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Efficacy of curative radiotherapy for the treatment of elderly patients with muscle-invasive bladder cancer: a systematic review

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Abstract

Introduction In recent years, a chemoradiotherapy has been developed as a radical treatment for stage II–III muscle-invasive bladder cancer (MIBC) that can preserve the bladder for patients who cannot tolerate radical cystectomy (RC) or who do not wish to undergo RC. However, most of the studies were conducted on younger patients with MIBC, and it is not clear if it is effective for elderly patients with MIBC. In this study, we reviewed the effects and adverse events after radical radiotherapy in elderly patients with MIBC to determine if radiotherapy has been/can be equally recommended for younger patients with MIBC.

Methods We extracted full research reports in English comparing treatment results between different age groups and reports targeting elderly patients with MIBC. A keyword search of the PubMed database was conducted in the decade ending on December 8, 2021. Studies reporting post-treatment overall survival (OS), relapse-free/progression-free/disease-free survival (RFS/PFS/DFS), disease-specific/cancer-specific survival (DSS/CSS), and complete response (CR) rate, adverse events (AEs), and quality of life (QOL) in elderly patients with MIBC were searched. Thirty-nine full articles, including those with comparisons by age group or treatments for elderly patients, were retrieved.

Results OS was significant or tended to be poor in elderly patients. There were no differences in PFS and CSS between younger and elderly patients. No differences in the rates of grade 3 morbidities between younger and elderly patients were also observed.

Conclusion The lack of a difference in PFS/CSS and toxicities between elderly and younger MIBC patients indicated that curative chemoradiotherapy is effective for not only younger but also elderly patients. With advances in treatment, further prospective studies are needed to optimize the management of MIBC in elderly patients.

Keywords Muscle invasive bladder cancer, Radiotherapy, Elderly patients

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Introduction

The standard treatment for muscle-invasive bladder cancer (MIBC) is radical cystectomy (RC) with pelvic lymphadenectomy and urinary diversion. However, besides being highly invasive [1], RC is a treatment that greatly impairs quality of life (QOL) [2]. Therefore, in recent years, a chemoradiotherapy has been developed as a radical treatment for stage II–III MIBC that can preserve the bladder for patients who cannot tolerate RC or who do not wish to undergo RC. Particularly, the developed treatment is expected to be less invasive and comparable to surgery for elderly patients with MIBC [3]. On the other hand, although there are ongoing trials evaluating various bladder-preserving strategies, a growing body of literature supports the use of trimodality therapy (TMT) in which radiotherapy and chemotherapy are combined after transurethral bladder tumor resection [3, 4]. This method has been shown in multiple clinical trials to improve radiotherapy outcomes by performing maximum transurethral resection of bladder tumors and concurrently administering chemotherapy with radiotherapy. However, because most of the TMT studies were conducted on younger patients with MIBC, it is not clear if it is effective for elderly patients with MIBC. In this study, we reviewed the survival and adverse events (AEs) after radical radiotherapy in elderly patients with MIBC by comparing them with those of younger patients to determine if radiotherapy has been/can be equally recommended for younger patients with MIBC.

Evidence acquisition

Study concept

A systematic review was conducted to consider the following predefined research question:

1) Is radiotherapy equally recommended for elderly and younger patients with MIBC?
2) Are there significant differences in the rates of overall survival (OS), relapse-free/progression-free/disease-free survival (RFS/PFS/DFS), disease-specific/cancer-specific survival (DSS/CSS), and complete response (CR) between elderly and younger patients with MIBC?
3) Are the rates of AEs higher after definitive treatment in elderly patients with MIBC than in younger patients with MIBC?
4) What is the QOL and cost-effectiveness after definitive treatment for elderly patients with MIBC?

Information sources and search method

A keyword search of the PubMed database was conducted by an experienced information specialist for literature in the decade ending on December 8, 2021. The search strings in Table 1 were used. Other important unpublished conference reports and articles found in the references section of the searched articles were also identified by a manual search for review. Articles were extracted from the search results for #12, #15, and #17.

