg) as a salvage therapy.

Statistics. Simple and multiple logistic regression analyses were conducted to evaluate the significance of the following variables as risk factors of treatment failure: Age, sex, tumor stage, LN status and histology. Life table probabilities of OS (defined as the time from the start of treatment to mortality) and progression-free survival (PFS; defined as the time from the start of treatment to disease progression) were determined using Kaplan-Meier analysis and the log-rank test. Cox proportional hazards analysis was conducted to assess the inter-associations of the aforementioned factors. SPSS version 24 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Patient characteristics. Between April 1988 and March 2018, the 102 patients with LN^+ disease were treated with the Azuma regimen. All patients completed the treatment protocol. The characteristics of the patients and the distributions of their clinical stages are presented in Table I.

Response. Table II summarizes the treatment response, duration of response and patient characteristics, including age, sex, T-stage, N-stage and tumor histology [urothelial carcinoma (UC) vs. non-UC]. Overall, 57.8% of patients (59/102) achieved CR, as defined by the absence of persistent disease evaluated by TURBT at the 6th week post-therapy. Furthermore, 81.4% (48/59) of patients who achieved CR were able to retain their bladder, with no evidence of recurrence or distant metastasis, within a mean follow-up period of 121 weeks (range, 3-519 weeks; 1st-3rd quartile, 38-171 weeks) following evaluation. Simple and multiple logistic regression analyses identified N2-3 stage (vs. N1) and T4-stage (vs. Tis-3) as significant risk factors for treatment failure (Table III). In

