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The updated outcomes of bladder-preserving trimodal therapy using a real-time tumor-tracking radiotherapy system for patients with muscle-invasive bladder cancer

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Abstract

Objective: Bladder-preserving trimodal therapy is recognized as a promising alternative treatment for muscle-invasive bladder cancer. We report the updated outcomes of muscle-invasive bladder cancer patients that were treated using our treatment protocol, which involves radiotherapy delivered with a real-time tumor-tracking radiotherapy system.

Methods: Thirty-eight patients who were diagnosed with T2-T4N0M0 bladder cancer between 1998 and 2016 and had clinically inoperable disease or refused to undergo surgery were enrolled. The treatment protocol included maximal transurethral resection followed by whole-bladder radiotherapy (40 Gy). Concurrent nedaplatin-based chemotherapy was administered to patients with adequate renal function. At the time of the first evaluation (via transurethral resection of the tumor bed), fiducial markers were endoscopically inserted into the bladder wall around the tumor. A boost of 25 Gy was administered using the real-time tumor-tracking radiotherapy system. The second evaluation (via transurethral resection of the tumor bed) was performed 6 months after the start of treatment. The Kaplan–Meier method and Cox hazards analysis were used to analyze overall survival and cancer-specific survival.

Results: The median duration of the follow-up period was 28 months (range: 3–161 months). The 5- and 10-year overall survival rates were 54.9 and 41.2%, respectively. Twenty-five (65.8%) and twenty (74.1%) patients had achieved complete responses to chemoradiation at the first and second evaluations, respectively. In univariate and multivariate analyses, performance status was found to be significantly associated with overall survival [$P = 0.03$, hazard ratio: 3.48, 95% confidence interval: 1.15–10.6] and cancer-specific survival [$P = 0.02$, hazard ratio: 4.57, 95% confidence interval: 1.32–16.9], and sex was shown to be significantly associated with cancer-specific survival [$P = 0.03$, hazard ratio: 3.07, 95% confidence interval: 1.09–8.30].

Conclusions: Our bladder-preserving trimodal therapy protocol, which involves the use of a real-time tumor-tracking radiotherapy system, produced an acceptable overall survival rate. This therapy is a reasonable alternative for patients that are medically unfit for or do not want to undergo cystectomy.

Key words: bladder cancer, chemoradiation, trimodal therapy, complications, mortality

Introduction

Bladder cancer is common among people aged over 70 years old (1). Muscle-invasive bladder cancer (MIBC) has a poor prognosis, with <50% of patients surviving for 5 years regardless of the type of treatment employed (2–4). Although the standard treatment for MIBC is radical cystectomy (5), this procedure is invasive and inevitably results in major complications, such as ileus, thrombosis, cardiovascular events or various types of infection (6). A previous study showed that among patients aged over 80 years old the perioperative mortality rate of radical cystectomy within 90 postoperative days was ~11% (7). In daily clinical practice, we often encounter patients with MIBC that are not fit enough to undergo this type of invasive surgery.

Bladder-preserving trimodal (BPT) therapy is one of the alternative treatment options for patients with MIBC who are not fit enough to undergo radical cystectomy. An analysis of the data entered into a bladder cancer registry run by the Japan Urology Association between 2008 and 2011 demonstrated that radical cystectomy was performed in 45.8% of MIBC patients, while 27% of them underwent radiotherapy and/or chemotherapy (8). BPT therapy for MIBC is also actively performed in Japan, and treatment results have been reported from several facilities (9–12).

There are two difficult challenges associated with radiotherapy targeting bladder cancer. Firstly, the volume of the bladder changes according to the amount of urine it contains and pressure from the small bowel. Secondly, bladder tumors cannot be identified by computed tomography (CT) after transurethral tumor resection. These challenges can result in worse local tumor control and greater toxicities affecting the normal bladder and adjacent normal organs. To overcome these challenges, we have used a real-time tumor-tracking radiotherapy (RTRT) system combined with gold fiducial markers to treat bladder cancer since 1999, which has minimal effects on bladder mobility and causes minimal radiation-induced toxicities (13, 14). Herein, we report the updated outcomes of this approach and suggest potential prognostic clinical factors for patients with MIBC that undergo such treatment.