Eligibility criteria

Only full articles in English were extracted; conference abstracts, case studies, and duplicate publications were excluded. We did not exclude patients even if the number of patients was small. Because there were no randomized controlled trials in the literature extraction, we extracted research reports comparing treatment results between different age groups and reports targeting elderly patients with MIBC. Therefore, age stratification was an essential factor in selecting studies for review. Studies reporting post-treatment OS, RFS/PFS/DFS, DSS/CSS, CR rate, AEs, and QOL for elderly patients with MIBC were included. Studies that excluded treatments for elderly patients with MIBC were excluded. Other studies with poor relevance to elderly patients with MIBC, such as review articles on urological cancer, palliative treatment, treatment for metastasis, radiotherapy before or after RC, and radiotherapy for recurrent tumors, were also excluded.

Article selection

A two-step screening process was used to select the articles. In the first step, one reviewer screened the title and abstract to determine whether the article met the criteria and excluded articles that did not. Three independent reviewers performed a second screening of the full-text manuscripts. If there was disagreement about inclusion of a study, the four reviewers (including the first screening reviewer) tried to reach a consensus on inclusion or exclusion through discussion.

Data collection

Each of the three reviewers extracted data after perusing the full text. Treatment results (OS, RFS/PFS/DFS, DSS/CSS, CR rate) and the significant differences between younger and elderly people, AEs, and QOL were extracted. The primary aim was to compare the treatment results of various younger age groups with those of patients aged ≥ 70 years old. The stratification of elderly and younger patients varied among the selected articles (mainly ≥ 70 or ≥ 75 years old) but many studies defined elderly patients as ≥ 70 years old. In addition,

Table 1 Search strings

#1	"Urinary Bladder Neoplasms/therapy"[Majr]
#2	"Neoplasms/radiotherapy"[Mesh] OR "Radiotherapy"[Mesh]
#3	Vulnerable Populations"[Mesh] OR ("Aged"[Mesh] AND (vulnerable[TI] OR aged[TI] OR elderly[TI] OR old[TI] OR geriatric*[TI])) OR "Geriatric Assessment"[Mesh]
#4	#1 AND #2 AND #3
#5	(Bladder cancer*[TIAB] OR Bladder carcinoma*[TIAB]) AND (aged[TIAB] OR elderly[TIAB] OR old[TIAB] OR geriatric*[TIAB]) AND (radiation*[TIAB] OR radiotherap*[TIAB] OR irradiation*[TIAB])
#6	#4 OR #5
#7	#6 AND (JAPANESE[LA] OR ENGLISH[LA])
#8	#7 AND ("2011/1"[Date - Publication] : "3000"[Date - Publication])
#9	#8 AND ("Meta-Analysis"[PT] OR "Meta-Analysis as Topic"[Mesh] OR "meta-analysis"[TIAB])
#10	#8 AND ("Cochrane Database Syst Rev"[TA] OR "Systematic Review"[PT] OR "Systematic Reviews as Topic"[Mesh] OR "systematic review"[TIAB])
#11	#8 AND ("Practice Guideline"[PT] OR "Practice Guidelines as Topic"[Mesh] OR "Consensus"[Mesh] OR "Consensus Development Conferences as Topic"[Mesh] OR "Consensus Development Conference"[PT] OR guideline*[TI] OR consensus[TI])
#12	#9 OR #10 OR #11
#13	#8 AND ("Randomized Controlled Trial"[PT] OR "Randomized Controlled Trials as Topic"[Mesh] OR (random*[TIAB] NOT medline[SB]))
#14	#8 AND ("Clinical Trial"[PT] OR "Clinical Trials as Topic"[Mesh] OR "Observational Study"[PT] OR "Observational Studies as Topic"[Mesh] OR ((clinical trial*[TIAB] OR case control*[TIAB] OR case comparison*[TIAB]) NOT medline[SB]))
#15	(#13 OR #14) NOT #12
#16	#8 AND ("Epidemiologic Methods"[Mesh] OR "Comparative Study"[PT] OR "Multicenter Study"[PT] OR ((cohort*[TIAB] OR comparative stud*[TIAB] OR follow-up stud*[TIAB] OR prospective stud*[TIAB] OR Retrospective study*[TIAB]) NOT medline[SB]))
#17	#16 NOT (#12 OR #15)

since no reports have specified an upper age limit, we also did not set one. Similarly some reports included patients < 50 years old, so no lower age limit was set for the younger group.