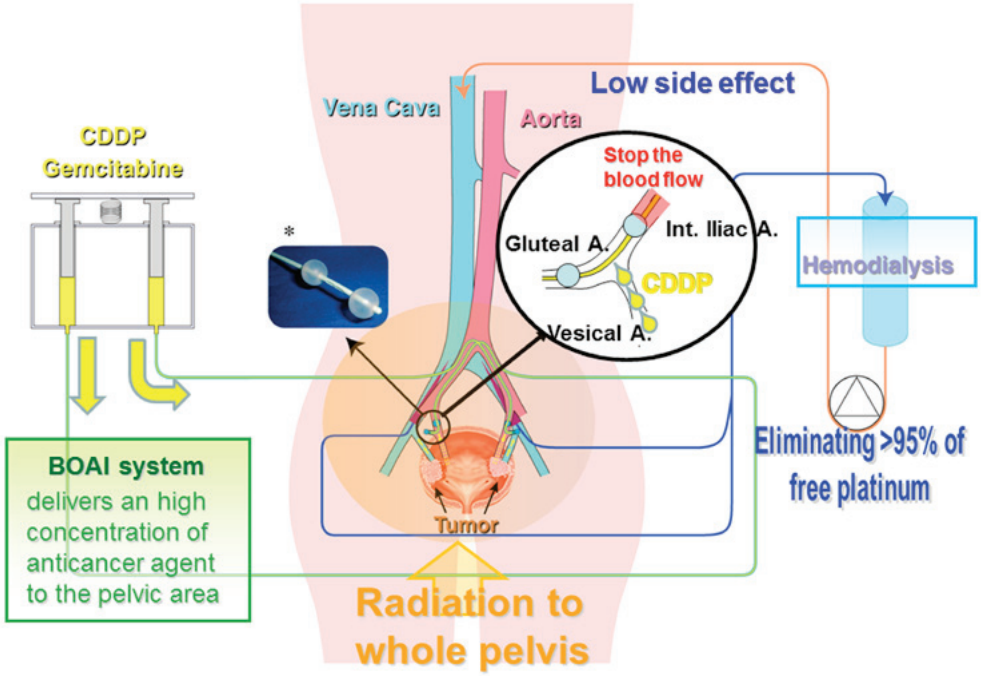

Figure 1. Schematic representation of the BOAI of anticancer agents concurrent with hemodialysis. The extracorporeal circuit allowed BOAI of CDDP/gemcitabine concurrent with hemodialysis. An intra-arterial catheter equipped with two occlusion balloons was introduced into the posterior trunk of the internal iliac artery on each side through the femoral arterial approach. The distal and proximal balloons were inflated and immobilized at a position allowing the 'vesical arteries' to be isolated between the balloons. Various amounts of anticancer agent were infused through the side holes of the catheter between the inflated balloons over a 1-h period. Simultaneously, hemodialysis was performed via two double-lumen catheters placed in the bilateral common iliac vein for 2 h following the start of arterial infusion (or one double-lumen catheter placed in the vena cava). The panel marked with an asterisk is an image of the intra-arterial catheter (cat. no. M6F-28-70-TBSB4-ST; Clinical Supply, Tokyo, Japan), which is made of polyethylene, is 6 Fr in size and is equipped with two occlusion balloons separated by a distance of 40 mm. It has side holes between the balloons facilitating the injection of contrast medium or anticancer agent. Radiation therapy was administered to the whole pelvis using a computed tomography-planned three-dimensional conformal technique to a total of 60 Gy. BOAI, balloon-occluded arterial infusion; CDDP, cisplatin.

fact, among the patients who achieved a CR, 79.7% (47/59) presented with stage N1 and 86.4% (51/59) with Tis-3 tumors. The CR-induction rate was 72.3% (vs. 32.4% in N2-3; P<0.001) in patients with N1-stage disease, 68% (vs. 22.2% in T4; P=0.001) in patients with Tis-3 stage tumors and 78.8% (vs. 36.0% in N2-3 or T4; P<0.001) in patients with N1 and Tis-3 stage disease. Furthermore, >80% of patients who achieved CR were able to retain their bladder with no evidence of recurrence or distant metastasis (N1, 85.1%; Tis-3, 82.4%; N1 and T1-3, 87.8%) within a mean follow-up period of >2 years (N1, 115 weeks; Tis-3, 117 weeks; N1 and Tis-3, 116 weeks).

By contrast, >65% of patients with stage N2-3 (25/37; 67.6%) and stage T4 tumors (19/27; 70.4%) failed to achieve a CR. Among the patients with N2-3 stage tumors, 67.6% (25/37) experienced disease progression or recurrence with metastasis to distant LNs above the pelvis, including the para-aortic LNs, and to distant organs, including the lungs, liver and bones. The principal treatment was systemic chemotherapy with CDDP and gemcitabine; however, 84% (21/25) of these patients succumbed following therapy. With regard to patients with T4 disease, 70.4% (19/27) of patients experienced disease progression or recurrence with distant metastasis (distant LNs in 7 patients and distant organs in 6 patients) and/or local recurrence (7 patients) as a consequence of disease progression. A total of 3 patients who had only local recurrence were treated with secondary BOAI using an increased amount of CDDP (200 or 300 mg) and

Table I. Patient characteristics.

Characteristic	Value	95% CI
Age, years		
Mean	64	
Range	38-86	
Sex, n (%)		
Male	79 (77.5)	68.1-85.1
Female	23 (22.5)	14.9-33.9
T-stage, n (%)		
Tis	1 (0.98)	0.25-5.34
T1	3 (2.94)	0.61-8.36
T2	31 (30.4)	21.7-40.3
T3	40 (39.2)	29.7-49.4
T4	27 (26.5)	18.2-36.1
N-stage, n (%)		
N1	65 (63.7)	53.6-73.0
N2	30 (29.4)	20.8-39.3
N3	7 (6.86)	2.80-13.6
Histology, n (%)		
UC	91 (89.2)	81.5-94.5
Non-UC	11 (10.8)	5.51-18.5

CI, confidence interval; UC, urothelial carcinoma.

Table II. Response.

