Survival outcomes of non-definitive therapy for muscle-invasive bladder cancer

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Abstract. To analyze the risks and survival outcomes of non-definitive therapy (nDT) for muscle-invasive bladder cancer (MIBC), which may provide useful information for future treatment selection, the present study analyzed 124 patients who were diagnosed with MIBC (cT2-4aN1-2M0) and treated at Kurume University Hospital (Kurume, Japan) with definitive therapy (DT; including radical cystectomy and trimodal therapy) or nDT [transurethral resection of bladder tumor (TURBT) monotherapy or TURBT plus chemotherapy]. Differences in survival outcomes between the two groups were estimated using the Kaplan-Meier method and analyzed using the log-rank test. Cox proportional hazards regression models were used for multivariate analysis of each survival outcome. Of the 124 patients, 45% were treated with nDT, and among these, 50% were treated with TURBT monotherapy and 50% were treated with TURBT plus chemotherapy. Of the patients who chose definitive treatment, 69% were treated with radical cystectomy. The median age in the nDT group was 77 years, which was significantly higher than that in the DT group. Additionally, the proportion of patients with poor performance status, high Charlson comorbidity index and high neutrophil-lymphocyte ratio values was significantly higher in the nDT group. nDT was associated with significantly reduced overall survival, cancer-specific survival and progression-free survival rates, and was a poor prognostic factor for all survival outcomes compared with DT. In conclusion, nDT was associated with a high cancer-related mortality risk. The most appropriate treatment method should be discussed with the patients after providing them with sufficient information on the risks and benefits of each treatment method.

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Abbreviations: MIBC, muscle invasive bladder cancer; nDT, non-definitive therapy; DT, definitive therapy; RC, radical cystectomy; TURBT, transurethral resection of bladder tumor; PS, performance status; QOL, quality of life; CCI, Charlson comorbidity index; TMT, trimodal therapy; OS, overall survival; CSS, cancer-specific survival; PFS, progression-free survival

Key words: RC, bladder-sparing therapy, TURBT, TMT, health-related quality of life

Introduction

Over the past 20 years, the incidence and mortality of bladder cancer in Japan have increased approximately 1.8 and 2.1 times, respectively. However, given that the age-adjusted morbidity and mortality rates are almost stable (around 7.2/100,000 population/year and 2.0/100,000 population/year in 2018, respectively), the increase in the number of cases and deaths can be attributed to population aging. In general, most patients with bladder cancer are elderly, with more than 95% being over 45 years old and 80% over 65 years old (1).

About 25% of diagnosed bladder cancers are classified as muscle-invasive bladder cancer (MIBC) at the time of initial diagnosis (2). Non-muscle-invasive bladder cancer without intrinsic muscle layer invasion is often curable with minimally invasive treatments such as transurethral resection of bladder tumor (TURBT) and intravesical chemotherapy. However, when bladder cancer progresses to MIBC, the standard treatment is radical cystectomy (RC) with urinary tract diversion, which may lead to treatment-related serious complications and a decline in postoperative quality of life (QOL). Elderly patients with poor performance status (PS) and serious comorbidities are considered ineligible to undergo highly invasive surgery, originating challenges in the current population aging scenario. Furthermore, due to the growing interest in health-related QOL, a considerable number of patients refuse to undergo surgery, regardless of their favorable PS. Regarding bladder-sparing therapy for muscle-invasive cancer, TURBT followed by external beam radiation or chemotherapy has been used as an alternative treatment to RC for patients who refused the latter. However, previous studies have reported limited effectiveness of TURBT or chemotherapy only, and its routine use is not recommended (3-6). Currently, the most common bladder-sparing therapy for MIBC is trimodal therapy (TMT), which consists of maximum TURBT followed by external beam radiation and chemotherapy for radiosensitization (3,4). However, in clinical practice, some patients who refuse RC

are still treated with TURBT monotherapy or TURBT plus chemotherapy, even though the risks of these non-definitive therapies have not been extensively reported. Furthermore, to date, there have been few reports on the risks and outcomes of inadequate treatment for MIBC.

In this study, we analyzed the risks and survival outcomes of non-definitive therapy for MIBC at our hospital, which may provide valuable information for patient informed consent in future treatment selection.