Statistical analysis

Because each study's subjects were heterogeneous, we did not combine the data from each study. Instead, we examined each treatment result within each study to determine if the results showed statistically significant differences between younger and elderly patients with MIBC. If the target was only elderly patients with MIBC or there was no comparison of treatment outcomes between elderly and younger patients, we extracted the treatment outcomes of the elderly patients with MIBC to compare them with those of the other selected studies.

Evidence synthesis

Figure 1 shows how the articles were screened. As a result of first reviewer's search using #12, 15, and 17, 89 articles were extracted for evaluation. The first screening of titles and abstracts identified 89 articles and excluded 32 articles in PubMed that clearly differed from the predefined criteria. The three reviewer's second screening for eligibility assessed full-text articles. Fifty-seven articles were reviewed, and 18 full articles were excluded because they did not address the study questions. Finally, 39 full articles, including those with comparisons by age group or treatments for elderly patients, were retrieved, and 17 articles contained information about the study questions presented in this article [5–21]. Ten articles reported OS results, three reported RFS/PFS/DFS results, four reported DSS/CSS results, two reported initial responses, two reported bladder-preservation results and one reported rate toxicity. None of the studies assessed cost-effectiveness and QOL after radiotherapy.

Studies that compared elderly and younger people

OS

Estimates of OS for each age group are shown in Table 2. Of the five studies that investigated the effect of age on OS mainly treated by chemoradiotherapy, one reported that OS was not significantly different between younger and elderly ($P = 0.10$) [5], two reported that it was significantly worse in elderly patients [6, 7], and two reported [8, 9] that it tended to be poor in elderly patients. In a study by Mak et al. [6] involving 468 patients enrolled in five radiation therapy oncology trials, multivariate analysis showed that the prognosis was significantly worse in elderly patients [Hazard ratio (HR):1.02, range: 1.01–1.04, $P = 0.0056$]. Similarly, Lee et al. [7] conducted a study in 70 patients treated with transurethral resection of bladder tumors before combined chemoradiotherapy, and their multivariate analysis showed significantly worse outcomes in elderly patients (HR: 1.064, range: 1.023–1.107, $P = 0.002$). On the other hand, in a study