	CR		PR		SD		PD	
Parameter	Value	95% CI	Value	95% CI	Value	95% CI	Value	95% CI
Total number of patients, n (%)	59 (57.8)	47.7-67.6	9 (8.8)	5.14-19.8	15 (14.7)	8.47-23.1	19 (18.6)	11.6-27.6
Duration of response, weeks								
Mean	118		100		128		0	
Range	3-519		24-217		1-531		0	
1st-3rd quartiles	38-163		57-138		40-135		0-0	
Recurrence, n (%)	11 (18.6)	9.69-30.9	6 (66.7)	29.9-92.5	11 (73.3)	44.9-92.2		
Mortality, n (%)	11 (18.6)	9.69-30.9	5 (55.6)	0.28-48.2	9 (60.0)	32.2-83.7	13 (68.4)	43.4-87.4
Age, years								
Mean	61		67		67		68	
Range	38-85		53-77		52-85		39-86	
Sex, n (%)								
Male	48 (81.4)	69.1-90.3	8 (88.9)	51.8-99.7	11 (73.3)	44.9-92.2	12 (63.2)	38.4-83.7
Female	11 (18.6)	9.69-30.9	1 (11.1)	0.3-48.2	4 (26.7)	7.8-55.1	7 (36.8)	16.3-61.6
T stage, n (%)								
Tis	0 (0.0)	0.00-8.60	0 (0.0)	0.0-33.6	1 (6.7)	0.2-31.9	0 (0.0)	0.0-17.6
1	3 (5.1)	1.06-14.1	0 (0.0)	0.0-33.6	0 (0.0)	0.0-21.8	0 (0.0)	0.0-17.6
2	22 (37.3)	25.0-50.9	5 (66.7)	29.9-92.5	2 (13.3)	1.66-40.5	2 (10.5)	1.30-33.1
3	26 (44.1)	31.2-57.6	3 (22.2)	2.81-60.0	5 (33.3)	11.8-61.6	6 (31.6)	12.6-56.6
4	8 (13.6)	6.04-25.0	1 (11.1)	0.28-48.2	7 (46.7)	21.3-73.4	11 (57.9)	33.5-79.7
N stage, n (%)								
1	47 (79.7)	61.2-89.0	6 (66.7)	29.9-92.5	7 (46.7)	21.3-73.4	5 (26.3)	9.15-51.2
2	9 (15.3)	7.2-27.0	1 (11.1)	0.28-48.2	7 (46.7)	21.3-73.4	13 (68.4)	43.4-87.4
3	3 (5.1)	1.1-14.1	2 (22.2)	2.81-60.0	1 (6.67)	0.17-31.9	1 (5.26)	0.13-26.0
Histology, n (%)								
UC	56 (94.9)	85.9-98.9	8 (88.9)	51.8-99.7	12 (80.0)	51.9-95.7	15 (78.9)	54.4-93.9
Non-UC	3 (5.1)	1.06-14.1	1 (11.1)	2.5-100	3 (20.0)	4.33-48.1	4 (21.1)	6.05-45.6

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; UC, urothelial carcinoma; CI, confidence interval.

Table III. Risk factors for treatment failure selected by logistic regression analyses.

		Simple analysis			Multiple analysis		
Factor	Category	P-value	Risk ratio	95% CI	P-value	Risk ratio	95% CI
N-stage	N2-3 vs. N1	<0.001	0.184	0.076-0.442	0.002	0.214	0.081-0.566
T-stage	T4 vs. T<4	0.001	0.198	0.076-0.516	0.007	0.220	0.072-0.666
Histology	Non-UC vs. UC	0.085	2.154	1.327-3.591	0.074	4.282	0.868-21.124
Age, years	Cont. variable	0.072	2.283	1.464-3.905	0.068	2.781	1.597-4.956
Sex	Male vs. female	0.272	1.683	0.663-4.300	0.654	1.300	0.412-4.100

CI, confidence interval; Cont. variable, continuous variable; UC, urothelial carcinoma.

gemcitabine combined with hemodialysis, which permits injection of more than two to three times the standard amount of anticancer agent. Although the effect was not strong enough to achieve a CR, 66.7% (2/3) of patients survived with the remaining cancer. Patients with distant metastasis were primarily treated with systemic chemotherapy using CDDP and gemcitabine; however, 87.5% (14/16) of patients succumbed following therapy.

Table IV. Predictors of OS and PFS evaluated by univariate and multivariate Cox regression analyses.