Materials and methods

Patient eligibility

We performed a retrospective analysis of the cases of patients with bladder cancer who were treated with BPT therapy at Hokkaido University Hospital between August 1998 and June 2016. We identified 38 consecutive eligible patients. This study was approved by the ethics committee of Hokkaido University Graduate School of Medicine. The eligible patients had histologically confirmed stage T2–4N0M0 muscle-invasive bladder carcinoma according to the current American Joint Committee on Cancer (AJCC) staging system (7th edition), which was evaluated using CT, magnetic resonance imaging and bone scintigraphy. All of the patients had surgically or medically inoperable disease or refused to undergo surgery. In addition, all of the patients were free from extensive inflammatory bowel disease, and none of them had undergone pelvic irradiation. Two patients who were only followed up for short periods (<3 months) were excluded from the analysis. Written informed consent was obtained from all patients before treatment.

Treatment protocol

The treatment plan (Fig. 1) was described in our previous report (13). Briefly, maximal transurethral resection (TUR) was initially performed to confirm the pathological diagnosis and to reduce the volume of the tumor. Such patients who still had visibly residual bladder tumor after primary maximal TUR were recommended to have repeat maximal TUR. Repeat maximal TUR was especially performed for the referred patients who had undergone primary TUR at different institutions. Maximal TUR means the thoroughly wide and deep resection of the tumor in order to achieve visibly complete resection.

Radiotherapy. Following the resection procedure, whole-bladder radiotherapy (40 Gy in 20 fractions) with a margin of 1.5–2 cm was started (day 1). Thereafter, 4–6 gold markers (2 mm) were implanted around the tumor bed. A localized boost (25 Gy/10 fractions) was administered to the tumor bed using the RTRT system.

Chemotherapy. The chemotherapy consisted of concurrent nedaplatin chemotherapy (70 mg/m^2 intravenously) on days 1, 22 and 50. The concurrent chemotherapy was only administered to patients with moderate renal function (creatinine clearance rate $\geq$ 45 ml/min). The number of rounds of chemotherapy administered depended on the patients' renal function and side effects. Nedaplatin (*cis*-diammineglycolatoplatinum) is a platinum analog (Shionogi Pharmaceutical, Osaka, Japan), which is known for its diminished nephrotoxicity (15). Nedaplatin is also reported to be a radiosensitizer (16) and exhibits comparable antitumor efficacy to cisplatin against bladder cancer (17).

Treatment evaluation. A percutaneous full-thickness bladder biopsy and TUR of the tumor bed were performed at the time of the marker implantation (the first evaluation). After the radiotherapy boost (25 Gy/10 fractions) was administered using RTRT, a second tumor evaluation was performed via TUR of the tumor bed (the second evaluation; around day 180). The patients underwent a physical examination, laboratory evaluations, urinary cytological tests and cystoscopy every 3 months for 2 years, then every 6 months for 3 years, and annually or more frequently thereafter, as clinically indicated.

Outcomes and statistics

Response definition, outcomes and statistical design. The overall survival (OS) and cancer-specific survival (CSS) were defined as the time

