Research Article

Bladder preservation with concurrent chemoradiotherapy for muscle-invasive bladder cancer: Retrospective comparison of three regimens

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Abstract

Objectives: The objectives of the study are to evaluate the oncological and functional outcomes of three bladder preservation regimens: radiotherapy alone (RT-alone group), concurrent chemoradiotherapy (CRT) using gemcitabine plus platinum (GP-RT group), and low-dose gemcitabine (LD-Gem-RT group) for muscle-invasive bladder cancer. **Methods:** The three oncological outcomes, bladder-intact distant metastasis-free survival (BI-DMFS), cancer-specific survival, and overall survival (OS), were compared among RT alone (n = 10), GP-RT (n = 16), and LD-Gem-RT (n = 11) groups. Treatment-related adverse events were evaluated against the Common Terminology Criteria for Adverse Events (version 5.0). In the LD-Gem-RT group, time-course changes in the domains and scales related to the quality of life were evaluated by utilizing three questionnaires. **Results:** Age was significantly higher in the RT alone group (84 ± 7.2 years old) than in the GP-RT (74 ± 9.0) and LD-Gem-RT (75 ± 6.7) groups (P = 0.016). At a median follow-up of 26 months, the 2-year BI-DMFS rates were 80, 81, and 55% in the RT alone, GP-RT, and LD-Gem-RT groups, respectively, and the 2-year OS rates were 69, 62, and 81%, respectively. In the CRT groups, only the baseline CRP ≥ 1.0 mg/dL was associated with poor survival outcomes. Common early-onset adverse events included diarrhea, urinary frequency, and hematotoxicity. A questionnaire survey in the LD-Gem-RT group revealed patients experienced significant deterioration in the global health status/quality of life and the physical component summary score. **Conclusion:** We reported the oncological and functional outcomes of bladder preservation therapy using three different regimens, yielding acceptable outcomes.

Keywords: Muscle invasive bladder cancer, Bladder preservation, Chemotherapy, Radiotherapy, Outcomes

1. INTRODUCTION

Muscle-invasive bladder cancer (MIBC) is aggressive and is associated with an increase in cancer morbidity and mortality, raising an urgent need to develop better treatment strategies to manage the high-risk disease population [1]. Cisplatin-based neoadjuvant chemotherapy followed by radical cystectomy (RC) is the current standard of care for MIBC, supported by level 1 evidence [2-4]. However, some patients decline RC, while others are deemed unsuitable for the procedure owing to advanced age, pre-existing comorbidities, vulnerability, and frailty. Bladder preservation using trimodality therapy (TMT), which consists of maximal transurethral resection of the bladder tumor (TURBT) followed by concurrent chemoradiotherapy (CRT), is a globally accepted approach for MIBC, with oncological and functional outcomes comparable to those of RC [5,6]. The Radiation Therapy Oncology Group (RTOG)/NRG Oncology Bladder Organ-Preservation Trials (eight Phase I/II trials and

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one Phase III trial) have reported the outcomes of a wide variety of treatment regimens in terms of chemotherapies and radiation doses/fractionation [7]. However, an optimal treatment regimen has not yet been established.

NRG/RTOG 0712 trial demonstrated that intravenous low-dose gemcitabine and once-daily radiation (LD-Gem-RT regimen) could be a well-supported alternative to cisplatin-unsuitable patients with a favorable bladder-intact distant metastasis-free survival (BI-DMFS) and toxicity profile [8]. Nara Urological Research and Treatment Group has treated patients with MIBC using three regimens based on patients' preference, physicians' discretion, and institutional guidelines: RT alone, LD-Gem-RT regimen, and concurrent CRT using gemcitabine plus platinum (GP) (cisplatin or carboplatin) intravenous systemic therapy (GP-RT regimen). The present study evaluated the oncological outcome, toxicity, and patient-reported outcomes (PROs) of these regimens in real-world practice.

2. METHODS

2.1. Patients with MIBC receiving radiotherapy and data collection

This multi-center study was approved by the Ethics Committee of Nara Medical University (protocol ID: NMU-1719 and 2891) and performed in compliance with the provisions of the Declaration of Helsinki (2013). Inclusion criteria were as follows: (1) patients who were treated with RT-based bladder preservation therapy and (2) radiographically and/or pathologically diagnosed as having MIBC. Exclusion criteria were as follows: patients missing critical data, such as follow-up and pathological findings. We retrospectively reviewed the medical charts of 37 MIBC patients who received RT alone, GP-RT, or LD-Gem-RT between 2016 and 2023 at Nara Medical University Hospital, Yamatotakada Municipal Hospital, and Kouseikai Takai Hospital. Of the 37 patients, 10 (27%), 16 (43%), and 11 (30%) underwent radiotherapy alone (RT-alone), GP-RT, and LD-Gem-RT, respectively. The recorded clinicopathological characteristics of the patients included age, sex, body mass index (BMI), Eastern Cooperative Oncology Group performance status, smoking history, laboratory data at the time of MIBC diagnosis, T category, lymphovascular invasion, presence of CIS, presence of variant histology, and follow-up data. We evaluated the prognostic impact of inflammation and nutrition indices at the time of MIBC diagnosis, including the neutrophil-to-lymphocyte ratio, monocyte-to-lymphocyte ratio, platelet-to-lymphocyte ratio, systemic immune inflammation index, systemic inflammation response index, and prognostic nutritional index. These indices were quantified by calculating the composite inflammatory indicators from blood examinations as previously described [9,10].

2.2. Treatment regimen for RT alone

A diagram of the treatment regimens is shown in Figure 1. Radiotherapy consisted of 2 Gy/fr delivered to the entire pelvic volume once daily for the first 20 days, followed by 2 Gy/fr delivered to the bladder for 10 days. Cystoscopic assessment with tumor site biopsy was performed to evaluate the efficacy of CRT 4−8 weeks after the completion of radiation therapy if indicated and available.