Materials and methods

Study cohort and design. In this study, we retrospectively analyzed 124 patients who were diagnosed and treated for MIBC (cT2-4aN1-2M0) at Kurume University hospital (Kurume, Japan) from 2013 to 2020. The criteria for MIBC diagnosis include the following for all cases: TURBT with histopathological diagnosis of the invasion of the muscularis propria, lamina propria or further, and the invasion of the muscle layer or further were confirmed by imaging (computed tomography/magnetic resonance). As for lymph node metastasis, only cases with pelvis metastasis were included, while cases with distant metastasis, such as common iliac lymph node metastasis and visceral metastasis, were excluded. Clinical T (cT) stages were uniformly adjusted according to the 2017 Tumor-Node-Metastasis classification system (7). Post-treatment surveillance was performed by physical examination, urine cytology, and cystoscopy at 2 to 3-month intervals, and blood examinations and computed tomography at 4 to 6-month intervals. Metastasis and local recurrence were defined as urothelial tumor recurrence outside the residual urinary tract. The choice of treatment was at the discretion of each attending physician, considering the patient's physical findings. The patients were classified into RC (the standard treatment) and TMT (an alternative treatment option for patients with MIBC) treatment groups, defined as the definitive therapy (DT) group, according to the European Association of Urology and the National Comprehensive Cancer Network guidelines (3,4); and TURBT monotherapy or TURBT plus chemotherapy, defined as the non-definitive therapy (nDT) group. All pathological diagnoses were performed by expert pathologists at our hospital. All clinical data were obtained from hospital medical records.

Statistical analysis. Statistical analysis data were presented as the median and interquartile range for continuous variables because, Shapiro-Wilk test confirmed the non-normality distribution of continuous variables, while categorical variables were presented as percentages of events. Therefore, we used the Mann-Whitney U test, the Chi-square test, and Fisher's exact test as appropriate, to evaluate differences between the DT and nDT groups. Since this study was conducted in elderly patients with advanced cancer, we evaluated the overall survival (OS), cancer-specific survival (CSS) excluding the effect of death from other causes, and progression-free survival (PFS) reflecting disease progression. Survival outcomes were estimated using the Kaplan-Meier method and compared using the log-rank test. Survival data were collected on April 30, 2021. For patients with whom the hospital had lost contact during follow-up, we considered the data from the date of the last contact. Survival outcomes were based on the date of TURBT: OS was calculated from the date of TURBT to the date of mortality from any cause, while CSS and PFS rates were calculated from the date of TURBT to the date of cancer-associated mortality or disease progression. Disease progression was determined by the appearance of distant metastases and local relapse. The following clinical variables were analyzed as survival-affecting: age at the time of TURBT, sex, Eastern Cooperative Oncology Group PS, smoking history, Charlson comorbidity index (CCI), cT stage, lymph node metastasis, tumor size, presence of hydronephrosis, neutrophil-lymphocyte ratio (NLR), and treatment method. A high NLR (≥2.1) was defined according to receiver operating characteristic (ROC) curves. ROC curves were plotted for the NLR for the evaluation of OS and CSS rates. The NLR threshold was 2.1 for both OS and CSS, and the area under the curve was 0.618 and 0.604, respectively. The NLR sensitivity for OS and CSS was 46.6 and 44.1%, respectively, and the specificity was 78.4 and 80%, respectively (data not shown). Cox proportional hazards regression models were used for univariate and multivariate analyses. All statistical analyses were performed using JMP version 16.0.0 (SAS Institute Inc.). All tests were two-sided, and $P<0.05$ was considered statistically significant. This study was approved by the Research Ethics Committee of our hospital.