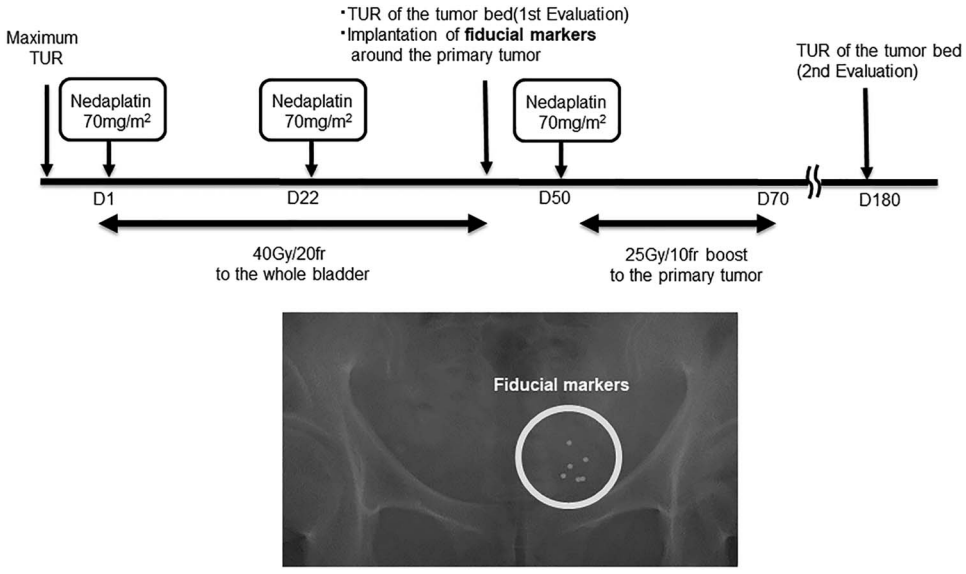

Figure 1. The treatment protocol.

from the first day of treatment to death due to any cause or bladder cancer, respectively. The progression-free survival (PFS) and bladder preservation were defined as the time from the first day of treatment to recurrence or salvage cystectomy, respectively. Patient information, including regarding age, sex, World Health Organization performance status, concurrent chemotherapy, histology, clinical T stage, pathological grade, the number of tumors, the maximum tumor size, hydronephrosis, concomitant carcinoma *in situ* (CIS) and whether the maximal TUR was pathologically complete, was obtained from the patients' charts. We also evaluated the acute and late toxicities of this treatment. The primary endpoint was OS. CSS, PFS and bladder preservation were assessed as secondary endpoints. The Kaplan–Meier method was used for the survival analysis. Predictors of OS, CSS and PFS were analyzed using univariate and multivariate Cox proportional hazards models. All of the variables that exhibited *P*-values < 0.05 in the univariate analyses were included in the multivariate analysis. All statistical analyses were performed with JMP® Pro 14.0 (SAS Institute, Japan).

Results

Patient characteristics

A total of 38 patients with clinical T2-T4N0M0 bladder cancer were treated at our hospital between 1998 and 2016. The median duration of the follow-up period was 28 months (range: 3–161 months). The patients' characteristics are listed in Table 1. Of these patients, 29 (76.3%) were male and 9 (23.7%) were female, and their median (interquartile range) age was 80 (73–83) years. The clinical T stage was T2 in 21 patients (55.3%), T3 in 14 patients (36.8%) and T4 in 3 patients (7.9%), and 5 patients (13.2%) had concomitant CIS. Twenty-nine patients (76.3%) had a single tumor, 24 (63.2%) had tumors that measured >3 cm in diameter, 9 (23.7%) had hydronephrosis and 21 (55.3%) received full courses of chemotherapy. In addition, 28 patients (74%) had repeat maximal TUR following primary TUR. Among them, no residual malignant disease was detected in six patients at repeat maximal TUR.

OS, CSS and PFS

The 3-, 5- and 10-year OS rates were 62.8, 54.9 and 41.2%, respectively (Fig. 2a), and the 3-, 5- and 10-year CSS rates were 70.3, 61.5 and 51.2%, respectively (Fig. 2b). The 3-, 5- and 10-year PFS rates were 42.8, 42.8 and 23.3%, respectively (Supplementary Fig. 1).

Response to induction therapy

Twenty-five patients (65.8%) exhibited CR to chemoradiation at the first evaluation, and 20 patients (74.1%) displayed CR at the second evaluation. The pattern of treatment failure and the subsequent treatments are shown in Fig. 3. The patients who developed bladder recurrence with synchronous distant metastasis were included in distant recurrence group. Of the 24 patients who suffered recurrence, 14 developed local recurrence (non-muscle-invasive tumors: seven patients, muscle-invasive tumors: seven patients) and ten patients suffered distant metastasis. The sites of metastasis were the lungs in two patients, the bone in five patients and the lymph nodes in four patients, and intra- or retroperitoneal dissemination occurred in two patients. In this cohort, only one patient required salvage cystectomy combined with the production of an ileal conduit for MIBC. The 3-, 5- and 10-year bladder preservation rates were 100, 100 and 75%, respectively (Supplementary Fig. 2). All of the patients who had T0 disease at the maximal TUR ($n = 6$) displayed CR at both the first and second evaluations. In addition, none of the patients that demonstrated T0 disease at the maximal TUR suffered recurrence (median duration of the follow-up period: 67.5 months). Interestingly, more than half of the patients with residual tumors exhibited CR at the second evaluation (68%).

