



Efficacy and safety of systemic chemotherapy and intra-arterial chemotherapy with/without radiotherapy for bladder preservation or as neo-adjuvant therapy in patients with muscle-invasive bladder cancer: A single-centre study of 163 patients

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Abstract

Introduction: Patients with muscle-invasive bladder cancer (MIBC) often undergo various preoperative treatments to improve survival; however, their efficacy and safety remain unclear.

Materials and methods: The anti-tumour effects and adverse events were evaluated in 163 MIBC patients who received systemic chemotherapy (SC, $n = 34$), intra-arterial chemotherapy (IAC, $n = 50$), or combined IAC and radiotherapy (IAC + R, $n = 79$).

Results: Pathological complete responses were observed in 17.6%, 22.0%, and 43.0% of patients in the SC, IAC, and IAC + R groups, respectively, with respective 5-year overall survival rates of 42.0%, 46.7%, and 50.3%. Multivariate analysis showed that successful IAC + R protocol administration was a significant predictor for survival (hazard ratio = 0.16, $p = 0.028$). The incidence of severe adverse events was higher in the IAC + R group (36.7%) than in the SC (9.8%) and IAC groups (16.0%).

Conclusions: IAC + R was useful for patients with MIBC. Successful completion and optimal patient selection were important for this treatment strategy.

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Keywords: Preoperative treatment; Chemotherapy; Radiotherapy; Bladder cancer; Adverse events; Prognosis

Introduction

Radical cystectomy is a conventional treatment for patients with muscle-invasive bladder cancer (MIBC). However, the high frequencies (50%) of subsequent metastasis and local recurrence remain unresolved.¹ Additionally, the 5-year survival rates after radical cystectomy for locally invasive bladder cancer were reported to range from 35% to 50%.^{2–4} Therefore, preoperative treatments are often employed to improve survival. For this purpose,

chemotherapy is often administered via 2 methods, namely systemic chemotherapy (SC) and intra-arterial chemotherapy (IAC). Although SC is currently common, advantages of the intra-arterial method over other infusion methods have been reported with respect to drug distribution and intratumour drug concentrations.⁵ Other investigators also support this finding.⁶ Meanwhile, combined SC and radiotherapy is more effective against primary tumours than is SC or radiotherapy alone.^{7,8} However, little information is available regarding the superiority of and adverse events associated with IAC and radiotherapy (IAC + R) versus SC or IAC monotherapy.

The main purpose of this retrospective study was to evaluate the safety and rates of pathological complete response

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(pCR) and survival after the administration of 3 different types of preoperative chemotherapies: SC and/or radiotherapy, IAC, and IAC + R, in patients with MIBC. We also analyzed the anticancer activities, including the pCR and survival rates, according to IAC + R intensity. Another purpose of this study was to clarify the long-term impact of the clinicopathological features and variables of the treatment methods on the rates of these anticancer activities at a single centre.

Materials and methods

Patients

We analyzed patients with MIBC who received preoperative chemotherapy at Nagasaki University Hospital between 1988 and 2013. The final population comprised 163 patients: 130 men (79.8%) and 33 women (20.2%). The mean age \pm standard deviation (SD) at the time of treatment was 68.9 ± 11.8 years. The patients' clinicopathological features are listed in Table 1. All pathological diagnoses were determined before treatment using biopsy and/or transurethral resection (TUR) specimens. All patients were evaluated via cystoscopy, chest radiography, bladder and renal ultrasonography, and abdominal and pelvic computed tomography (CT) to determine the clinical stage. Patients with pure squamous cell carcinoma (SCC) or adenocarcinoma, N2 or 3 staging, and M1 staging were excluded. However, patients with N1 staging who received treatment for downstaging were enrolled ($n = 15$). All patients had Grade 0–2 Eastern Cooperative

Oncology Group performance statuses (PS), and approximately half of the patients in our population ($88/163 = 54.0\%$) qualified as “fully active, able to carry on all pre-disease performance without restriction” (Grade 0). Additionally, as shown in Table 1, there was no significant difference in the high PS (Grade 2) frequency between the treatment groups. Almost all patients had comorbidities such as hypertension and sleep disorders. However, no patient was unable to receive chemotherapy because of severe comorbidities.