2.3. Treatment regimen for GP-RT

Radiotherapy was delivered on the same schedule as the radiation-alone group. Concurrent chemotherapy consisted of gemcitabine at 1000 mg/m^2 on days 1 and 8 and cisplatin at 70 mg/m^2 on day 2, repeated every 21 days for a maximum of three cycles. If cisplatin was ineligible, the carboplatin area under the curve 4−5 was allowed as a substitute. When adverse events (AEs) of grade 3 or higher occurred, the drug was discontinued, or a reduced dose was administered as appropriate. Cystoscopic assessment with tumor site biopsy was performed to evaluate the efficacy of CRT, 4−8 weeks after the completion of GP-RT if indicated and available.

2.4. Treatment regimen for LD-Gem-RT

Induction therapy involved 2 Gy/fr delivered to the whole pelvic region once daily for the first 10 days, followed by 2 Gy/fr delivered to the bladder for 4 days, and 2 Gy/fr delivered to the tumor site for the final 6 days (Figure 2). The total induction radiation doses were 20, 28, and 40 Gy to the pelvis, bladder, and tumor site, respectively. Concurrent chemotherapy included LD-Gem at 27 mg/m^2 administered twice a week on days 1, 4, 8, 11, 15, 18, 22, and 25 of induction therapy. After induction therapy, cystoscopic assessment with tumor site biopsy was conducted to evaluate the efficacy of CRT 4−8 weeks after completion of GC-RT. Patients without pathologically proven MIBC continued to receive consolidated CRT, as described below. Others were recommended for the prompt salvage of RC. Consolidation therapy comprised 2 Gy/fr delivered to the entire pelvic area for 12 days. The total radiation doses to the pelvis, bladder, and tumors were 44, 52, and 64 Gy, respectively. LD-Gem at 27 mg/m^2 was administered twice weekly on days 1, 4, 8, 11, and 15 of the consolidation therapy. When AEs of grade 3 or higher occurred, the drug was discontinued, or a reduced dose was administered as appropriate.

Adjuvant chemotherapy was given to all patients approximately 12 weeks after consolidation CRT completion. It consisted of gemcitabine at 1000 mg/m^2 on days 1, 8, and 15 and cisplatin at 70 mg/m^2 on day 2, repeated every 28 days for three cycles.

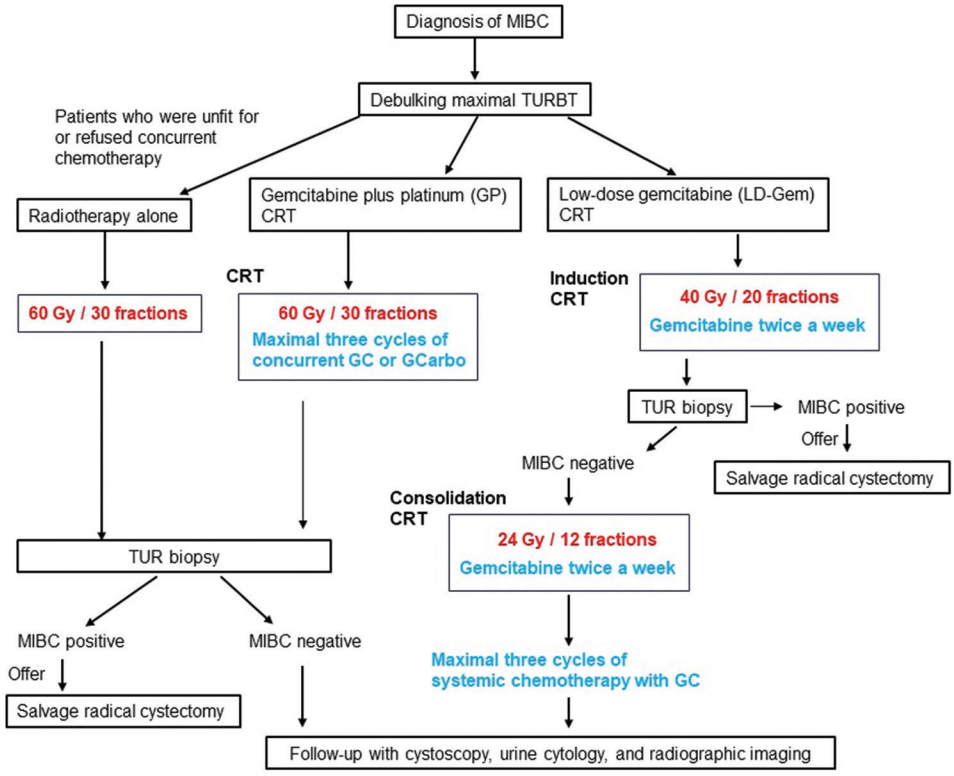

Figure 1. Flowchart of treatment regimens
MIBC: Muscle-invasive bladder cancer; TURBT: Transurethral resection of bladder tumors; CRT: Concurrent chemoradiotherapy; GC: Gemcitabine plus cisplatin combination chemotherapy; GCarb: Gemcitabine plus carboplatin combination chemotherapy. The red font indicates radiotherapy and the blue font is indicative of systemic chemotherapy.

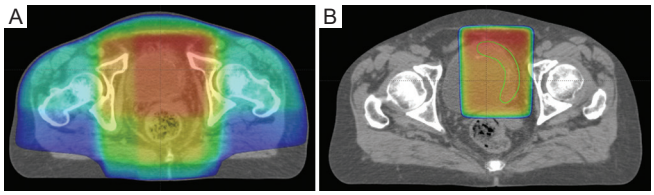

Figure 2. Example of a radiotherapy planning approach for muscle-invasive bladder cancer. Three-dimensional conformal radiation therapy (3D CRT) to the pelvis (A) and the bladder and tumor sites (B) in a female patient with Stage IIIA muscle-invasive bladder cancer.