Results

Clinicopathological characteristics of MIBC. The characteristics for the 124 patients with MIBC are shown in Table I. Of the 124 patients, 56 (45%) were treated with nDT, of whom 28 out of 56 (50%) were treated with TURBT monotherapy and 28 (50%) with TURBT plus chemotherapy. Meanwhile, RC, the most common treatment, was performed in 47 out of 124 patients (38%) whereas TMT was performed in the remaining 21 (17%) patients. For TURBT plus chemotherapy, the median number of chemotherapy cycles was 4; 23 out of 28 patients (82%) were treated with a combination of gemcitabine and cisplatin, whereas the remaining 5 patients (18%) were treated with a gemcitabine and carboplatin combination due to renal dysfunction. There were no statistically significant differences in outcomes between the groups treated with TURBT monotherapy and TURBT plus chemotherapy (median OS: 562 vs. 738 days, P=0.274; median PFS: 349 vs. 402 days, P=0.768, respectively; log-rank test). The TMT group was treated with radiotherapy (median: 58 Gy) delivered to the bladder with concurrent multiple-agent radiosensitizing chemotherapy with cisplatin. The median age of patients treated with nDT was 77 years (69-81 years), which was significantly higher than that of patients treated with DT. In addition, the proportion of patients with poor PS, high CCI, and high NLR values was significantly higher in the nDT group compared to the DT group (P=0.003, P=0.044, and P=0.001, respectively). However, there were no significant differences in clinical stage or presence of lymph node metastasis between the two groups (Table I).

The choice of treatment varied significantly by age. Younger patients had the highest rate of RC, which steadily decreased with age. Conversely, the rate of bladder-sparing therapies such as TURBT and TMT increased with age (Fig. 1).

Table I. Clinicopathological characteristics of the 124 patients with muscle invasive bladder cancer.

Variables	All patients (n=124)	Definitive therapy (n=68)	Non-Definitive therapy (n=56)	P-value
Median age, years (IQR)	73 (68-80)	71 (66-77)	77 (69-81)	0.002[a,b]
Sex, n (%)				
Male	92 (74.2)	52 (76.5)	40 (71.4)	0.543[c]
Female	32 (25.8)	16 (23.5)	16 (28.6)	
ECOG performance status, n (%)				
0 or 1	108 (87.1)	65 (95.6)	43 (76.8)	0.003[b,d]
≥2	16 (12.9)	3 (4.4)	13 (23.2)	
Smoking history, n (%)				
Yes	78 (63.4)	46 (67.7)	32 (58.2)	0.347[c]
No	45 (36.6)	22 (32.3)	23 (41.8)	
Charlson comorbidity index, n (%)				
≤2	99 (79.8)	59 (86.8)	40 (71.4)	0.044[b,c]
≥3	25 (20.2)	9 (13.2)	16 (28.6)	
Presence of hydronephrosis, n (%)				
Yes	37 (29.8)	21 (30.9)	16 (28.6)	0.845[c]
No	87 (70.2)	47 (69.1)	40 (71.4)	
Median tumor size, mm (IQR)	35.0 (22.0-49.8)	33.5 (21.3-49.8)	35.0 (23.0-49.5)	0.833[a]
cT stage, n (%)				
cT2	43 (34.7)	23 (33.8)	20 (35.7)	0.950[d]
cT3	62 (50.0)	34 (50.0)	28 (50.0)	
cT4a	19 (15.3)	11 (16.2)	8 (14.3)	
Lymph node involvement, n (%)				
Positive	104 (83.9)	60 (88.2)	44 (78.6)	0.219[d]
Negative	20 (16.1)	8 (11.8)	12 (21.4)	
Tumor grade, n (%)				
High	115 (95.8)	63 (94.0)	52 (98.1)	0.382[d]
Low	5 (4.2)	4 (6.0)	1 (1.9)	
Median NLR (IQR)	2.54 (1.97-3.65)	2.24 (1.73-2.9)	3.19 (2.11-4.41)	0.001[a,b]
Treatment, n (%)				
Radical cystectomy	47 (37.9)	47 (69.1)	-	
Chemoradiotherapy	21 (16.9)	21 (30.9)	-	
Chemotherapy	28 (22.6)	-	28 (50.0)	
TURBT monotherapy	28 (22.6)	-	28 (50.0)	

Statistical analysis was performed using a [a]Mann-Whitney U test for continuous variables or a [c]χ^2 test and [d]Fisher's exact test for categorical variables. [b]Statistically significant (P<0.05). IQR, interquartile range; ECOG, Eastern Cooperative Oncology Group; NLR, neutrophil-to-lymphocyte ratio; cT, clinical T; TURBT, transurethral resection of bladder tumor.