Treatment protocol

Initially, we explained that radical cystectomy was the standard method for clinically determined MIBC and was recommended for all patients. Additionally, all patients who did not achieve a pCR following chemotherapy were strongly advised to undergo an additional radical cystectomy at that time. Although there were no strict criteria for treatment selection, we tended to recommend IAC + R for patients who strongly desired to retain their bladder function. Additionally, during the 1980s, we often recommended SC with a peplomycin-containing regimen and radiotherapy. Finally, we explained the expected efficacies and risks of our 3 methods and made treatment decisions after consulting with the patients and their families. We provided the patients with this information and obtained written informed consent.

As shown in Fig. 1, among the 34 patients treated via SC, cisplatin (CDDP)-based regimens were administered to 19 patients (55.9%). Carboplatin, 5-fluorouracil, and/or

Table 1
Clinicopathological features and treatment-related information.

	All patients $n = 163$	SC $n = 34$	IAC $n = 50$	IAC + R $n = 79$	<i>p</i> Value
Clinicopathological; n (%)					
Male	130 (79.8)	29 (76.0)	38 (79.7)	63 (85.3)	0.582
Old age (>75 years)	68 (41.7)	9 (26.5)	14 (28.0)	45 (57.0)	<0.001
High ECOG PS (2)	14 (8.6)	3 (8.8)	3 (6.0)	8 (10.1)	0.716
Recurrent tumour	37 (22.7)	10 (29.4)	12 (24.0)	15 (19.0)	0.463
With SCC/AC	16 (9.8)	5 (14.7)	2 (4.0)	9 (11.4)	0.218
High grade	94 (57.7)	20 (58.8)	25 (50.0)	49 (62.0)	0.399
T stage					0.014
T2	81 (49.7)	11 (32.4)	33 (66.0)	37 (46.8)	
T3	50 (30.7)	15 (44.1)	13 (26.0)	22 (27.8)	
T4	32 (19.6)	8 (23.5)	4 (8.0)	20 (25.3)	
High T stage (T3/4)	82 (50.3)	23 (67.6)	17 (34.0)	42 (53.2)	0.008
N stage (N1)	15 (9.2)	4 (11.8)	4 (8.0)	7 (8.9)	0.833
Treatment-related					
Before 2002	103 (63.2)	19 (55.9)	34 (68.0)	50 (63.3)	0.120
CDDP-based regimens	143 (87.7)	19 (55.9)	49 (98.0)	75 (94.9)	<0.001
With radiotherapy	97 (59.5)	18 (52.9)	–	79 (100)	–
Compl TUR before chemo	72 (44.2)	13 (38.2)	29 (58.0)	30 (41.7)	0.061
Cystectomy after chemo	57 (35.0)	26 (76.5)	17 (34.0)	14 (17.7)	<0.001
Adjuvant therapy	45 (27.6)	8 (23.5)	17 (34.0)	20 (25.3)	0.469

SC, systematic chemotherapy; IAC, intra-arterial chemotherapy; R, radiotherapy; ECOG, Eastern Cooperative Oncology Group; PS, performance status; SCC, squamous cell carcinoma; AC, adenocarcinoma; CDDP, cisplatin; Compl, complete; TUR, transurethral resection; chemo, chemotherapy.