2.5. Follow-up, endpoints, and evaluation of adverse events

Patients with preserved bladders were followed up with cystoscopy, urine cytology, and chest, abdomen, and pelvis computed tomography scans every 3 months in the 1st year, every 4 months in the 2nd year, every 6 months for the next 3 years, and annually thereafter. Tumor site re-biopsy was performed under anesthesia if needed. We evaluated three endpoints: BI-DMFS, urothelial cancer-specific survival (CSS), and overall survival (OS). BI-DMFS was defined as the time from the initiation of radiotherapy to salvage RC or the occurrence of distant metastasis, whichever came first.

The AEs observed during and after CRT were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0) [11]. Early-onset AEs were defined as those that occurred during radiotherapy and the first 180 days after completion of radiotherapy, whereas late-onset toxicities were defined as those that took place thereafter [8,12].

2.6. Assessment of health-related quality of life

Because the LD-Gem-RT regimen has been newly initiated in our treatment group since 2019, PRO-based health-related quality of life (QoL) was prospectively evaluated only in patients treated with LD-Gem-RT. Time-course changes on QoL scales were assessed using three questionnaires: the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) [13,14], Functional Assessment of Cancer Therapy-General (FACT-G) and FACT-bladder (FACT-BL) [15], and multi-item short form-8 (SF-8) [16]. Patients were asked to answer questionnaires at baseline, during CRT (2 and 4 weeks after the initiation of CRT), immediately before CRT and at 3, 6, 9, and 12 months after the completion of CRT. Global health status/quality of life (QoL) scores were calculated by following a scoring procedure [17]. Higher scores on the functional scale and global health status/QoL indicate better QoL. The FACT-G total scores and

FACT-BL bladder-specific subscale scores were calculated according to the FACT scoring guidelines and as previously described [18]. The SF-8 contains psychometrically-based physical and mental health summary measures that score two-component summaries, which are calculated by weighing each SF-8 item using a norm-based scoring method outlined in the instrument guidelines [19]. Higher domain, physical component summary (PCS), and mental component summary (MCS) scores indicate better health status. The cutoff for the minimally important difference (MID) for each scale was defined as half the standard deviation (SD) of the baseline scores [20]. A decrease of more than MID from the baseline score was defined as "deterioration."

Radiotherapy to the pelvic region is associated with bowel symptoms such as diarrhea and constipation. Patients were asked to answer the questions "Have you been constipated?" and "Have you had diarrhea?" in the questionnaire and rate them on a 4-point Likert-type scale as follows: "1 = Not at all," "2 = A little," "3 = Quite a bit," and "4 = Very much." The scores on the symptom scale were calculated with a formula: {(raw score−1)/3} × 100 [17]. A higher score signifies higher symptomatology.

2.7. Statistical analysis

Data visualization and statistical analyses were performed using PRISM software (version 10) (GraphPad Software, Inc., San Diego, CA, USA). A $P < 0.05$ was considered statistically significant. The way of handling missing data in the analysis was omitting variables which had many missing values. Clinicopathological characteristics were compared using the Kruskal–Wallis test, followed by the *Post hoc* test (Dunn test), Chi-squared test, and Fisher's exact test, as appropriate. BI-DMFS, CSS, and OS after radiotherapy initiation were estimated using the Kaplan–Meier method and compared using the log-rank test for each arm. Patients who remained alive without experiencing any events were censored on the date of their last follow-up. To evaluate changes in patient-reported bowel symptom scores before, during, and after radiotherapy in patients receiving the LD-Gem-RT, the Wilcoxon matched-pairs signed rank test was used to compare each data with the baseline data.

3. RESULTS

3.1. Patients

The baseline clinicopathological variables of the 37 patients included in this study and a comparison among the three groups are depicted in Table 1. Age was significantly higher in the RT-alone group (84 ± 7.2 years old) than in the GP-RT (74 ± 9.0) and LD-Gem-RT (75 ± 6.7) groups ($P = 0.016$). No other variables differed significantly among the three groups. There was a tendency that systemic immune inflammation index was higher in the GP-RT group than in the LD-Gem-RT group (1116 ± 779 vs. 971 ± 484, $P = 0.077$).

A total of 27 patients were treated with the TMT CRT regimens because they were unfit for RC or declined to receive RC. Specifically, 5 out of 16 patients in the GP-RT group and three out of 11 patients in the LD-Gem-RT group were unfit for RC at a physician's discretion. The remaining patients refused to receive RC.

3.2. Completion of the planned treatment regimens

All the 10 patients in the RT-alone group completed a full course of radiation. In the GP-RT group, 15 out of 16 patients completed the full course of radiation, but one patient discontinued radiotherapy at 40/60 Gy due to adverse events. In the LD-Gem-RT group, nine out of 11 patients completed induction and consolidation radiotherapy (64Gy), but one patient discontinued radiotherapy (24/64Gy) due to patient preference and one patient received 40Gy induction radiotherapy and salvage radiotherapy due to residual MIBC in TUR biopsy specimen.

As to the chemotherapy, in the GP-RT group, five out of 16 patients completed three cycles of concurrent chemotherapy with GC or GCarbo. Out of 16 patients in the GP-RT group, two patients were treated with GCarbo from the start of CRT and one patient switched from GC to GCarbo due to hematotoxicity. In the LD-Gem-RT group, seven out of 11 patients completed planned concurrent chemotherapy with LD-Gem, but one patient withdrew due to patient preference, one patient received salvage RC after induction therapy, and one patient discontinued LD-Gem due to grade 3 neutropenia.

3.3. Outcomes and survivals

The follow-up after the initiation of radiotherapy lasted for 26 months (range, 3−86 months). During follow-up, three patients in the LD-Gem-RT group underwent salvage RC owing to residual MIBC after induction therapy, radiation-induced contracted bladder, and bladder perforation. The other groups did not include patients who underwent salvage RC. Of the 37 patients, 6 (16%) developed distant metastasis and 11 (30%) succumbed to various causes, among whom four patients died because of the progression of urothelial carcinoma. No patients in the LD-Gem-RT group died from urothelial carcinoma progression.