The patients who were tumor-free at the first evaluation, i.e. after being irradiated with 40 Gy, exhibited good prognoses, i.e. their 5-year OS rate was 69.8%, whereas that of the patients with residual tumors was 28.8% (log-rank test, $P = 0.0047$, Supplementary Fig. 3).

Although not all patients received the second evaluation, i.e. after localized boost radiation with 25 Gy, there was no significant difference in OS rates between the patients with tumor-free ($n = 20$) and the patients with residual tumor ($n = 7$) (log-rank

Table 1. The patient characteristics

Characteristic		No.	%
Age	Median (IQR)	80 (73–83)	
	<79	20	52.6
	≥80	18	47.3
PS	0–1	27	71.1
	≥2	11	28.9
Sex	Male	29	76.3
	Female	9	23.7
Clinical T stage	T2	21	55.3
	T3	14	36.8
	T4	3	7.9
Pathological grade	2	5	13.2
	3	31	81.6
	Unknown	2	5.3
Histology	UC	31	81.6
	UC with other	4	10.5
	Other	3	7.9
Hydronephrosis	No	29	76.3
	Yes	9	23.7
CIS	No	31	81.6
	Yes	5	13.2
	Unknown	2	5.3
Tumor number	Single	29	76.3
	Multiple	9	23.7
Tumor size	≤3 cm	14	36.8
	>3 cm	24	63.2
Maximum TUR	Pathologically complete	6	15.8
	Pathologically incomplete	32	84.2
Chemotherapy	Full	21	55.3
	Reduction	17	44.7

IQR, interquartile range; CIS, carcinoma *in situ*; TUR, transurethral resection; PS, Performance Status; UC, Urothelial Carcinoma.

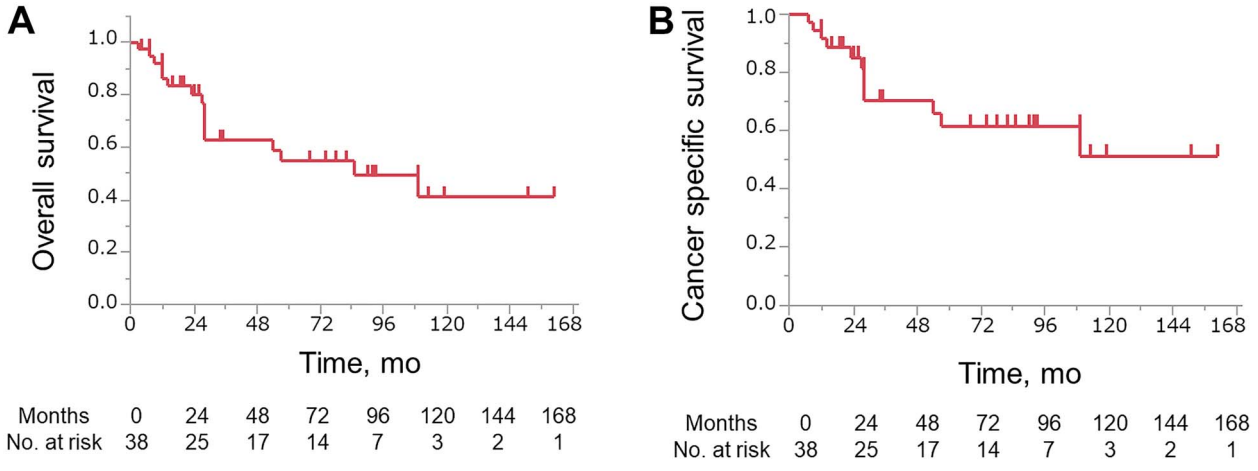

Figure 2. Kaplan–Meier estimates of overall survival (OS) (a) and cancer-specific survival (CSS) (b) for patients treated with bladder-preserving trimodal (BPT) therapy. The 3-, 5- and 10-year OS rates were 62.8, 54.9 and 41.2%, respectively (a), and the 3-, 5- and 10-year CSS rates were 70.3, 61.5 and 51.2%, respectively (b).

test, $P = 0.67$, Supplementary Fig. 4). The 5-year OS rate of those with or without residual tumor were 64.3 and 76.5%, respectively. Even in the patient with residual disease at the second evaluation, three of seven patients had non-muscle bladder tumor, all of which was completely resected by TUR. Such patients showed long OS.