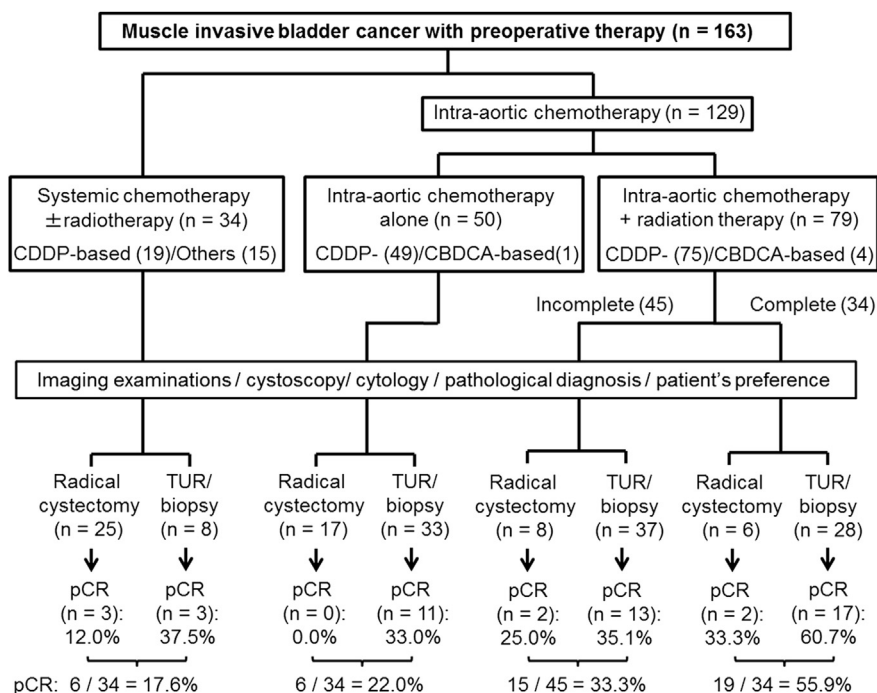


Figure 1. Trial profile. Among 163 patients, 34 (20.9%) and 129 (79.1%) patients were treated with systematic chemotherapy and intra-arterial chemotherapy, respectively. Among our treatment groups, the rates of pathological complete response in the complete IAC + R group were higher than those in other treatment groups.

peplomycin were administered to the other 15 patients (44.1%) because of reduced renal function and the presence of SCC. All patients received 2 ± 0.3 cycles of chemotherapy, and 18 (52.9%) patients were treated with radiotherapy after the initial cycle of chemotherapy. The mean \pm SD total radiotherapy dose in the SC group was 21.1 ± 11.1 Gy.

Overall, 129 patients (79.1%) received IAC via the femoral artery. Digital subtraction angiography was performed to determine the tumour blood supply, and agent infusion was determined according to the major feeding artery. Two courses of chemotherapy with CDDP (70 mg/m^2) and doxorubicin (30 mg/m^2 ; 1988–1994)/epirubicin (30 mg/m^2 ; 1993–present) were administered in a 30–40-min sequence. A mean of 2 ± 0.2 courses of chemotherapy was administered, and each course of chemotherapy was repeated approximately every 4 weeks.

For IAC + R, radiotherapy began the day after chemotherapy administration, and the dose was delivered in 5 daily 2-Gy fractions per week by a megavoltage linear accelerator (10-MV) for a 4-week period. A total dose of 40 Gy was administered to the urinary bladder and surrounding tissues. However, the pelvic lymphatics of patients with N1 tumours were included in the radiotherapy target area. Two-dimensional treatment was performed until May 2002, and 3-dimensional treatment began in June 2002. Accordingly, we divided the patients into 2 groups according to the treatment period for statistical analysis.

After a 4–8-week break, the treatment responses were evaluated using ultrasonography, magnetic resonance imaging, CT, cystoscopy, and cytological examination.

Additionally, we recommended radical cystectomy, and patients who wished to undergo this underwent the procedure. Patients who refused radical cystectomy underwent TUR surgery. Finally, in this study, pCR was judged according to the pathological examination results. Furthermore, we recommended salvage cystectomy for patients who failed to achieve a pCR. If these patients with residual tumours did not agree to undergo radical surgery in this situation, we performed additional chemotherapy, radiotherapy, and/or a repeat-TUR (named adjuvant therapy in this study) and again recommended radical cystectomy. To this chemotherapy, we added intra-vesicle chemotherapy to SC in some patients with residual tumours that included non-MIBC.

Chest radiography and pelvic and abdominal CT were performed every 6 months for 5 years after treatment and annually for an additional 5 years. This protocol was approved by the Human Ethics Review Committee of Nagasaki University Hospital. Additionally, we provided this information to the patients and obtained written informed consent.

Statistical analyses

Data are expressed as means \pm SD. Student’s *t* test and the Scheffé test were used to analyze continuous variables and multiple data comparisons respectively. The chi-square test and Fisher’s exact test were used for categorical data comparisons. Survival rates were measured from the first day of preoperative treatment to the day of patient death or last patient contact. Survival was evaluated and analyzed using

Kaplan–Meier curves and the log-rank p test. Variables that achieved statistical significance ($p < 0.050$) in univariate analyses were subsequently entered into multivariate analysis, which was conducted using a Cox proportional hazards model. All statistical analyses were performed using the statistical software package StatView version 5.0 for Windows (Abacus Concept, Inc., Berkeley, CA, USA).