Survival curves for BI-DMFS, CSS, and OS after radiotherapy initiation were compared among the three treatment groups (Figure 3). The 2-year BI-DMFS rates were 80, 81, and 55% in the RT-alone, GP-RT, and LD-Gem-RT groups, respectively, and the 2-year OS rates were 69, 62,

Table 1. Baseline demographics of patients with muscle-invasive bladder cancer receiving bladder-preserving radiotherapy with or without concurrent chemotherapy

Variables	Overall	RT alone	Concurrent chemoradiotherapy		*P* value # Three groups	*P* value ## GP-RT *versus* LD-Gem-RT
			GP-RT	LD-Gem-RT		
Total, *n*	37	10	16	11	-	-
Age, years-old						
Mean±SD	77±8.6	84±7.2	74±9.0	75±6.7	0.016	0.93
Median (range)	79 (58-94)	85 (69-94)	78 (58-85)	76 (62-82)		
Sex						
Male	26 (74%)	7 (84%)	10 (63%)	9 (82%)	0.59	0.40
Female	11 (26%)	3 (16%)	6 (37%)	2 (18%)		
ECOG-PS						
0 or 1	30 (79%)	6 (84%)	14 (87%)	10 (91%)	0.21	0.99
2 or 3	7 (19%)	4 (16%)	2 (13%)	1 (9.1%)		
Mean±SD						
BMI	22±3.8	23±3.9	21±4.0	23±2.9	0.14	0.13
eGFR, mL/min/1.73 m^2	59±18	52±22	63±15	58±18	0.43	0.22
CRP	0.96±2.1	0.84±1.4	0.92±2.7	1.1±2.0	0.88	0.84
NLR	4.1±2.8	3.2±2.3	4.4±3.2	4.7±2.9	0.38	0.34
MLR	0.32±0.81	0.096±0.024	0.36±0.80	0.47±1.1	0.33	0.14
PLR	187±87	173±96	227±99	152±32	0.086	0.10
SII	941±654	681±614	1116±779	971±484	0.12	0.077
SIRI	1.58±1.30	1.22±1.22	1.35±0.87	2.19±1.65	0.25	0.52
PNI	45±7.0	43±8.8	45±6.5	48±5.3	0.20	0.69
Hydronephrosis						
No	27 (73%)	6 (60%)	13 (81%)	8 (73%)	0.46	0.66
Yes	10 (27%)	4 (40%)	3 (19%)	3 (27%)		
Clinical T category						
2	28 (74%)	8 (80%)	11 (69%)	9 (82%)	0.46	0.81
3b	4 (74%)	2 (20%)	1 (6.3%)	1 (9.1%)		
4a	5 (74%)	0	4 (25%)	1 (9.1%)		
Concomitant CIS						
No	34 (92%)	9 (90%)	14 (92%)	11 (100%)	0.60	0.50
Yes	3 (8.1%)	1 (10%)	2 (7.7%)	0		
Non-UC variant histology						
No	33 (89%)	9 (90%)	14 (88%)	10 (91%)	0.99	0.99
Squamous differentiation	2 (5.4%)	1 (10%)	1 (6.3%)	0		
Nested variant	1 (2.7%)	0	0	1 (9.1%)		
Giant cell	1 (2.7%)	0	1 (6.3%)	0		

Notes: #Kruskal–Wallis (continuous value) or Chi-squared test (categorical value); ## *post hoc* Dunn's test (continuous value) or Fisher's exact test (categorical value). RT: Radiotherapy; SD: Standard deviation; ECOG-PS: Eastern Cooperative Oncology Group performance status; eGFR: Estimated glomerular filtration rate; CRP: C-reactive protein; NLR: Neutrophil-to-lymphocyte ratio; MLR: Monocyte-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; SII: Systemic immune inflammation index; PNI: Prognostic nutritional index; SIRI: System inflammation response index; CIS: Carcinoma *in situ*; UC: Urothelial carcinoma; GP: Gemcitabine plus platinum combination chemotherapy; LD-Gem: Low-dose gemcitabine

and 81%, respectively. The survival analysis revealed no significant differences.

3.4. Prognostic factors in the concurrent RCT groups

We explored the possible prognostic factors in patients with MIBC who received bladder-preserving CRT. GP-RT and LD-Gem-RT groups were subjected to survival analysis of the three endpoints (Table 2). Among the various variables, only the baseline CRP ≥ 1.0 mg/dL was associated with a poor prognosis for CSS (hazard ratio [HR]: 13.3, 95% confidence interval [CI]: 1.18−150) and OS (HR: 4.31, 95% CI: 0.93−19.9) (Figure 4). There was no significant difference in survival between the GP-RT and LD-Gem-RT groups. The cutoff values for inflammation and nutrition markers were determined based on the median values. No other variables, including systemic inflammation and nutritional markers,