A, OS

		Univariate			Multivariate		
Factor	Category	P-value	Risk ratio	95% CI	P-value	Risk ratio	95% CI
N-stage	N2-3 vs. N1	0.001	3.150	1.649-6.019	0.004	2.670	1.372-5.495
T-stage	T4 vs. T<4	0.040	1.981	1.032-3.801	0.049	1.891	1.018-3.792
Histology	Non-UC vs. UC	0.248	0.573	0.222-1.476	0.417	0.858	0.263-1.772
Age, years	Cont. variable	0.075	1.028	0.997-1.061	0.218	1.020	0.989-1.052
Sex	Male vs. female	0.429	0.747	0.363-1.539	0.791	0.904	0.430-1.900

B, PFS

		Univariate			Multivariate		
Factor	Category	P-value	Risk ratio	95% CI	P-value	Risk ratio	95% CI
N-stage	N2-3 vs. N1	0.001	2.523	1.449-4.392	0.014	2.040	1.155-3.604
T-stage	T4 vs. T<4	0.008	2.177	1.229-3.856	0.047	1.887	1.026-3.211
Histology	Non-UC vs. UC	0.117	0.524	0.233-1.176	0.216	0.599	0.266-1.349
Age, years	Cont. variable	0.093	1.352	0.901-1.726	0.075	1.026	0.997-1.055
Sex	Male vs. female	0.434	0.777	0.414-1.460	0.656	0.867	0.464-1.657

CI, confidence interval; Cont. variable, continuous variable; UC, urothelial carcinoma; OS, overall survival; PFS, progression-free survival.

Survival. OS. The present study investigated the significance of potential factors, including age, sex, LN status, pretreatment T-stage and tumor pathology (UC vs. non-UC), as predictors of OS using a Cox regression model. As presented in Table IV, univariate and multivariate Cox regression analyses selected an LN-status of N2-3 (vs. N1) and T4-disease (vs. Tis-3) as significant factors affecting OS. For all patients, the 10-year OS rate was 54.5% (Kaplan-Meier curves are shown in Fig. 2A; median survival and mean estimate survival are shown in Table V). Notably, the 10-year OS-rate was 67.6% (vs. 33.6% in N2-3; P=0.0003; Fig. 2B) for patients with N1 disease, 61.5% (vs. 37.9% in T4; P=0.0485; Fig. 2C) for patients with Tis-3 disease, and 75.1% (vs. 35.5% in N2-3 or T4; P=0.0002; Fig. 2D) for patients with N1 and Tis-3 disease (Table V).

PFS. As with predictors of OS, univariate and multivariate Cox proportional hazards regression analysis identified N2-3 stage (vs. N1) and T4 stage (vs. Tis-3) as the significant risk factors for PFS (Table IV). Notable also was the 10-year PFS rate for patients with LN^+ disease, which was 43.2% of the total patients (Fig. 3A). The 7-year PFS rate was 53.6% (vs. 24.7% in N2-3; P=0.0005; Fig. 3B) for patients with N1 disease, 49.4% (vs. 26.9% in T4; P=0.0043; Fig. 3C) for patients with Tis-3 disease, and 59.2% (vs. 26.2% for N2-3 or T4; P<0.0001; Fig. 3D) for patients with N1 and Tis-3 disease (Table VI).

Toxicity. The observed toxicities are summarized in Table VII. None of the patients had grade IV toxicities. Furthermore, ~70% of the patients experienced blood and lymphatic system disorders, including anemia and granulocytopenia. A total of 2 patients suffered febrile neutropenia. All patients recovered with the administration of recombinant human granulocyte colony-stimulating factor or erythropoietin. In total, >30% of patients (32.9%; 27/82) presented with gastrointestinal disorders. The most common gastrointestinal toxicity was diarrhea in 80 patients (78.4%), including 58 with grade I, 19 with grade II and 3 with grade III diarrhea. Recovery from grade III diarrhea took 3 weeks with cessation of pelvic radiation for 2 weeks. Neuropathy (another toxicity which may not be ignored despite its low incidence) occurred in 3 patients (2.94%). The primary symptoms were numbness and tingling in the peroneal nerve area in the 2 patients with grade I neuropathy, which disappeared within 3 months, and stabbing pain in addition to numbness and tingling, which lasted ~1 year, in the 1 patient with grade II neuropathy. Another common adverse effect was urinary frequency. A total of 78 patients (76.5%) suffered with this symptom. Administration of an anticholinergic agent was not particularly effective. However, the majority of patients recovered by 1 year post-treatment without medication. Overall, there were no life-threatening complications, including respiratory and cardiovascular complications.