Results

Clinicopathological features

As shown in Table 1, the frequency of older patients was significantly higher in the IAC-R group than in the other groups ($p < 0.001$). Meanwhile, the frequency of high T-stage tumours was significantly lower in the IAC group than in the other groups ($p = 0.008$). Radical cystectomy was performed in 26 (76.5%) patients in the SC group but in only 14 (17.7%) in the IAC + R group ($p < 0.001$).

Adverse events

Severe toxicities occurred in 29 (36.7%) patients in the IAC + R group, and this incidence was significantly higher ($p = 0.005$) than those in the SC ($n = 6$, 17.6%) and IAC groups ($n = 7$, 16.0%). The most frequently occurring symptoms in all groups were haematological, including leucopenia and anaemia, and occurred in 14.7% (5/34), 14.0% (7/50), and 22.8% (18/79) of patients in the SC, IAC, and IAC + R groups, respectively. However, the differences in frequencies between the 3 groups did not reach statistical significance ($p = 0.374$). On the other hand, the incidence of urinary disorders such as urinary tract pain and haematuria was remarkably higher in the IAC + R group ($n = 14$, 17.7%) than in the SC (0%) and IAC groups ($n = 3$, 6.0%). Nearly all of these events improved after several months of treatment; however, 27 of the IAC + R patients

(34.2%) required reduction in the chemotherapy doses and radiotherapy intensities. Major adverse events that led to dosage decreases in the IAC + R group included altered renal function, delayed haemorrhagic recovery, and vomiting. Additionally, 18 of the 79 IAC + R patients (22.8%) required decreased dosages during the initial treatment due to older age and/or the avoidance of severe adverse events. Finally, 45 of the 79 IAC + R patients (57.0%) did not complete the planned treatment. Therefore, we divided the IAC + R patients into 2 subgroups, the incomplete and complete IAC + R groups (latter: ≥ 2 cycles of standard regimen and ≥ 40 Gy of radiotherapy). Among the clinicopathological features, significant differences were detected between the incomplete IAC ($n = 45$) and complete IAC + R groups ($n = 34$) in terms of the frequencies of older age (32/45, 71.1% and 13/34, 38.2%; $p = 0.004$) and recurrent tumours (12/45, 26.7% and 3/34, 8.8%; $p = 0.045$). There were no other significant differences on clinicopathological features between these 2 groups.

Pathological complete responses in the local mass

As shown in Fig. 2, pCR was achieved in 6 (17.6%), 11 (22.0%), and 34 (43.0%) patients in the SC, IAC, and IAC + R groups, respectively, with the highest incidence in the IAC + R group; this difference was significant ($p = 0.007$). In the IAC + R subgroups, the pCR incidence was significantly higher in the complete IAC + R group (19/34, 55.9%) than in the incomplete group (15/44, 33.3%; $p < 0.001$). Progressive disease was observed in 3 (8.8%) of the 34 SC patients. Therefore, 8 SC patients (23.5%) received adjuvant therapy, including systemic and intravesical chemotherapy. Additionally, in the SC group, 1 of 8 patients (12.5%) who received conservative treatment also underwent salvage cystectomy. Furthermore, adjuvant therapy was also administered to 17 (34.0%) of the 50 IAC patients, 13 (28.9%) of the 45 incomplete

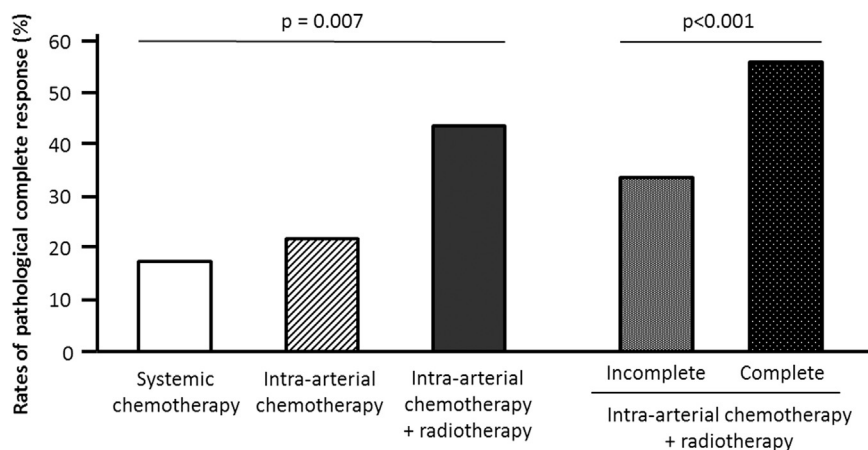


Figure 2. Rates of pathological complete responses (pCR) after chemotherapy and chemoradiotherapy. The patients treated with IAC + R exhibited a significantly higher rate of pCR, compared with the other groups. In addition, the pCR rate in the complete IAC + R group was significantly higher than that in the incomplete IAC + R group.