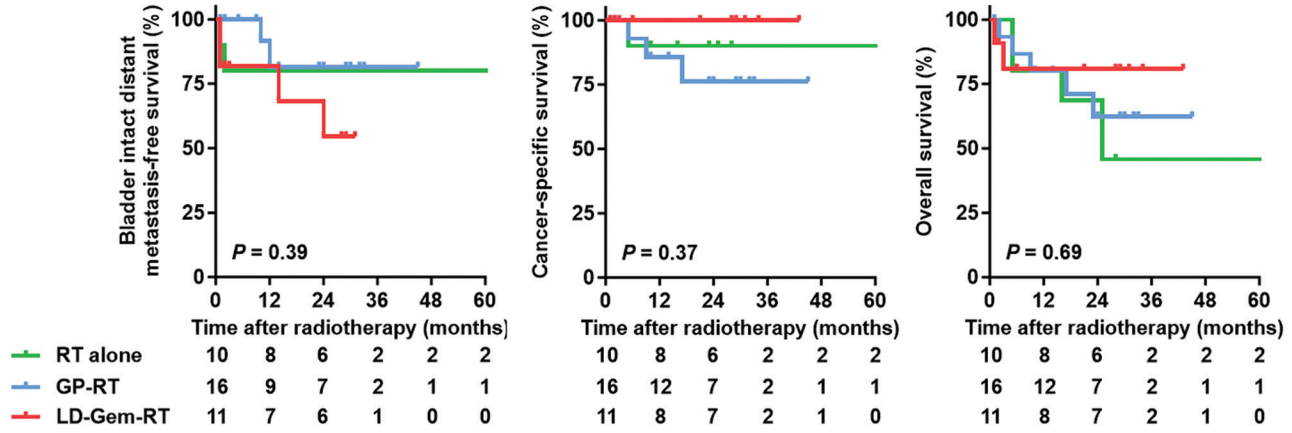

Figure 3. Survival curve comparison in patients with muscle-invasive bladder cancer receiving radiotherapy. The bladder-intact distant metastasis-free survival, cancer-specific survival, and overall survival rates after the initiation of radiotherapy were estimated using the Kaplan–Meier method and compared utilizing the log-rank test for each arm.

showed a significant prognostic impact on patients with MIBC who received concurrent CRT.

3.5. Adverse events

Early- and late-onset treatment-related AEs are summarized in Supplementary Tables S1 and S2, respectively. The most common early-onset AE was diarrhea, with an incidence rate of 30%. Approximately 15−35% of the patients receiving CRT experienced grade 3 or higher hematotoxicity. One of 16 patients receiving GP-RT died of treatment-related interstitial lung disease 1 month after the completion of radiotherapy, and one of 11 patients receiving LD-Gem-RT died of treatment-related severe colitis (vesicorectal fistula) 2 months after the completion of radiotherapy.

With regard to the late-onset AEs, diarrhea and hematotoxicity were uncommon, whereas some patients suffered from radiation cystitis and hydronephrosis, requiring interventions, such as transurethral coagulation and percutaneous nephrostomy. One of 16 patients receiving GP-RT died of late-onset severe colitis 23 months after the completion of radiotherapy and one of 10 patients who received RT alone died of severe urinary infection 25 months after treatment.

3.6. Health-related quality of life in patients receiving LD-Gem-RT

At baseline, global health status/QoL in the EORTC QLQ-C30, FACT-G total score, FACT-BL bladder-specific subscale, SF-8 PCS, and SF-8 MCS was 63 ± 21 (mean ± SD), 70 ± 16, 21 ± 5.8, 49 ± 7.5, and 42 ± 6.9, respectively. In general, these scores dropped during chemoradiotherapy and recovered over time post-treatment (Figure 4A). Global health status/QoL and PCS significantly deteriorated (decreased by more than 10 and 4 points, respectively), and PCS did not return to baseline levels.

As to treatment-induced bowel symptoms, patients' diarrhea was exacerbated during CRT and the symptom recovered to baseline levels after CRT (Figure 4B). In contrast, the constipation scores did not change during and after CRT.

4. DISCUSSION

In this study, we investigated the oncological outcomes and safety of three bladder-preserving therapy regimens in patients with MIBC: RT alone, GP-RT, and LD-Gem-RT. Owing to the retrospective nature of this study and potential differences in patient backgrounds, it may be challenging to fairly compare the oncological outcomes. The 2-year OS rates were 69, 62, and 81%; the 2-year CSS rates were 90, 76, and 100%; and the 2-year BI-DMFS rates were 80, 81, and 55%, respectively. One of the primary endpoints of this study was freedom from RC and distant metastasis (BI-DMFS). This endpoint was selected because bladder preservation is one of the main goals for patients with bladder cancer, and distant metastasis is the primary mode of disease failure in these patients and precedes a cancer-specific death. The LD-Gem-RT group had a favorable survival prognosis, whereas its BI-DMFS rate was lower than that of the other two treatment groups. Three of the 11 patients in the LD-Gem-RT group underwent RC because of residual MIBC after induction CRT, severe radiation-induced cystitis, and bladder perforation. In the other two treatment groups, no patients underwent salvage RC, but two patients had distant metastasis during the follow-up.

A couple of decades ago, Kent *et al.* conducted a phase I trial of gemcitabine, administered twice weekly with concurrent radiotherapy at a dose of 60 Gy/30 fr in patients with MIBC [21]. The maximum tolerated dose was determined to be 27 mg/m^2 based on dose-limiting toxicity, including liver function profile, malaise, and edema. Subsequently, the

Table 2. Univariate survival analysis of patients with muscle-invasive bladder cancer receiving bladder-preserving concurrent chemoradiotherapy