Prognostic factors for OS and CSS

In the univariate Cox proportional hazards analysis (Table 2), performance status was found to be significantly associated with both OS and CSS ($P = 0.03$ and $P = 0.02$, respectively), and sex was shown to be significantly associated with OS ($P = 0.03$). Next, the variables that demonstrated P-values < 0.1 in the univariate

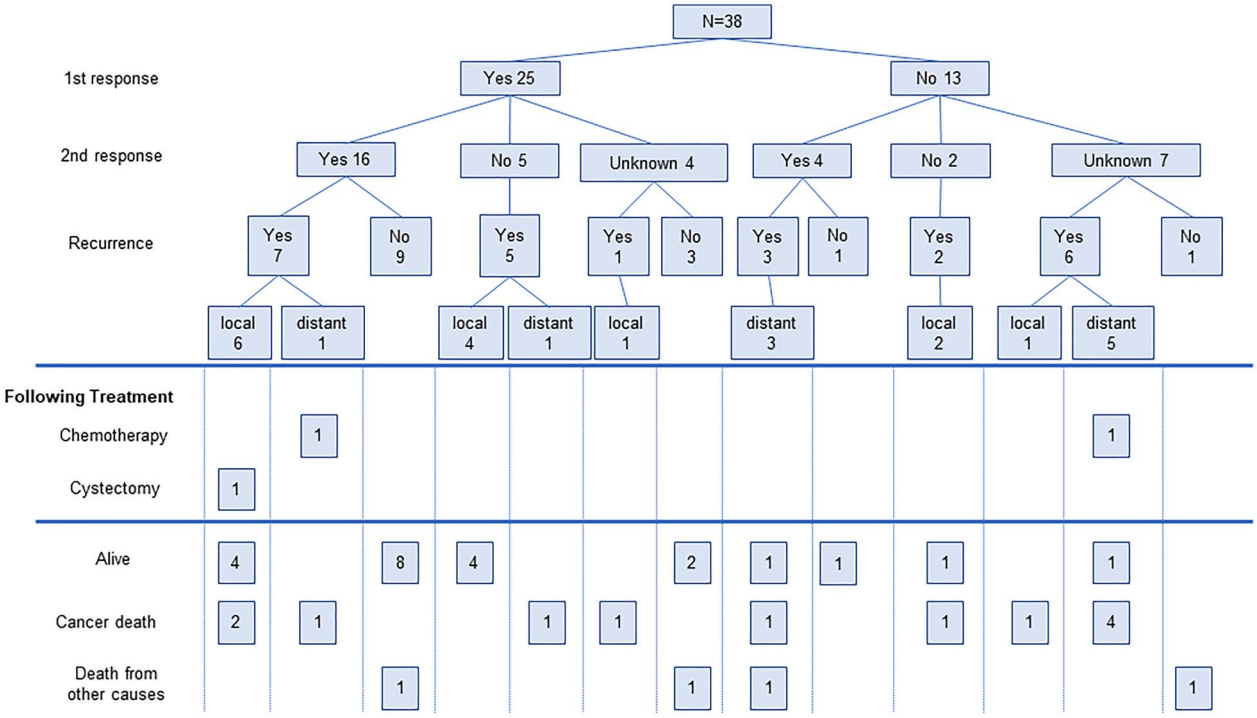

Figure 3. Patient flow through the treatment.

analyses were included in the multivariate analysis. As a result, performance status was confirmed to be significantly associated with OS [P = 0.03, hazard ratio (HR): 3.48, 95% confidence interval (CI): 1.15–10.6] and CSS [P = 0.02, HR: 4.57, 95% CI: 1.32–16.9], and sex (female vs male) was found to be significantly associated with OS [P = 0.03, HR: 3.08, 95% CI: 1.10–8.30] (Table 2). None of the examined clinical variables, including age, performance status, histology, pathological stage, the number of tumors, the maximum tumor size, hydronephrosis, CIS and concurrent chemotherapy, differed significantly between males and females. Only histology was found to be associated with PFS in the univariate analyses [P = 0.02, HR: 3.75, 95% CI: 1.30–9.64], but this was not confirmed in the multivariate analysis [P = 0.07, HR: 3.04, 95% CI: 0.927–9.74] (Supplementary Table 1).