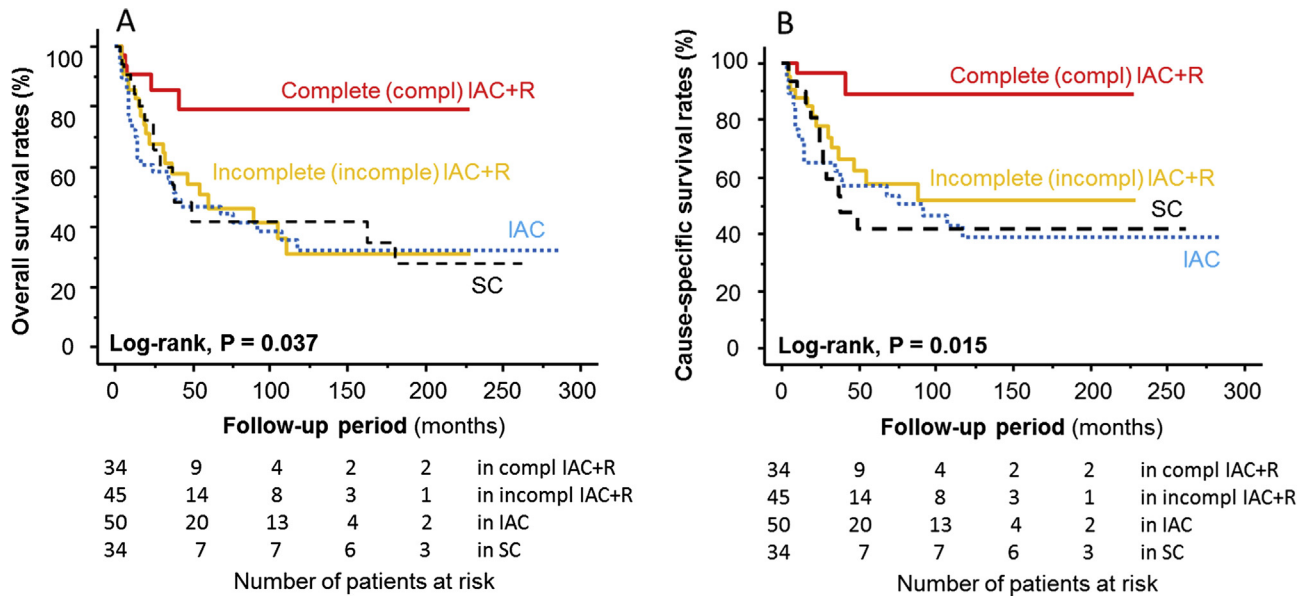


Figure 3. Kaplan–Meier curves of overall (A) and cause-specific survival (B). In both analyses, the patients who completed the IAC + R treatment had significantly better survival. The mean ± SD follow-up periods from the initial date of chemotherapy to the last available follow-up dates for the patients treated with SC, IAC, and IAC + R were 55.3 ± 78.6, 58.3 ± 66.7, and 46.5 ± 54.0 months, respectively. Complete (Compl) IAC + R, red; incomplete (incompl) IAC + R, orange; IAC, blue; SC, black line.

IAC + R patients, and 7 (20.6%) of the 34 complete IAC + R patients. Salvage cystectomy was performed in 4 (12.1%) of the 33 IAC patients and 4 (10.8%) of the 37 incomplete IAC + R patients. In contrast, in the complete IAC + R group, only 1 (3.6%) of the 28 patients underwent salvage cystectomy.