Variables	Category	Bladder intact distant metastasis-free survival			Cancer-specific survival			Overall survival		
		HR	95% CI	*P* value #	HR	95% CI	*P* value #	HR	95% CI	*P* value #
Age, years old	<75	1		0.81	1		0.57	1		0.33
	≥75	0.82	0.16–4.1		0.50	0.045–5.5		2.3	0.43–11.7	
Sex	Male	1		0.45	1		0.87	1		0.98
	Female	0.43	0.05–3.7		1.23	0.11–13.6		0.98	0.19–5.0	
ECOG-PS	0 or 1			NA	1		0.12	1		0.40
	2 or 3				7.01	0.62–78.8		2.53	0.29–21.8	
BMI	<22	1		0.23			NA	1		0.17
	≥22	2.84	0.52–15.6					0.23	0.03–1.89	
eGFR, mL/min/1.73 m^2	<60	1		0.66			NA	1		0.98
	≥60	0.69	0.13–3.53					0.98	0.22–4.44	
CRP, mg/dL	<1.0	1		0.12	1		0.036	1		0.062
	≥1.0	3.91	0.68-22.3		13.3	1.18–150		4.31	0.93–19.9	
NLR ##	<4.1	1		0.97	1		0.99	1		1.0
	≥4.1	0.96	0.19–4.84		0.98	0.06–15.8		1.00	0.20–4.97	
MLR ##	<0.32	1		0.74			NA	1		0.80
	≥0.32	1.44	0.16–13.0					1.33	0.15–11.4	
PLR ##	<187	1		0.50	1		0.86	1		0.84
	≥187	0.55	0.10–3.07		1.29	0.08–20.8		1.18	0.24–5.9	
SII ##	<941	1		0.99	1		0.93	1		0.93
	≥941	0.99	0.20–4.93		0.89	0.06–14.19		0.94	0.19–4.64	
SIRI ##	<1.58	1		0.72	1		0.80	1		0.71
	≥1.58	0.73	0.13–4.04		1.44	0.09–23.0		0.72	0.13–3.98	
PNI ##	<45	1		0.29	1		0.66	1		0.19
	≥45	3.17	0.37–27.3		0.54	0.03–8.65		0.32	0.06–1.77	
Hydronephrosis	No	1		0.94	1		0.31	1		0.81
	Yes	1.09	0.13–9.33		3.45	0.31–38.2		1.31	0.15–11.2	
Clinical T category	cT2	1		0.56	1		0.15	1		0.29
	cT3 or cT4	1.66	0.30–9.14		5.77	0.52–63.7		2.26	0.50–10.11	
Non-UC variant histology	No	1		0.71	1		0.27	1		0.79
	Yes	1.52	0.17–13.02		3.93	0.34–45.31		1.33	0.16-11.18	
Treatment regimen	LD-Gem-RT	1		0.21			NA	1		0.55
	GP-RT	0.34	0.06–1.86					1.65	0.32–8.52	

Notes: #Log-rank test; ##Cutoff values for inflammation and nutrition markers were determined based on the median values. HR: Hazard ratio; CI: Confidence interval; NA: Not available; RT: Radiotherapy; ECOG-PS: Eastern Cooperative Oncology Group performance status; BMI: Body mass index; eGFR: Estimated glomerular filtration rate; CRP: C-reactive protein; NLR: Neutrophil-to-lymphocyte ratio; MLR: Monocyte-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; SII: Systemic immune inflammation index; PNI: Prognostic nutritional index; SIRI: System inflammation response index; UC: Urothelial carcinoma; GP: Gemcitabine plus platinum combination chemotherapy; LD-Gem: Low-dose gemcitabine.

NRG/RTOG 0712 randomized control trial reported that the 2-year BI-DMFS was approximately 80% in the LD-Gem-RT group using 64 Gy/32 fr with 27 mg/m^2 of gemcitabine administered twice weekly [8], which was higher than that in our cohort (2-year BI-DMFS: 55%).

TMT (TURBT + CRT) for MIBC has been gaining clinical relevance recently. In 2024, many studies have validated the role of TMT as an alternative treatment for MIBC. Ditonno *et al.* conducted a systematic review and meta-analysis of comparative studies using multiple databases involving patients with cT2-4 Nany M0 MIBC [22]. Between RC and TMT, no significant difference was observed in OS (HR: 1.07, 95% CI: 0.81–1.4; $P = 0.6$), CSS (HR: 1.12, 95% CI: 0.79–1.57, $P = 0.5$), and metastasis-free survival (HR: 0.88, 95% CI: 0.66–1.16; $P = 0.3$). Although the mean medical cost of TMT was significantly higher than that of RC, TMT was associated with significantly higher general QoL scores, with greater cost-effectiveness per quality-adjusted life-year. The Surveillance, Epidemiology, and End Results database analysis by de Angelis *et al.* demonstrated that TMT rates have increased over time in organ-confined (cT2N0M0) MIBC in a guideline-consistent fashion [23]. In the non-