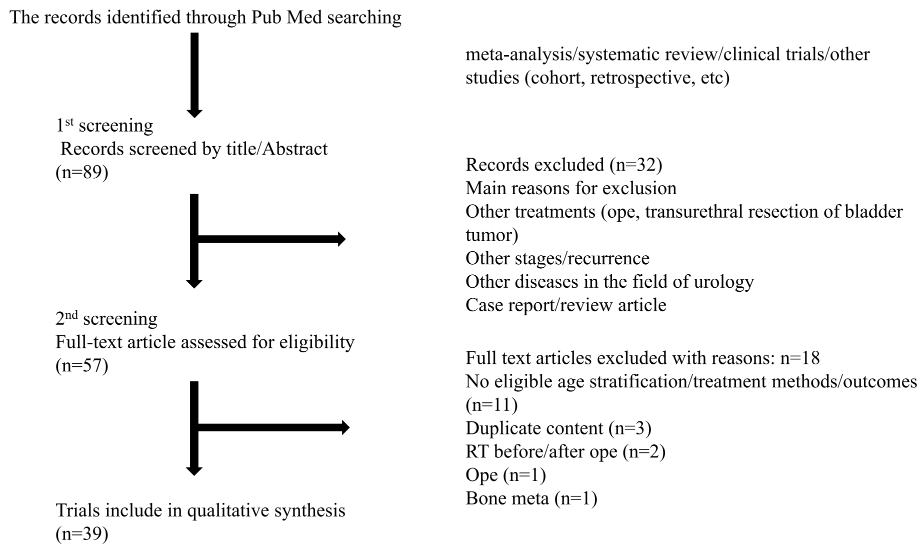

Fig. 1 Article selection for the systematic review

by Christodoulou et al. [8], the 3-year OS was 73.1% for younger patients and 63.3% for elderly patients, but the difference did not reach the significant level (HR: 1.04, range: 1.00–1.08, $P=0.068$). Similar results were obtained in a report of radiotherapy combined with arterial injection therapy in Japan [Odds ratio (OR): 1.259, $P=0.0644$] [9]. On the other hand, in five other studies that predominantly performed radiotherapy alone, three showed poorer prognosis in the elderly [70–79 years, relative risk (RR): 1.31, range: 1.11–1.53; > 80 years old, RR: 1.49, range: 1.22–1.81 [10]; 61–74 years, HR: 1.3, range: 1.1–1.5; > 75 years, HR: 2.0, range: 1.7–2.4 [11]; $P=0.0002$] [12], whereas the remaining two studies found no significant difference between younger and elderly patients ($P=0.52$) [13], ($P=$ no data) [14].

PFS/RFS/DFS

PFS was defined as the length of time during and after the treatment of a disease in which the disease does not worsen. RFS/DFS was defined as the length of time after primary cancer treatment ends during which the patient survives without any signs or symptoms of that cancer. Since both indicate any death or recurrence or progression after treatment, PFS, DFS, and RFS were extracted as similar indicators.

Estimates of *RFS/PFS/DFS* for each age group are shown in Table 3. Of the two studies relevant to PFS after chemoradiotherapy, no effect of age on PFS was observed (HR: 1.00, $P=0.989$) [8], (OR: 1.128, $P=0.1426$) [9]. Similarly, one study relevant to RFS performed radiotherapy alone, but no effect of age on RFS was observed ($P=$ no data) [14]. However, in reports by Azuma et al. [9] and Canyilmaz et al. [14], direct comparisons between younger and elderly patients were not possible, but elderly patients were stratified by age and comparisons were made between the age groups within the elderly patients group.

DSS/CSS

Estimates of DSS/CSS for each age group are shown in Table 4. Of the two studies, there was no significant difference in the effect of age on DSS/CSS after chemoradiotherapy between younger and elderly patients [6, 8]. Mak et al. found that the 10-year DSS rate was 64% in patients < 75 years old and 65% in patients ≥ 75 years ($P=0.84$) [6]. Christodoulou et al. reported that the 3-year DSS rate was 79.0% in patients < 75 years old and 77.8% in patients ≥ 75 years old [HR: 1.00, range: 0.95–1.04, $P=0.916$] [8]. Among the two studies that performed radiotherapy alone, one study found that the 5-year CSS rate was 26% in patients < 75 years old and 19% in those ≥ 75 years old, and there was a significantly poor prognosis in patients aged ≥ 75 years old ($P=0.010$) [12]. In contrast, another study found no significant difference in the effect of age on CSS ($P=$ no data) [14].

CR rate

Estimates of the CR rate for each age group are shown in Table 5. Three studies reported the results of initial local effects after treatment in younger and elderly patients. Of these, in the two studies that performed chemoradiotherapy, CR rates were not affected by age in either study ($P=0.78$) [6], ($P=$ No data) [9]. On the other hand, in a study that performed radiotherapy alone, the CR rate was low in patients aged ≥ 75 years old ($P=0.0007$) [12].