Survival

Twelve (35.3%) of the 34 SC patients, 24 (48.0%) of the 50 IAC patients, and 16 (20.3%) of the 79 IAC + R patients died of bladder cancer. In contrast, only 2 (5.9%) of the 34 complete IAC + R patients died of bladder cancer. The Kaplan–Meier overall and cause-specific survival curves are shown in Fig. 3. The 5-year overall survival rates in the SC, IAC, and incomplete IAC + R groups were 42.0%, 46.7%, and 50.3%, respectively. In contrast, the 5-year overall survival rate of the complete IAC + R group was 79.0%, and this was significantly better than the rates in the other groups (log-rank $p = 0.037$, Fig. 3A). Similarly, for cause-specific survival, the complete IAC + R patients exhibited a better prognosis than did those who received other treatments (log-rank $p = 0.014$; Fig. 3B). A univariate Cox proportional hazards analysis revealed significant associations of N1 disease and complete IAC + R treatment with cause-specific survival (Table 2). A multivariate analysis model that included these 2 significant predictors found that complete IAC + R was an independent predictive factor of cause-specific survival (hazard ratio [HR] = 0.16, 95% confidence interval [CI] = 0.03–0.72, $p = 0.028$). In addition, in a multivariate analysis model

that included all factors, N1 disease and complete IAC + R were also found to be significant predictive factors of cause-specific survival in patients with MIBC (Table 2). Similar results were obtained for overall survival in the univariate analysis. Additionally, a similar multivariate analysis model that included all factors showed that complete IAC + R was a significant predictive factor for overall survival in these patients (HR = 0.27, 95% CI = 0.10–0.79, $p = 0.017$).

Discussion

Chemotherapy with or without radiotherapy has been administered either as neo-adjuvant chemotherapy or as bladder preservation therapy in patients with MIBC.^{9,10} Although the initial purposes of these 2 treatment strategies differed, the results of these strategies often overlap with respect to the antitumour effects and adverse events. For example, although some patients receive chemotherapy as a neo-adjuvant therapy before radical cystectomy, they might refuse radical surgery because of downstaging after treatment. In contrast, some patients who hope for bladder preservation might undergo radical cystectomy because multimodal therapy could not be completed owing to severe adverse events. In fact, many patients in this study made their final decisions after preoperative treatment. Therefore, we analyzed all patients who received preoperative chemotherapy, regardless of initial intent.

Our results showed that the patients who received IAC + R had the highest pCR achievement rate. A well-performed review found that the combination of

Table 2
Cause-specific survival analyses.

	Univariate analysis			Multivariate analysis		
	HR	95% CI	<i>p</i> Value	HR	95% CI	<i>p</i> Value
Male	1.72	0.79–3.87	0.172	2.82	1.15–6.90	0.023
Old age (>75 years)	1.45	0.83–2.54	0.192	2.05	0.97–4.33	0.060
High ECOG PS (2)	1.48	0.53–4.15	0.453	0.86	0.28–2.70	0.801
Recurrent tumour	1.59	0.89–2.84	0.117	0.75	0.37–1.52	0.428
With SCC/AC	1.72	0.68–4.36	0.249	1.64	0.63–4.31	0.312
High grade	1.36	0.78–2.38	0.281	1.39	0.76–2.57	0.289
High T stage (T3/4)	0.97	0.56–1.67	0.915	0.91	0.47–1.79	0.791
N stage (N1)	2.73	1.21–6.16	0.015	4.47	1.73–11.58	0.002
Before 2002	0.65	0.33–1.08	0.089	0.54	0.26–1.12	0.098
CDDP-based regimens	0.97	0.44–2.15	0.932	0.69	0.25–1.93	0.477
With radiotherapy	1.12	0.65–1.93	0.689	0.91	0.45–1.83	0.794
Compl TUR before chemo	1.16	0.67–2.01	0.596	1.10	0.53–2.27	0.810
Cystectomy after chemo	0.59	0.31–1.12	0.107	0.51	0.25–1.06	0.070
Adjuvant therapy	0.53	0.25–1.13	0.100	–	–	–
Complete IAC + R	0.16	0.04–0.70	0.015	0.15	0.03–0.77	0.024

HR, Hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; PS, performance status; SCC, squamous cell carcinoma; AC, adenocarcinoma; CDDP, cisplatin; compl, complete; TUR, transurethral resection; IAC + R, intra-arterial chemotherapy and radiotherapy.