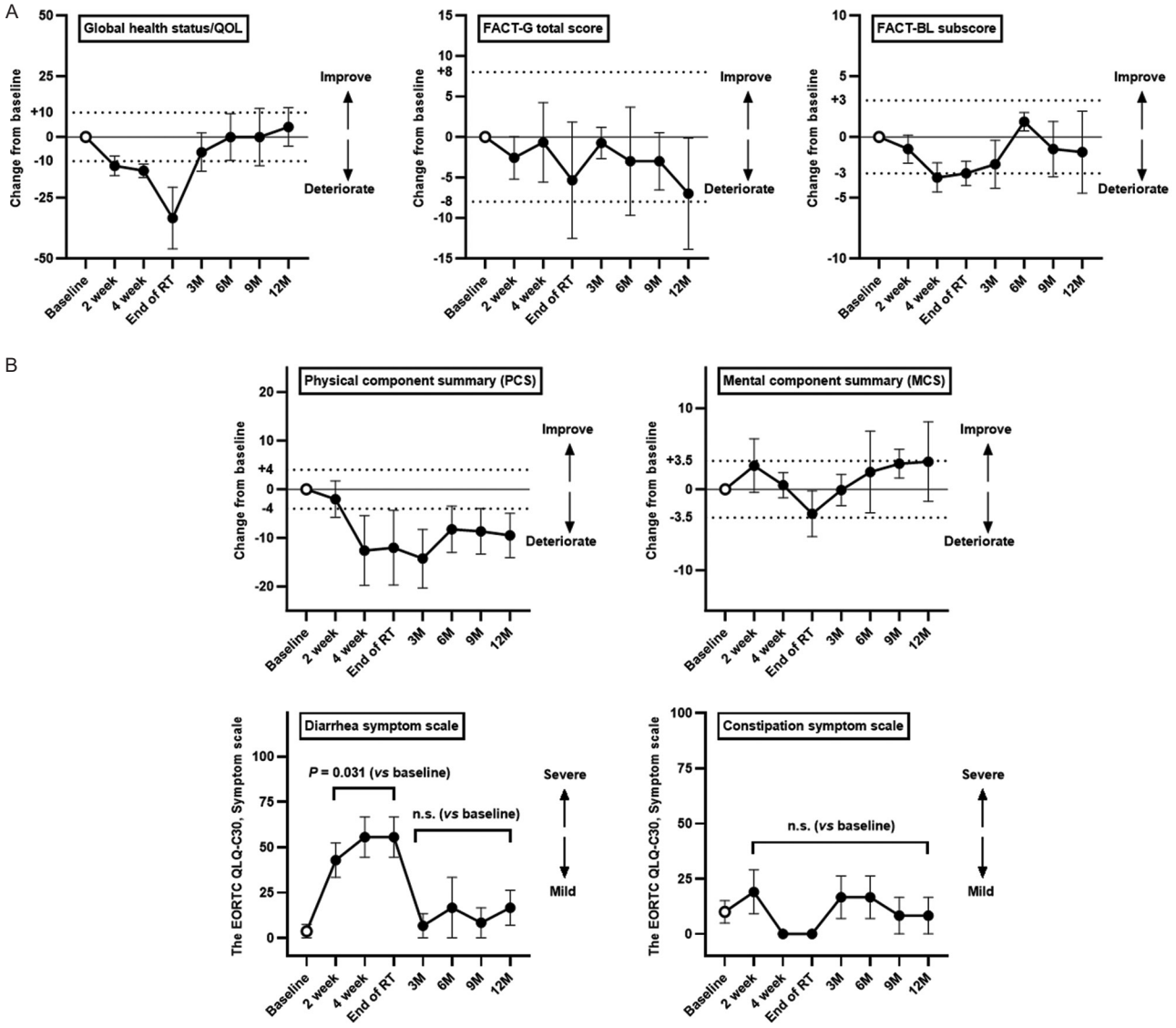

Figure 4. Changes in QoL, functional, and symptom scores before, during, and after radiotherapy in patients receiving the LD-Gem-RT. Data are expressed as means±standard deviations (SD). (A) A higher score indicates a higher quality of life (QoL). Global health status/QoL was assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30. The Functional Assessment of Cancer Therapy-General (FACT-G) and Functional Assessment of Cancer Therapy-Bladder (FACT-BL) questionnaires were used to calculate FACT-G total scores and FACT-BL subscores. The physical component summary (PCS) and mental component summary (MCS) were based on a multi-item short form-eight questionnaire. Dashed lines indicate the minimally important difference (MID) for each scale, defined as half the SD of the baseline scores. A decrease of more than MID from the baseline score was defined as "deterioration." (B) Time-course change of patient-reported bowel symptoms was assessed using the EORTC QLQ-C30 questionnaire. A higher score indicates higher symptomatology. Wilcoxon matched-pairs signed rank test was employed to compare each data with the baseline data.

organ-confined disease (cT2–T4N0–N3M0), the use of TMT resulted in dismal cancer-specific mortality, regardless of urothelial cancer MIBC and non-urothelial cancer MIBC histology. Another population-based analysis concluded that the strict TMT offered the best cancer control in organ-confined MIBC (cT2N0M0) as compared to TURBT plus chemotherapy compared to TURBT plus RT or TURBT plus chemotherapy [24]. In addition, when strict trimodal therapy could not be delivered, chemotherapy served as the second-best option and radiotherapy without chemotherapy offered the worst cancer control. A substantial population of patients with MIBC are relatively old and intolerable to high-intensity treatment, and thus, less-intense CRT regimens are needed. Lynch *et al.* reported that maximal TURBT followed by radiotherapy with concurrent capecitabine (twice-daily, goal dose at 825 mg/m^2) attained favorable oncological outcomes with an acceptable toxicity profile [25].

Recently, enfortumab vedotin plus pembrolizumab has been approved for patients with locally advanced or metastatic urothelial carcinoma as the first-line setting [26]. However, GC chemotherapy could be selected as the first-

line systemic treatment for patients with locally advanced or metastatic urothelial carcinoma. Gemcitabine and cisplatin are well-known radio-sensitizing agents expected to act synergistically against bladder cancer [27]. In our treatment group, carboplatin was chosen as a substitute for cisplatin in patients who were ineligible for cisplatin. Previous evidence provided by pre-clinical and clinical studies has shown that carboplatin can potentially radio-sensitize cancer cells [28,29]. Caffo *et al.* reported long-term follow-up data (a median of 74 months) of concurrent radiotherapy (54 Gy/30 fr) and GC chemotherapy (gemcitabine 200–500 mg/m^2/week and cisplatin 100 mg/m^2 every 3 weeks), concluding that the 5-year OS, CSS, and bladder intact survival rates were 70.1%, 78.9%, and 73.8%, respectively [27]. A Japanese single-arm, single-center, phase II study evaluated the efficacy, survival, and safety of concurrent radiotherapy (54 Gy/30 fr) and GC chemotherapy (gemcitabine 300 mg/m^2 and cisplatin 30 mg/m^2/week) in 35 patients with MIBC [30]. The authors reported that pathological complete response after CRT was observed in 31 patients (82%); the 5-year OS, CSS, and BI-DMFS rates were 75%, 85%, and 76%, respectively, which were similar to those reported by Caffo *et al.* [27] Although grade 3/4 AEs included neutropenia (63%), anemia (18%), and thrombocytopenia (37%), no treatment-related deaths were observed. In the GP-RT group of our cohort, the 3-year OS, CSS, and BI-DMFS rates were 62%, 76%, and 81%, respectively, which are comparable to those reported by previous reports [27,30]. Neutropenia was found in six patients (38%; grade 1/2 in two patients and Grade 3/4 in 4 patients). Two patients succumbed to AEs: one owing to early-onset interstitial lung disease and the other because of late-onset severe colitis.