Survival analysis. The median OS, CSS, and PFS times for patients treated with nDT were 605, 753, and 382 days, respectively. For those treated with DT, the median OS and CSS were not reached, and for PFS it was 2492 days. The 5-year OS, CSS, and PFS rates were 23, 33, and 15%, respectively, for patients treated with nDT, and 69, 74, and 61%, respectively, for those treated with DT. The Kaplan-Meier curves demonstrated that nDT is associated with significantly reduced OS, CSS, and PFS rates compared with DT (P<0.001) (Fig. 2).

Univariate and multivariate analysis. Univariate analysis revealed that female sex, a high PS (≥2), advanced cT stage (≥T3), high NLR (≥T2.1), and nDT were significantly associated with OS, CSS, and PFS. According to multivariate analysis, nDT was a significant poorer prognostic factor for OS (HR 2.91, 95% CI 1.47-5.77, P=0.002), CSS (HR 3.28, 95% CI 1.58-6.81, P<0.001), and PFS (HR 3.54, 95% CI 1.88-6.66, P<0.001). Additionally, an advanced cT stage (≥T3) was a significant poorer prognostic factor for OS (HR 4.89, 95% CI 2.27-10.5, P<0.001), CSS (HR 8.34, 95% CI 2.84-24.5, P<0.001), and PFS (HR 5.22, 95% CI 2.39-11.4, P<0.001) (Table II).

Overall survival analysis of cT stage. Kaplan-Meier curves for survival outcomes stratified according to cT stage are presented in Fig. 3. For cT2 cases, the median OS was not