Table 2 Reported overall survival rate per age and per study

Author	N	Treatment	Measure unit	Age									p-value
				<50	50-54	55-59	60-64	65-69	70-74	75-79	80-84	≥85	
Mak [6]	468	CRT	Survival time	Better (*N*=388)						Worse (*N*=80)			0.0056
Hayter [10]	1372	RT	Survival time	0.71 (0.47-1.09) (*N*=51)	0.82 (0.64-1.06) (*N*=150)		1.0 (*N*=404)		1.31 (1.11-1.53) (*N*=549)		1.49 (1.22-1.81) (*N*=218)		No data
Goossens-Laan [11]	2445	RT/RC	Survival time	1.0 (*N*=444)			1.3 (1.1-1.5) (*N*=1062)			2.0 (1.7-2.4) (*N*=939)			No data
Fosså [12]	317	RT265/CRT 52	5y	T2-T3a: 46% (*N*=98)						T2-T3a: 20% (*N*=37)			0.0002
				T3b-T4: Unknown (*N*=119)						T3b-T4: Unknown (*N*=54)			NS
Christodoulou [8]	167	CRT	3y	73.1% (*N*=106)						63.3% (*N*=61)			0.068
Manig [5]	42	RT10/CRT 32	3y	58% (*N*=26)						79% (*N*=16)			0.10
Lee [7]	70	CRT	Survival time	Better					Worse				0.002
Janssen [13]	29	RT:16/CRT13	3y	39% (*N*=15)					*Cut-off; 83 years		48% (*N*=14)		0.52
Canyilmaz [14]	188	RT	MST/3/5/10y	No data					Similar (N:No data)		Similar (N:No data)		NS
Azuma [9]	89	OMC-CRT	5/10y	No data					Similar (Continuous)				0.0644

CRT chemoradiotherapy, *RT* radiotherapy, *OMC* Osaka Medical College, *y* year, *MST* median survival time, *NS* not significant

Table 3 Reported progression/relapse/disease-free survival rate per age and per study

Author	N	Treatment	Measure unit	Age									p-value
				<50	50-54	55-59	60-64	65-69	70-74	75-79	80-84	≥85	
Christodoulou [8]	167	CRT	3y	57.0% (*N*=106)						59.7% (*N*=61)			0.989
Canyilmaz [14]	188	RT	MST/3/5/10y	No data					Similar (N:No data)		Similar (N:No data)		NS
Azuma [9]	89	OMC-CRT	5/10y	No data					Similar (Continuous)				0.1426

CRT chemoradiotherapy, *RT* radiotherapy, *OMC* Osaka Medical College, *y* year, *NS* not significant

Table 4 Reported disease/cancer-specific survival rate per age and per study

Author	N	Treatment	Measure unit	Age									p-value
				<50	50-54	55-59	60-64	65-69	70-74	75-79	80-84	≥85	
Mak [6]	468	CRT	5y	71% (*N*=388)						70% (*N*=80)			0.84
			10y	64% (*N*=388)						65% (*N*=80)			
Fosså [12]	317	RT265/CRT 52	5y	26% (*N*=217)						19% (*N*=91)			0.010
Christodoulou [8]	167	CRT	3y	79.0% (*N*=106)						77.8% (*N*=61)			0.916
Canyilmaz [14]	188	RT	MST/3/5/10y	No data					Similar (N:No data)		Similar (N:No data)		NS

CRT chemoradiotherapy, *RT* radiotherapy, *y* year, *MST* median survival time, *NS* not significant

Table 5 Reported initial response per age and per study

Author	N	Treatment	Measure unit	Age									p-value
				<50	50-54	55-59	60-64	65-69	70-74	75-79	80-84	≥85	
Mak [6]	468	CRT	Overall	72% (*N*=388)						73% (*N*=80)			0.78
Fosså [12]	317	RT265/CRT 52	2-4 months	Better (*N*=217)						Worse (*N*=91)			0.0007
Azuma [9]	89	OMC-CRT	3 months	No Data					Similar				NS

CRT chemoradiotherapy, *RT* radiotherapy, *OMC* Osaka Medical College, *NS* not significant

Bladder-preserving-rate

Estimates of the bladder-preserving-rate for each age group are shown in Table 6. The 5-year bladder-preserving-rates after chemoradiotherapy were not significantly different between the younger (81%) and elderly patients (76%) ($P=0.55$) [6], but the bladder-preserving survival rate, including death as an event, was poor in the patients ≥ 80 years old ($P=$No data) [10].