Discussion

Overall, >900 patients have been treated with the OMC-regimen, a novel bladder preservation therapy that uses BOAI to deliver an extremely high concentration of anticancer agents (cisplatin/gemcitabine) to the bladder and the surrounding tissues in the pelvis. The majority of patients received 60 Gy of irradiation to the whole pelvis. We have

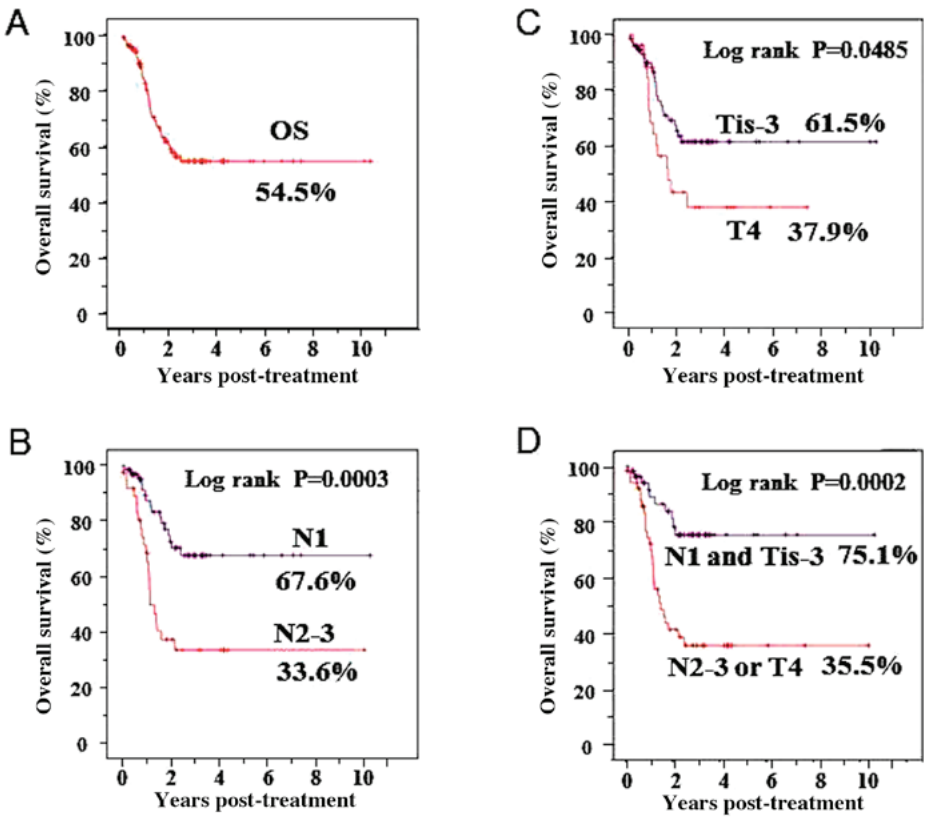

Figure 2. Kaplan-Meier curves for the OS of the patients. (A) All patients. (B) Comparison between the two subgroups of patients at N1 stage and N2-3 stage. (C) Comparison between the two subgroups of patients at Tis-3 stage and T4 stage. (D) Comparison between the two subgroups of patients comprising two sets of criteria, N1 stage with Tis-3 stage and others (N2-3 stage or T4 stage). OS, overall survival.