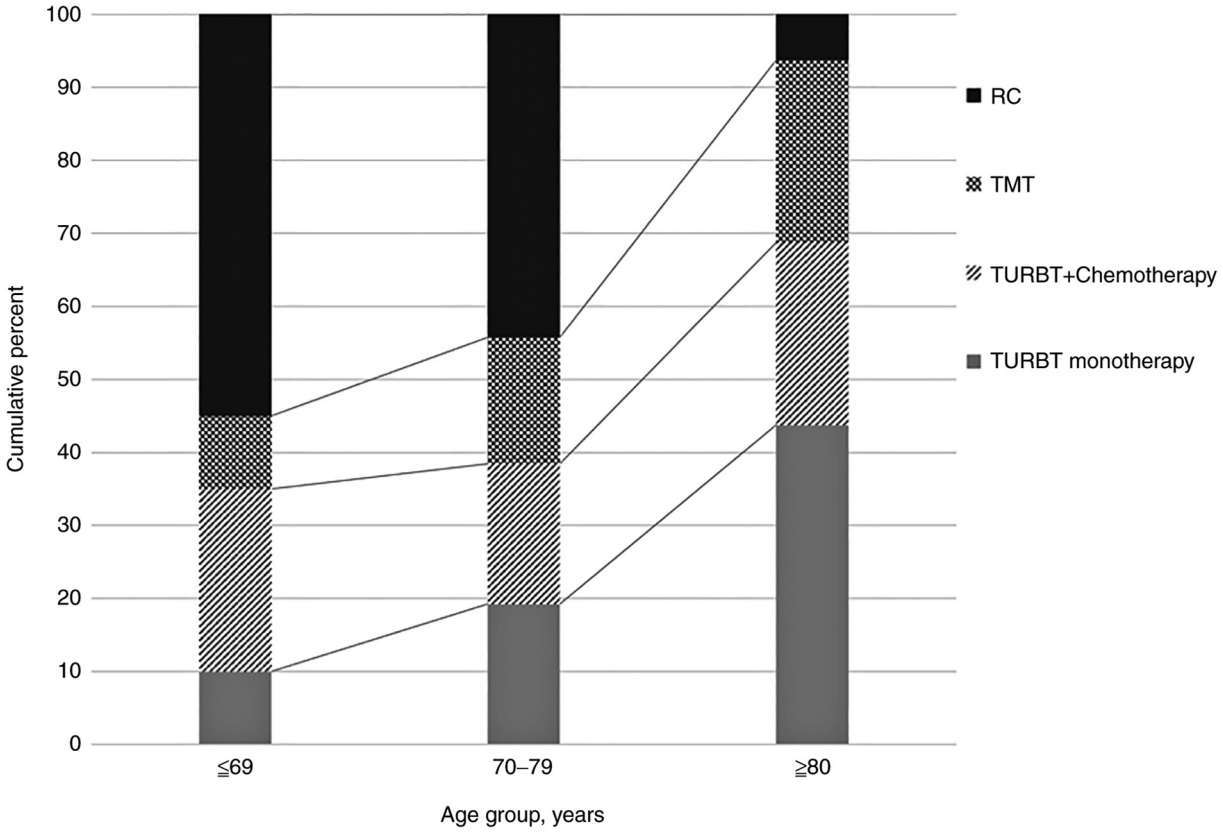

Figure 1. Age distribution of patients with muscle invasive bladder cancer receiving different primary treatments. TURBT, transurethral resection of bladder tumor; RC, radical cystectomy; TMT, trimodal therapy.

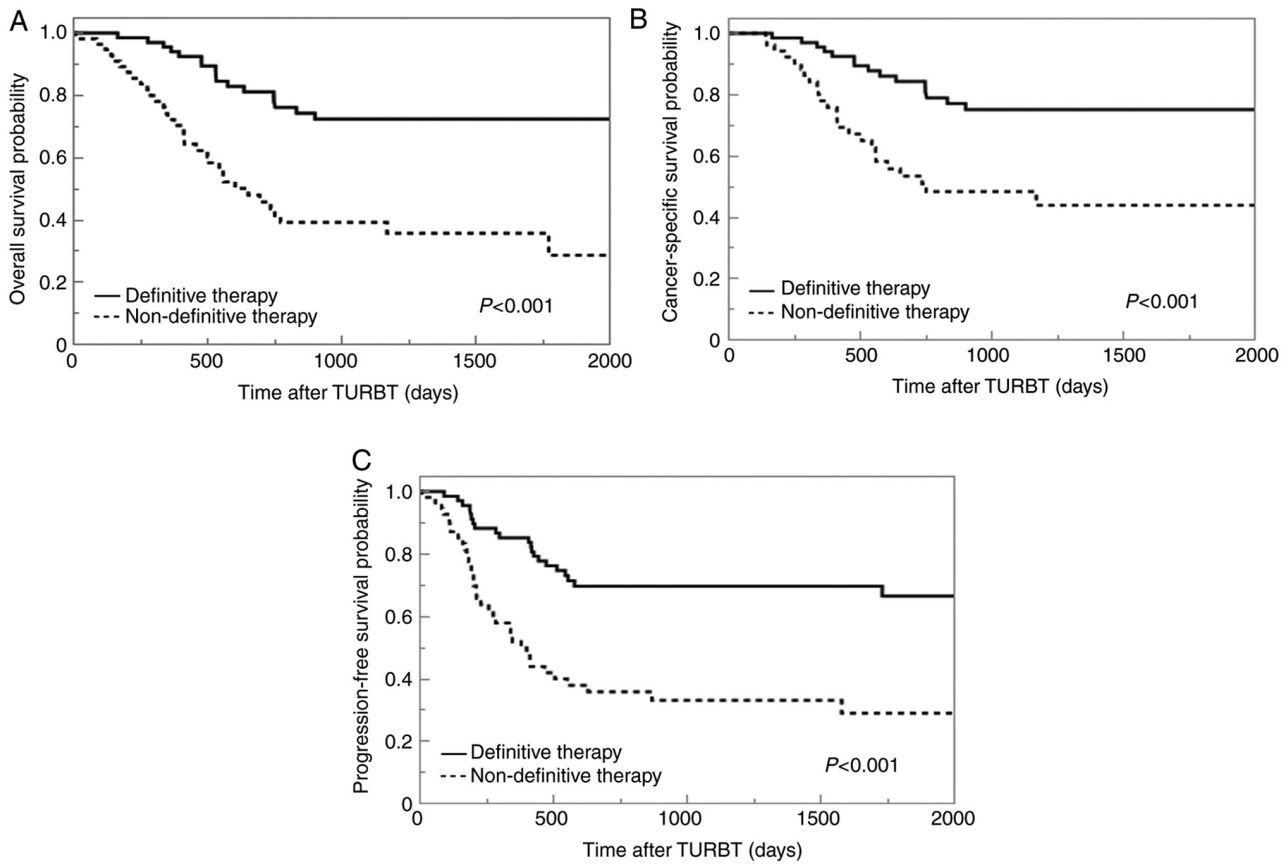

Figure 2. Survival analysis according to treatment methods for the 124 patients with muscle invasive bladder cancer. Kaplan-Meier curves for (A) overall survival, (B) cancer-specific survival and (C) progression-free survival. TURBT, transurethral resection of bladder tumor.