chemotherapy and radiotherapy was more effective for local control and outcomes when compared with chemotherapy or radiotherapy alone.¹¹ Therefore, many investigators have addressed the anti-cancer effects and adverse events associated with these multimodal therapies and have compared their results with those of others. However, strict comparisons with other studies are very difficult because of the wide variety in chemotherapeutic regimens, radiotherapy methods, and patient backgrounds. For example, regarding the chemotherapeutic regimens, some studies used systemic MVEC (methotrexate/vinblastine/epirubicin/cisplatin),^{9,12} MCV (methotrexate/cisplatin/vinblastine),^{7,12,13} or other CDDP-based chemotherapies.^{6,14,15} Moreover, non-CDDP-based regimens have often been used for SC.^{8,16,17} In addition to SC, the intra-arterial administration of chemotherapeutic agents^{6,14,18} or both systemic and intra-arterial administration²¹ have also been reported. Regarding the radiotherapy irradiation range, several patterns have been reported, including the bladder only,¹⁸ bladder plus surrounding tissues,^{10,16} and bladder plus pelvis.^{7,12,14,17,19} The irradiation intensity also varies widely, with total doses to the pelvis of <40 Gy,^{17,18} 54–60 Gy,⁸ >60 Gy,^{7,9,12–16} and 40 Gy and an additional 10–20 Gy to the bladder in cases with massive tumours.¹⁹ Furthermore, patient selection was divided into the following patterns: patients with T2 and T3^{6,9} or T2–4 disease^{7,8,13–15} and those with N0^{7,9,13,14} or N1 disease.^{8,12} In reality, these multimodal therapies yielded a wide range of CR achievement rates from 39.3% to 90.3%.^{7–19} Similarly, the 3-year overall survival rates associated with these bladder preservation therapies were reported to range from 47% to 83%.^{15,20} Therefore, it does not seem logical to clarify the antitumour effects of each treatment tool used in multimodal therapies. In contrast, our study was conducted according to a unified

policy at a single hospital. Accordingly, we believe that our results present more accurate differences in the anti-cancer effects and adverse events associated with the administration route or use of additional radiotherapy in patients with MIBC.

In the present study, the overall and cause-specific 5-year survival rates of patients who received complete IAC + R were 79.0% and 87.2%, respectively. A possible reason for this improved prognosis is that IAC + R was successfully completed by patients with a better general condition and higher organ-sparing ability. Additionally, we emphasize the importance of receiving the full planned doses of chemotherapy and radiotherapy. A similar opinion was suggested by another study in which a reduced chemoradiotherapy dose was found to be a significant predictor of reduced survival in patients with MIBC.⁸

Urinary disorders were more characteristic of the IAC + R group than of the other groups. Given the fact that the frequency of this symptom was remarkably higher in the IAC + R group than in the IAC group, the addition of radiotherapy to IAC is thought to be associated partly with the occurrence of these urological symptoms. However, such high incidences of urinary disorders were not reported in previous reports of combined SC and radiotherapy.¹⁰ Furthermore, an earlier report stated that urinary complications of chemoradiotherapy occurred in 11.5% of cases, a frequency similar to that achieved with radiotherapy alone.⁷ Given these results, it is possible that radiotherapy, when administered along with higher concentrations of anticarcinogenic agent(s) delivered via intra-arterial infusion, is associated with the incidence of urinary disorders.

The European Association of Urology (EAU) guidelines mention the effectiveness and unknown issues of neo-adjuvant therapy and bladder-sparing treatments for localized disease.²¹ However, the guideline recommendations

and conclusions are based on results obtained with SC because this method is common, and information regarding IAC is too scarce. Therefore, we believe that our results are useful when discussing treatment strategies that include IAC. On the other hand, a limitation of this study is a treatment selection bias due to the lack of fixed criteria. Additionally, the relatively small number of patients in each group and differences in the patients' backgrounds, radiotherapy strategies, treatments after chemotherapy, and follow-up strategies after cystectomy are also potential sources of bias, given the retrospective nature of this study.²² Furthermore, the radiotherapy intensity used in this study differs from the recommended intensity in the EAU guidelines.²¹ Therefore, further studies, including a randomized study and a well-designed larger study, will be necessary to determine the usefulness of these therapies in patients with MIBC.

In conclusion, multimodal IAC + R therapy was found to be a useful therapeutic strategy for patients with MIBC. In particular, completion of the planned treatment was a key predictive factor of survival in these patients. Furthermore, a solution for addressing the adverse events and the development of countermeasures are important and necessary to increase the use of IAC + R.

Conflict of interest statement

The authors declare no conflicts of interest.

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