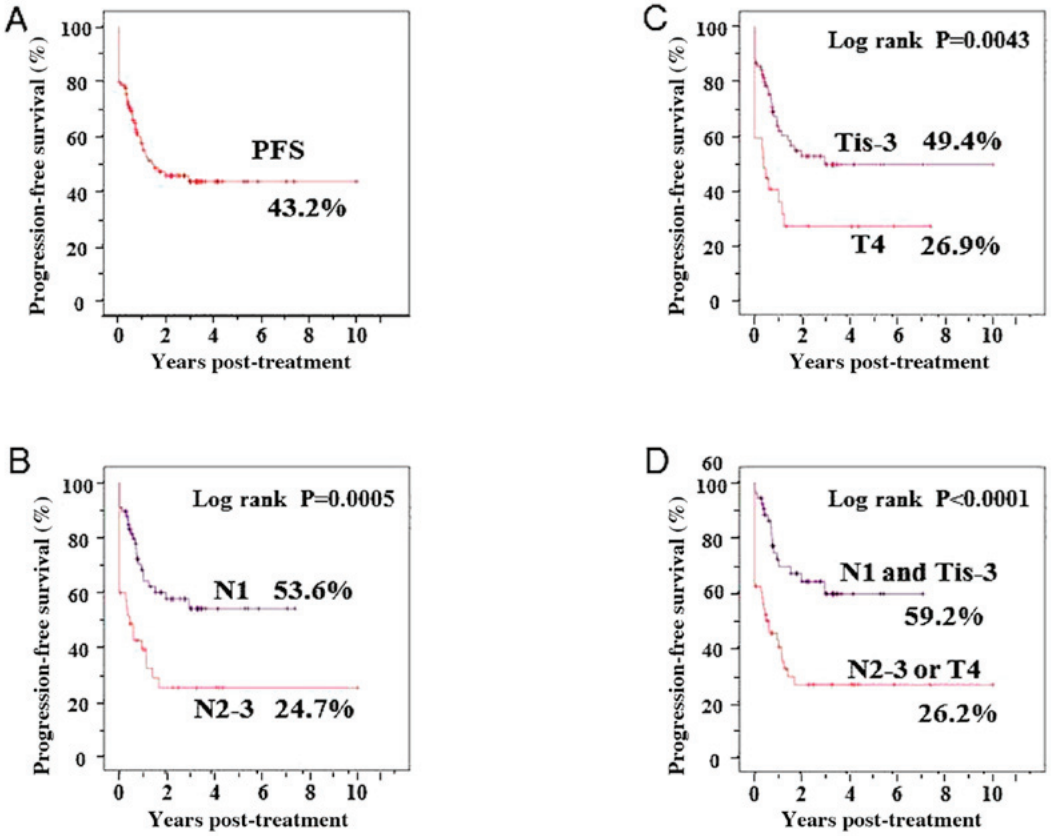

Figure 3. Kaplan-Meier curves for the PFS of the patients. (A) All patients. (B) Comparison between the two subgroups of patients at N1 stage and N2-3 stage. (C) Comparison between the two subgroups of patients at Tis-3 stage and T4 stage. (D) Comparison between the two subgroups of patients comprising two sets of criteria, N1 stage with Tis-3 stage and N2-3 stage or T4 stage. PFS, progression-free survival.

Table V. Median survival and mean estimate survival for overall survival.

A, OS

		Mean estimate survival, weeks		
Factor	Median survival, weeks	Estimate	SE	95% CI
All patients	114.9	316.1	26.2	264.7-367.5

B, N1 vs. N2-3

		Mean estimate survival, weeks		
Factor	Median survival, weeks	Estimate	SE	95% CI
N stage				
N1	127.4	381.7	31.2	320.5-442.9
N2-3	94.1	207.4	39.2	130.5-284.3

C, Tis-3 vs. T4

		Mean estimate survival, weeks		
Factor	Median survival, weeks	Estimate	SE	95% CI
T stage				
Tis-3	118.3	349.5	30.2	290.3-408.6
T4	86.2	181.0	32.9	116.5-245.5

D, N1 and Tis-3 vs. N2-3 or T4

		Mean estimate survival, weeks		
Factor	Median survival, weeks	Estimate	SE	95% CI
Combined stage				
N1 and Tis-3	128.6	415.3	32.1	352.3-478.3
N2-3 or T4	78.3	220.2	34.5	152.7-287.7

OS, overall survival; CI, confidence interval; SE, standard error.

previously reported the comparison between outcomes of this therapy and total cystectomy (13,14). In the study, a total of 301 patients were assigned to receive either this bladder preservation therapy (n=162) or total cystectomy (n=139). The OS and PFS rates were significantly higher in the OMC-regimen group compared with the cystectomy group (OS, 79.6 vs. 49.6%; PFS, 78.4 vs. 47.4%, at 10 years) (13).