Table II. Univariate and multivariate analyses of clinical factors influencing PFS, CSS and OS in the 124 patients with muscle invasive bladder cancer.

	PFS				CSS				OS			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
Variable	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Age (continuous)	1.01 (0.98-1.05)	0.402	-	-	1.02 (0.98-1.06)	0.373	-	-	1.04 (1.00-1.08)	0.051	-	-
Sex (female vs. male)	2.46 (1.44-4.21)	<0.001[a]	-	-	2.14 (1.12-4.11)	0.022[a]	-	-	1.79 (0.99-3.24)	0.055	-	-
ECOG PS (≥2 vs. ≤1)	2.29 (1.15-4.55)	0.019[a]	-	-	2.55 (1.13-5.79)	0.025[a]	-	-	4.14 (2.19-7.82)	<0.001[a]	2.55 (1.30-5.04)	0.007[a]
CCI (≥3 vs. ≤2)	0.77 (0.38-1.57)	0.468	-	-	0.79 (0.33-1.89)	0.602	-	-	1.54 (0.82-2.89)	0.179	-	-
Clinical stage (≥cT3 vs. cT2)	4.48 (2.19-9.15)	<0.001[a]	5.22 (2.39-11.40)	<0.001[a]	7.08 (2.52-19.90)	<0.001[a]	8.34 (2.84-24.50)	<0.001[a]	3.62 (1.76-7.45)	<0.001[a]	4.89 (2.27-10.50)	<0.001[a]
LNI (positive vs. negative)	2.45 (1.33-4.50)	0.004[a]	-	-	2.05 (1.00-4.20)	0.051	-	-	1.74 (0.89-3.42)	0.105	-	-
NLR (≥2.1 vs. 2.0)	2.30 (1.26-4.22)	0.007[a]	-	-	2.83 (1.30-6.15)	0.009[a]	-	-	2.58 (1.32-5.03)	0.006[a]	-	-
Treatment (nDT vs. DT)	3.06 (1.79-5.24)	<0.001[a]	3.54 (1.88-6.66)	<0.001[a]	3.04 (1.60-5.79)	<0.001[a]	3.28 (1.58-6.81)	<0.001[a]	3.46 (1.93-6.19)	<0.001[a]	2.91 (1.47-5.77)	0.002[a]

[a]Statistically significant (P<0.05). PFS, progression-free survival; CSS, cancer-specific survival; OS, overall survival; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; PS, performance status; CCI, Charlson comorbidity index; cT, clinical T; LNI, lymph node involvement; NLR, neutrophil-to-lymphocyte ratio; nDT, non-definitive therapy; DT, definitive therapy.