Toxicities

The treatment-related acute and late toxicities experienced by the patients are listed in Table 3. Grade 3 or more severe hematological toxicities were observed in three (7.9%) patients: one (2.6%) patient had grade 3 leukocytopenia, one patient (2.6%) had grade 3 thrombocytopenia and one patient (2.6%) had grade 4 thrombocytopenia. One patient (2.6%) experienced a grade 3 urinary tract infection. Regarding late toxicities, one patient (2.6%) suffered grade 3 rectal stenosis.

Discussion

Although neoadjuvant chemotherapy followed by radical cystectomy is the gold-standard treatment for MIBC, the procedure places significant physical and psychological burdens on patients and is associated with high perioperative morbidity and mortality (6). Therefore, it is not feasible for some elderly or frail patients or patients with multiple comorbidities. Thus, there is a need to develop effective and safe treatments for such patients that preserve urinary functions and produce good oncological outcomes. Currently, the most promising strategy for treating MIBC in such patients is trimodal therapy, which includes maximal TUR followed by radiotherapy (over 60 Gy) and concurrent chemotherapy as a radiosensitizer (18, 19). The main advantage of our treatment approach, which involves the use of fiducial markers and an image-guided local radiotherapy boost, is that it makes it possible to identify the target lesion during the delivery of the radiation beam while reducing the amount of radiation delivered to the small bowel.

In the largest recent single-center study of trimodal therapy for MIBC, which involved 475 patients, the 5-year and 10-year OS rates were 57 and 39%, respectively. In addition, the 5-year and 10-year CSS rates were 66 and 59%, respectively. Thus, taking our patients' characteristics into account, the OS (5-year OS: 54.9%, 10-year OS: 41.2%) and CSS (5-year CSS: 61.5, 10-year CSS: 51.2%) rates obtained in the present study look reasonable. As most of the patients included in this study were not eligible for radical cystectomy due to their comorbidities, as was the case in previous studies of trimodal therapy, our study population was heavily weighted toward patients with a poor prognosis (e.g. the median age of our patients was 80 years old, and one-third of the patients had a performance status of 2). In addition, the patients who had residual tumors after being irradiated with 40 Gy had worse prognoses than the patients who achieved CR. In previous studies, cystectomy was typically selected if any residual disease was detected during the evaluation performed after the initial radiotherapy, but our patients could not be treated with cystectomy due to their medical problems.

Patient selection is the key to the appropriate use of BPT therapy. Although there are currently no definitive criteria for identifying ideal candidates for BPT therapy, some clinical factors have been suggested to be useful for selecting such patients. These factors include cT2N0M0 disease (19), achieving complete TUR (20), the absence of hydronephrosis (21, 22), the absence of CIS and unifocal

Table 2. Univariate and multivariate analysis

		OS			CSS		
Covariates	Comparison	HR	*P*	95% CI	HR	*P*	95% CI
Univariate analysis							
Sex	Female vs Male	3.11	0.03	1.11–8.36	2.90	0.08	0.856–9.10
Age	≥80 vs <79	1.26	0.65	0.45–3.61	0.92	0.89	0.264–3.05
PS	≥2 vs 0–1	3.48	0.03	1.17–10.4	4.49	0.02	1.31–16.1
Histology	Others vs UC	1.67	0.45	0.379–5.33	2.57	0.20	0.557–9.04
Pathological Grade	3 vs 2	1.74	0.44	0.476–11.2	2.87	0.25	0.543–52.8
Clinical T stage	≥3 vs 2	2.07	0.16	0.756–5.92	2.21	0.18	0.692–7.64
Tumor number	Multiple vs Single	1.77	0.32	0.542–5.16	1.21	0.78	0.264–4.23
Tumor size	>3 cm vs ≤3 cm	0.88	0.80	0.325–2.59	0.53	0.27	0.164–1.69
Chemotherapy	Reduction vs Full	2.21	0.12	0.80–6.12	2.35	0.15	0.719–7.66
Hydronephrosis	Yes vs No	1.86	0.25	0.621–5.15	1.05	0.94	0.231–3.65
CIS	Yes vs No	0.49	0.45	0.0271–2.44	0.67	0.68	0.0365–3.47
Multivariate analysis							
Sex	Female vs Male	3.08	0.03	1.10–8.30	2.91	0.08	0.855–9.20
PS	≥2 vs 0–1	3.48	0.03	1.15–10.6	4.57	0.02	1.32–16.9

OS, overall survival; CSS, cancer-specific survival ; HR, hazard ratio; CI, confidence interval.