A simple and fundamental question arose as to how local therapy improves OS. An analysis of previous data relevant to this issue identified that the rate of para-aortic LN metastasis or distant organ metastasis is lower in patients treated with this therapy compared with that in patients treated with total cystectomy (13,14). We hypothesized that BOAI of extremely high-dose anticancer agents into the pelvic tissues, concomitant with irradiation of the whole pelvis, may reduce cancer cell metastasis, thereby contributing to an improved outcome for patient survival, despite the lack of direct evidence for this. A randomized trial with two arms of the Azuma regimen and total cystectomy may be ideal in order to prove this hypothesis. However, it is ethically and practically difficult to set up, since the majority of patients come to the hospital with a desire to undergo bladder preservation therapy, and those patients are unlikely to agree to receive the cystectomy. The present retrospective study investigating the effect of the Azuma regimen on patients with LN metastasis was thus conducted.

As is known, certain patients who undergo total cystectomy are eventually identified to have pathological LN metastasis (15,16). Those patients must be demonstrated to be free of radiologically identifiable LN metastasis prior to surgery. The rate of LN metastasis from non-muscle invasive bladder tumors (pT1) is 5-10%, and this increases to 15-20% for superficial muscle invasive tumors (pT2a), to 25-30% for deep

Table VI. Median survival and mean estimate survival for PFS.

A, PFS

		Mean estimate survival, weeks		
Factor	Median survival, weeks	Estimate	SE	95% CI
All patients	83.4	26.2	264.7-367.5	26.2

B, N1 vs. N2-3

		Mean estimate survival, weeks		
Factor	Median survival, weeks	Estimate	SE	95% CI
N stage				
N1	99.3	225.1	24.0	178.0-272.1
N2-3	45.2	143.5	38.2	68.7-218.4

C, Tis-3 vs. T4

		Mean estimate survival, weeks		
Factor	Median survival, weeks	Estimate	SE	95% CI
T stage				
Tis-3	92.6	276.7	31.5	215.0-338.3
T4	48.2	115.0	32.8	50.8-179.2

D, N1 and Tis-3 vs. N2-3 or T4

		Mean estimate survival, weeks		
Factor	Median survival, weeks	Estimate	SE	95% CI
Combined stage				
N1 and Tis-3	103.6	237.7	24.8	189.0-286.3
N2-3 or T4	44.5	151.6	33.9	85.1-218.1

PFS, progression-free survival; CI, confidence interval; SE, standard error.

muscle invasive tumors (pT2b) and to >40% for extravesical tumors (pT3-4) (1,17-19). A number of studies using extended LN resection and molecular biology techniques reported that 30-40% of patients presented with micrometastases (20-22). These reports emphasize the importance of LN status for prognosis, in addition to nodal control, for the treatment of patients with advanced bladder cancer.

The sentinel node concept, which assumes an orderly linear spread of the primary tumor to the LNs, is also an important issue for treatment and LN metastasis control. Kitamura *et al* (21) reported no LN metastases between the inferior mesenteric artery and aortic bifurcation. In addition, Jensen *et al* (22) reported the absence of skip lesions to LNs above the aortic bifurcation. Taken together, these observations suggest that LNs below the aortic bifurcation are the primary lymphatic landing sites of the disease, and that intensive treatment in the pelvic area may effectively control LN metastasis and thereby improve prognosis.

The present treatment protocol involves irradiation of the whole pelvis and high-dose chemotherapy delivered through the BOAI system to the pelvis. The present data from 102 patients with LN metastasis demonstrated that the 10-year OS rates were 54.5% in all patients. Furthermore, when limited to patients with N1 disease, 72.3% (47/65) of patients achieved CR, and 85.1% of patients who achieved CR were able to retain their urinary bladder with no evidence of recurrence or distant metastasis within a mean follow-up period of 115 weeks from the completion of therapy. The 10-year OS and 7-year PFS rates were 67.6 and 53.6%, respectively. These results indicate that focusing treatment on the pelvic area with high-dose anticancer agents, together with irradiation, may be a promising option for patients with

Table VII. Toxicity.