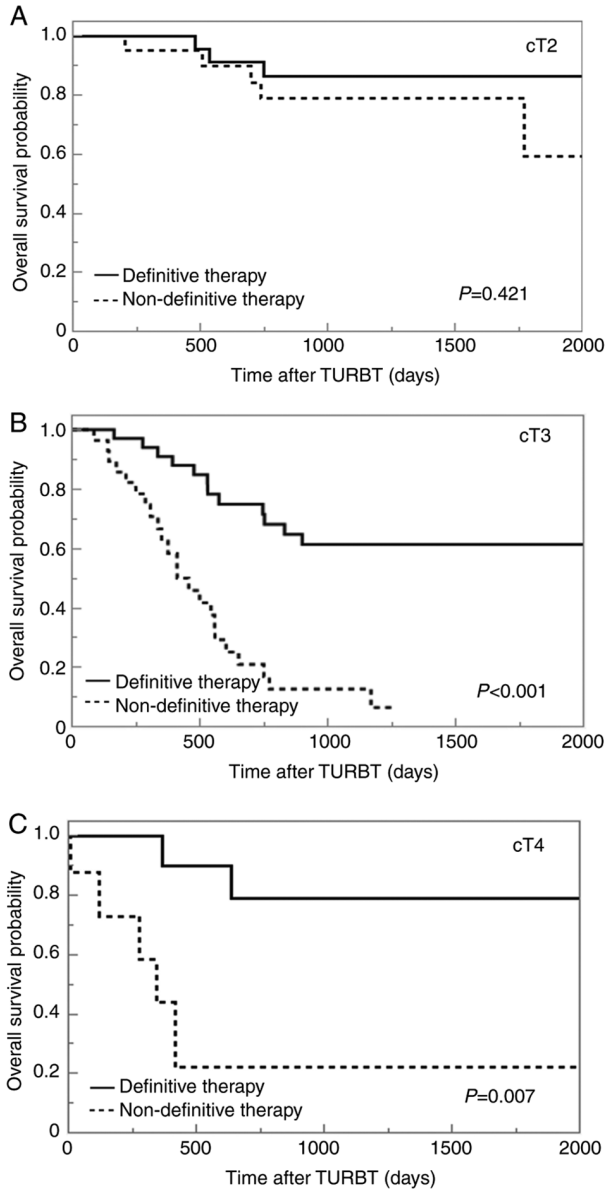

Figure 3. Overall survival analysis according to treatment methods for patients with muscle invasive bladder cancer stratified by clinical stage. Kaplan-Meier curves for (A) cT2, (B) cT3 and (C) cT4. cT, clinical T stage; TURBT, transurethral resection of bladder tumor.

significantly different between the two groups (not reached in either group, P=0.421), and that for cT3 and cT4a cases was significantly lower in the nDT group (not reached vs. 414 days, P<0.001 and not reached vs. 343 days, P=0.007, respectively) (Fig. 3).

Discussion

Generally, RC is the standard treatment for MIBC. However, it remains a high-risk procedure associated with high morbidity and high surgical mortality (8). Therefore, with population aging, there is an increasing number of cases in which MIBC is not adequately treated due to old age, poor PS, serious comorbidities such as cardiac dysfunction, or refusal to undergo RC due to health-related QOL concerns even in the absence of physical problems.

The choice of treatment for patients with MIBC varies widely. In a survey that included 28691 patients with MIBC in the United States, 52.5% of patients received active treatment such as RC or TMT. On the other hand, 25.9% of patients opted for observation or TURBT only. It was also reported that the proportion of patients opting for non-curative treatment increased with older age (9). The results of the present study were similar, with 54.8% of patients opting for aggressive treatment and 25.8% treated with TURBT only. Moreover, with increasing age, the proportion of patients who opted for aggressive treatment such as RC decreased significantly.

Patients who do not undergo RC are generally treated with TURBT, cisplatin-based chemotherapy, radiation therapy, or a combination of these. Nevertheless, only a limited number of patients respond to TURBT monotherapy or TURBT in combination with chemotherapy. Previous reports suggest that the ideal patient for TURBT monotherapy would be a cT2 patient with a tumor size of less than 3 cm, no hydronephrosis, no evidence of metastasis or adenocarcinoma, negative resection bed biopsies at initial TURBT or negative repeat TURBT, and no evidence of upper urinary tract cancer (5,10). Solsona *et al* (5) reported that, under these criteria, the outcomes of TURBT monotherapy were CSS rates of 81.9, 79.5, and 76.7% at 5, 10, and 15 years, respectively, and PFS rates with bladder preservation of 75.5, 64.9, and 57.8%, respectively. Meanwhile, TURBT plus chemotherapy may have been chosen due to concerns about the potential for short- and long-term adverse events affecting the QOL associated with radiation therapy. However, in a large retrospective study by Audenet *et al* (6), the OS percentages for TURBT plus chemotherapy at 2 and 5 years were only 49 and 32.9% for all patients and 52.6 and 36.2% for cT2 patients, respectively. In addition, they reported that patients who underwent TURBT plus chemotherapy had a significantly shorter OS than those who underwent RC (median: 23.9 months vs. 48.1 months) (6). In the current study, there was no significant difference in the survival outcomes of cT2 patients treated with TURBT monotherapy or TURBT plus chemotherapy and those treated with DT, which is similar to previous reports. On the other hand, these data indicate that there is a possibility of long-term survival for some patients, but the routine use of these therapies is not recommended.