Prognostic factors are crucial for the selection of treatment strategies for patients with cancer. As the current standard of care is RC for patients with MIBC, there might be some patients who should have undergone RC instead of bladder-preserving therapy. In this study, we evaluated the potential prognostic impact of clinicopathological variables and several inflammatory biomarkers on BI-DMFS, CSS, and OS. These inflammatory biomarkers could be easily calculated based on routine blood examination. Among several variables, only high CRP (≥1.0 mg/dL) at baseline was associated with CSS and OS (high vs. low levels; HR: 13.3, P = 0.036, and HR: 4.31, P = 0.062, respectively). An elevated CRP level is one of the signs of a systemic inflammatory response and is correlated with poor survival in various malignancies, including non-muscle invasive bladder cancer [31], localized upper urinary tract carcinoma [32], and metastatic urothelial carcinoma [33]. Yoshida *et al.* reported that elevation of CRP (>0.5 mg/dL) before treatment was predictive of a poor prognosis in patients with MIBC receiving CRT and that failure of CRP levels to normalize after CRT was associated with an extremely unfavorable prognosis [34]. Other inflammatory biomarkers, such as neutrophil-to-lymphocyte ratio and systemic inflammation response index, did not correlate with oncological survival prognosis. Russo *et al.* assessed the potential prognostic role of the SII in patients treated with RC and concluded that higher pre-operative SII values predicted worse oncological outcomes [35]. In addition, a possible association between the urinary microbiome (urobiome) and bladder cancer has been extensively researched recently. Nardelli *et al.* highlighted the potential of specific urinary bacteria, such as *Porphyromonas* and *Porphyromonas somerae*, as biomarkers for bladder cancer [36]. This finding is crucial for understanding the multifactorial nature of bladder cancer and its treatments, which include not only genetic and environmental factors but also microbial influences. There is still a critical lack of clinical biomarkers that can predict the outcomes after chemoradiotherapy. Such prediction can inform the decision-making of both patients and physicians.

To facilitate accurate diagnosis, treatment selection, and outcome prediction in patients with MIBC, various novel technologies have been emerging. One of the most promising technologies would be artificial intelligence (AI) [37]. Khoraminia *et al.* presented a comprehensive overview of the literature regarding the use of AI-based computational pathology in bladder cancer diagnosis [38]. Computational pathology can identify molecular subtypes by detecting such features as papillary structures and hyperchromatic/pleomorphic nuclei. Well-validated objective pathological diagnosis would enable accurate treatment selection, for example, RC or TMT.

QoL outcomes must be considered when selecting cancer treatments, especially in patients with MIBC who are candidates for either RC or bladder-preserving therapy. Unfortunately, the quality of evidence regarding QoL outcomes remains limited. Although the NRG/RTOG 0712 trial did not include an analysis of PRO-based health-related quality of life [8], we investigated the time-course changes from baseline to 12 months after the completion of CRT in sub-scores and domains in patients receiving LD-Gem-RT treatment. Our short-term assessment demonstrated that transient deterioration in some sub-scores was observed during and just after radiotherapy, especially in global health status/QoL and SF-8 PCS, partially owing to treatment-related diarrhea and/or urinary frequency. However, scores remained stable on FACT-G scale, FACT-BL bladder-specific subscale, and SF-8 MCS. A systematic review of two prospective and four retrospective studies focused on pre- and post-RT assessment of PROs in patients treated with RT alone or CRT. PROs were assessed using the EORTC QLQ-C30, FACT-G, FACT-BL, SF-36, and *Ad hoc* questionnaire [39]. According to the available literature, RT for bladder preservation appeared to provide similar or better

general QoL with satisfactory sexual and urinary functions, whereas gastrointestinal AEs are more detrimental than RC. A pooled analysis of prospective trials reported long-term oncological outcomes in patients undergoing multimodal bladder preservation treatment for MIBC, demonstrating that the 5- and 10-year OS rates were 57 and 53 %, whereas CSS rates were 71 and 65%, respectively, with approximately 80% of patients maintaining bladder-intact survival at the 5-year mark [5].

Diarrhea represents one of the most common AEs in patients treated with radiotherapy. In this study, 11 (30%) out of a total of 37 patients and 7 (64%) out of 11 patients in the LD-Gem-RT groups experienced any grade of diarrhea (Supplementary Table S1). Siracusano *et al.* reported that bowel disorders, including diarrhea and constipation, negatively affected QoL in patients undergoing RC and urinary diversion and these AEs could be underscored because patients frequently develop constipation and diarrhea postoperatively [40]. Therefore, we evaluated the time-course change of patient-reported bowel symptom scores during and after the LD-Gem-RT. Patients experienced worsening diarrhea but no constipation, during treatment, but recovered after treatment. This comparison using PROs would be pivotal in highlighting the potential benefits of the LD-Gem-RT, as bladder preservation can negatively affect these specific QoL issues.

5. CONCLUSION

The limitations of this study are as follows: (a) a possible selection bias cannot be excluded due to the retrospective nature of this study; (b) we could not compare the PRO data of the three cohorts because only PRO data of LD-Gem-RT were available; (c) the sample size was small ($n = 37$ patients); and (d) the follow-up duration was relatively short (median, 26 months). The small sample size and short follow-up limit the statistical power and the generalizability of the findings. Although these would be a drawback of this research, we believe that future studies will involve more patients with MIBC who opt for chemoradiotherapy. Further research should aim to include a larger cohort, possibly through multi-center collaborations, to validate the findings and improve statistical power.

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CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Writing – review & editing: Kiyohide Fujimoto

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The studies involving humans were approved by The Nara Medical University Ethics Committee (reference IDs: 1791 and 2891) of the Nara Urological Research and Treatment Group framework. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA

All data generated or analyzed during this study are included in this published article. The data underlying this article will be shared on reasonable request to the corresponding author.

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