Toxicity	Grade, n (%)			
	1	2	3	4
Blood and lymphatic system				
Anemia	50 (49.0)	16 (15.7)	2 (1.96)	0 (0.0)
Bone marrow hypocellularity	53 (52.0)	18 (17.6)	2 (1.96)	0 (0.0)
Febrile neutropenia			2 (1.96)	0 (0.0)
Gastrointestinal				
Abdominal distension	48 (47.1)	14 (13.7)	1 (0.98)	0 (0.0)
Abdominal pain	53 (52.0)	2 (1.96)	2 (1.96)	0 (0.0)
Constipation	11 (10.8)	2 (1.96)	0 (0.0)	0 (0.0)
Diarrhea	58 (56.9)	19 (18.6)	3 (2.94)	0 (0.0)
Nausea	18 (17.6)	2 (1.96)	0 (0.0)	0 (0.0)
Vomiting	10 (9.80)	2 (1.96)	0 (0.0)	0 (0.0)
Neuropathy				
Peripheral motor neuropathy	2 (1.96)	1 (0.98)	0 (0.0)	0 (0.0)
Peripheral sensory neuropathy	2 (1.96)	1 (0.98)	0 (0.0)	0 (0.0)
Renal and urinary				
Urinary frequency	57 (55.9)	21 (20.6)		

LN involvement, particularly for those with N1-stage disease. In addition, the present outcomes appear to emphasize the importance of nodal control for the treatment of advanced bladder cancer.

In contrast to the prognoses of patients with N1 disease or Tis-3 disease, which were good, those of patients with N2-3 disease and T4 disease were poor. Future protocols may target N2-3 stage and T4 disease. For patients with N2-3 stage disease, a protocol was recently designed in Osaka Medical College that includes secondary BOAI of an increased amount of CDDP and gemcitabine, with simultaneous hemodialysis, following the primary BOAI and chemoradiation therapy. Although the number of patients was small and the duration of the follow-up period was too short to draw any conclusions, it was found that 2 out of 5 (40.0%) recently treated patients with N2-3 disease achieved a CR. As the number of treated patients increases, the results of this novel treatment will become apparent and are to be reported in a subsequent study.

With regard to stage T4 disease, however, secondary BOAI of high-dose CDDP and gemcitabine was not effective. To explain this, we hypothesized that stage T4 tumors are able to survive due to blood flow from non-vesical arteries, although they are mostly occluded by balloons. There have been efforts to develop a special catheter that will occlude the whole internal iliac artery to reduce the blood supply in the pelvis as much as possible. The intent of this novel protocol is to improve treatment responses and to extend survival times.

In conclusion, tetramodal therapy, the Azuma regimen (a combination of radical TURBT, systemic chemotherapy, irradiation of the whole pelvis and BOAI of anticancer agents) may be a novel strategy for patients with lymph node metastasis, particularly N1 disease, as evidenced by the 10-year OS rate of 67.6%, as opposed to 36.5% for N2-3 disease. This intensive combined treatment may serve an important role in outcome improvement, and the prevention of metastasis may be its mechanism.

Acknowledgements

Not applicable.

Funding

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

HA was responsible for the conception and design of the study, the data acquisition, analysis and interpretation, the drafting and critical revision of the manuscript, and the statistical analysis. TI was responsible for the data acquisition, analysis and interpretation, and the statistical analysis. KT was responsible for the data acquisition, analysis and interpretation. NI, HN, KK, HU, KM, KY and YN were responsible for the data acquisition.

Ethics approval and consent to participate

The study was reviewed and approved by the Osaka Medical College Ethics Committee (approval number OMC-0536). Patients provided written informed consent prior to study enrollment.

Patient consent for publication

All patients were informed of the investigational nature of the study and provided written informed consent prior to study enrollment.

Competing interests

None.

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