Currently, TMT combining TURBT, chemotherapy with radiosensitizers, and radiation therapy is recommended as an effective alternative for patients who are unable or unwilling to undergo RC (3,4). Seisen *et al* (11) reported a comparative study of RC and TMT for MIBC in a large scale using the National Cancer Data Base. The survey was conducted on 1257 patients (9.8%) treated with TMT and 11586 patients (90.2%) treated with RC. TMT was associated with a significantly lower long-term OS at 25 months of follow-up or later (hazard ratio: 1.37, 95% CI 1.16-1.59) according to inverse probability of treatment weighting-adjusted Cox regression analysis with a time-varying covariate. However, the difference in treatment effectiveness between TMT and RC decreases with age (P=0.004). Therefore, the survival benefits of RC should be weighed against the risks of surgery, especially in older patients (11). On the other hand, a large systematic review reported that the OS and disease-specific survival (DSS) of RC and TMT were comparable. The

mean 10-year OS for the 1536 patients who received TMT was 30.9%, compared with 35.1% for the 5163 RC-treated patients (P=0.32). Meanwhile, the average 10-year DSS was 50.9% for the 1,205 patients who received TMT and 57.8% for the 4,856 RC-treated patients (P=0.26) (12). Overall, the outcomes of bladder preservation with TMT are acceptable and can be a reasonable treatment option in appropriately selected patients. Furthermore, TMT was reported to have a better post-treatment QOL than RC and may be a suitable treatment for patients who wish to receive bladder-sparing therapy (13). In this study and previous reports, the proportion of patients opting for non-curative treatment increased with older age; therefore, it may be necessary to recommend TMT for the elderly, which offers both survival benefit and QOL (9).

Patients diagnosed with bladder cancer had a significant decline in physical, mental, and social health-related QOL compared to healthy individuals, regardless of the progression degree. This decline was particularly pronounced in patients with MIBC. Further, patients who underwent RC had a significant decline in health-related QOL compared to patients who did not undergo RC (14). However, in another recent review, QOL after orthotopic urinary diversion (neobladder) was significantly improved compared to QOL after ileal conduit (15). Urinary incontinence is a complication of neobladder; daytime continence improved by 92% during more than 12 to 18 months post-operation, while nighttime continence improved from 28% on the first 3 months after the procedure to 51% during more than 18 to 36 months post-operation (16). For patients who value health-related QOL, RC with orthotopic urinary diversion or TMT may provide both cure and maintenance of QOL.

This study showed that nDT had a significantly poorer prognosis than DT not only in terms of OS but also in terms of CSS (HR 3.28, 95% CI 1.58-6.81). Moreover, cT3 and cT4a patients had an extremely poor prognosis, with a median survival of about 313-414 days due to inadequate treatment. On the other hand, although a high CCI (≥3) and older age were not poor prognostic factors in this study, Maffezzini *et al* (17) reported that RC worsened the prognosis in patients older than 70 years and with a high CCI (>3). In view of this, the survival benefits, and the disadvantages of treatment-related complications associated with DT, should be carefully considered when the patients with reduced physical function choose DT.

The limitations of this study are that it was a single-center, retrospective study with a small patient sample, and the possibility of selection bias cannot be excluded. Therefore, in future, further external validation and a large-scale multicenter trial is necessary to confirm and reinforce this study result. However, to the best of our knowledge, this is the first study on the clinical outcomes of nDT for MIBC in Japan, and the results may be meaningful to provide valuable data for adequate patient informed consent in future treatment selection.

In conclusions, nDT for patients with MIBC is associated with a high risk of cancer-related death, even in the elderly with serious comorbidities. The most appropriate treatment method should be discussed with the patient after providing sufficient information on the risks and benefits of each one, instead of simply choosing the easy route of nDT.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

KN, HK, KoU, SS and TI designed the study and revised the manuscript. NO, TH, KC, KE, KeU and MN contributed to the collection, analysis and interpretation of the data. HK and SS confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Research Ethics Committee of Kurume University (approval no. 21244; Fukuoka, Japan). The requirement for informed consent was waived due to the retrospective nature of the study using medical records only. The research content was available publicly on the website of the Research Ethics Committee of Kurume University, which ensured opportunities for participants to opt out of the research without any disadvantage.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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