Table 3. The treatment-related acute and late toxicities

	G1 *n* (%)	G2 *n* (%)	G3 *n* (%)	G4 *n* (%)
Acute toxicities				
Hematological				
Leukopenia or neutropenia	2 (5.2)		1 (2.6)	
Thrombocytopenia			1 (2.6)	1 (2.6)
Non-hematological				
Urinary frequency	3 (7.9)	5 (13.0)		
Urinary tract pain	2 (5.2)	1 (2.6)		
Nausea	1 (2.6)			
Diarrhea	2 (5.2)			
Cystitis non-infective	2 (5.2)			
Urinary tract infection		1 (2.6)	1 (2.6)	
Acute kidney injury	1 (2.6)			
Late toxicities				
Urinary tract hemorrhage	7 (18.4)			
Urinary tract obstruction		1 (2.6)		
Rectal stenosis			1 (2.6)	
Contracted bladder		2 (5.2)		

tumors (23, 24). We confirmed that both sex and performance status were associated with OS, whereas only the latter was significantly associated with CSS. Although associations between performance status and OS or CSS have not been routinely demonstrated in previous studies, Hussain et al. (25) reported that patients with medically inoperable disease exhibited worse survival than those who had medically operable disease, but refused to undergo radical cystectomy (5-year OS of 31% vs 45%). This resulted in a positive relationship between poor performance status and worse OS. Interestingly, we found that female sex was an important predictor of worse OS. While some previous studies have reported that female sex is associated with worse clinical outcomes after radical cystectomy for bladder cancer (26–28), no direct association between female sex and OS has been reported for BPT therapy. Recently, Radkiewicz et al. (29) reported that women with MIBC presented with more advanced T-stage disease compared to men. They also reported that the female survival disadvantage was limited to muscle-invasive disease and it was not related to clinicopathologic factors using a large cohort. The worse pathological stage distribution in women needs action to reduce delays in the treatment of bladder cancer.

It is also important to note that in our series no recurrent disease occurred in the patients that exhibited T0 disease after the maximal TUR. As reported previously, CR and improved oncological outcomes tended to be more common in the patients in which a visibly complete TUR was achieved (20, 30, 31). Even if a visibly complete TUR of a muscle-invasive bladder tumor actually leaves some undetected residual disease, maximal or aggressive tumor resection might effectively control some cases of MIBC when our treatment protocol

is employed. The biologic and clinical behavior of these patients is heterogeneous, highlighting the need for new prognostic markers that may allow advanced prediction of recurrence in this subset of patients.

The present study had several potential limitations that should be considered. Firstly, given the study's retrospective design, some important information was not available. In particular, data regarding whether the recurrent bladder lesions were the same as the primary lesion or were de novo lesions were not available in the current study. In addition, as our institution is a general hospital, the study population might have been affected by a certain degree of selection bias (e.g. it might have contained older patients with more comorbidities). Furthermore, our treatment protocol, which involved both the insertion of fiducial markers and an image-guided local radiotherapy boost, might be difficult to adopt in the community setting. Also, we did not evaluate our patients' health-related quality of life or investigate molecular markers that could be used to predict ideal candidates for this therapy. In addition, the relatively small number of patients and the short follow-up period limit the value of our study. Especially, the result of the second evaluation was not significantly associated with OS, which reflect low statistical power in light of the very few cases and low overall event rate.

Conclusions

Our data indicate that performing our BPT therapy using an RTRT system was well tolerated and produced encouraging oncological outcomes. Female gender and a poor performance status were found to be associated with poor oncological outcomes. In addition, patients who exhibit pathologically proven T0 disease after TUR are suggested to be good candidates for this treatment. This bladder-preserving treatment should be investigated further in a larger cohort study involving patients who are not surgical candidates or want to preserve their bladders.

Supplementary material

Supplementary material is available at *JJCOJ* online.

Conflict of interest statement

None declared.

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