AEs

Estimates of the AEs for each age group are shown in Table 7. In a study comparing younger and elderly patients with AEs as endpoints, the rates of grade-3 gastrointestinal (GI) and genitourinary (GU) AEs after chemoradiotherapy were 1.3% and 2.6%, respectively, in patients < 75 years old. In contrast, neither grade-3 GI nor GU AEs were observed in patients aged ≥ 75 years old [8]. In a study by Efstathiou et al., which analyzed multiple radiation therapy oncology group studies, the rate of grade-3 late AEs was 5.7% (GU) and 1.9% (GI), but no difference in the rates between the patients < 65 years old and those ≥ 65 years old ($P=0.88$) [15].

QOL and cost effectiveness

There were no available data in the selected articles.

Studies targeting the elderly only

Treatment outcome, Geriatric-8 (G8) score as the treatment index

The 3-year OS rate was 63.3% [95% confidence interval (CI): 47.6%–75.5%] in patients with MIBC and stage II–IV (92% for stage II–III) aged ≥ 75 years old (median: 78 years, range: 75–89 years) who received concomitant gemcitabine and radiotherapy after transurethral resection as TMT [8]. A retrospective analysis mainly in elderly patients (median: 80 years, range: 48–91 years) comparing radiotherapy with concurrent chemoradiotherapy combined with cisplatin or vinorelbine versus radiotherapy alone showed that the 3-year survival rates were 64.3% in the cisplatin group, 42.3% in the vinorelbine group, and 0% in the radiotherapy alone group; additionally, the 3-year CSS rates for primary disease were 71.4%, 61.5%, and 16.7%, respectively, in those three groups [16]. Similarly, in a retrospective analysis of T2-3N0M0 patients with MIBC aged ≥ 70 years old (median: 79 years; range: 72–88 years) who received TMT in combination with gemcitabine or cisplatin and 50 Gy in 20 fractions delivered via intensity-modulated radiation therapy (IMRT), the 3-year OS rate was 61%, and disease-free and functioning bladder outcomes occurred in 75% of the surviving cases [17]. In Japan, an analysis of 89 patients aged 70 years (median: 77 years, range: 70–91 years) who received TMT with the Osaka Medical College regimen, which is balloon-occluded arterial infusion of cisplatin/gemcitabine concomitantly with hemodialysis and concurrent irradiation, showed favorable 5-year OS and PFS rates of 88.4% and 87.2% [9]. Wujanto et al. reported that in patients with MIBC aged ≥ 65 years old (median: 77 years, range: 65–95 years), 21 (47%) of 45 patients received concomitant chemotherapy; the 5-year OS and RFS were 44% and 49%, respectively [18]. In that study, only one (2%) patient had a grade-3 acute diarrhea, and one (2%) patient had a late cystitis, but treatment interruption was required in 24% of the patients with or without concomitant chemotherapy. Patients who had poor performance status (PS) or low geriatric assessment scores, which are advocated by the International Society of Geriatric Oncology group, had poor prognoses. Similarly, multiple retrospective analyses of MIBC in the elderly showed significantly poor OS in patients with poor PS ($P=0.026$) (median: 69 years, range: 49–92 years) [7] or poor Karnofsky PS ($P\leq0.001$) (mean: 77 years), ($P=0.026$) (median: 83 years, range: ≥ 80–91 years) [5, 13]. Regarding the G8 score, 16 patients aged ≥ 75 years old (median: 83 years, range: 75–91 years) who received curative radiotherapy, including radiotherapy alone and radiotherapy combined with arterial infusion chemotherapy were retrospectively analyzed [19]. The median G8 score among the 10 patients who received radiotherapy alone was 10 (range: 9–11), compared with 13 (range: 12–15) for those who received combined arterial therapy. In that study, the OS and bladder-preservation rates tended to be higher in the combined arterial injection therapy group ($P=0.0614$) ($P=0.0713$), G8 was shown to be one tool for treatment selection, and combined arterial injection chemotherapy

Table 6 Reported bladder preservation per age and per study

Author	N	Treatment	Measure unit	Age									p-value
				<50	50-54	55-59	60-64	65-69	70-74	75-79	80-84	≥85	
Mak [6]	468	CRT	5y-BI	81% (*N*=388)						76% (*N*=80)			0.55
Hayter [10]	1372	RT	5y-BP	0.97 (0.48-1.97) (*N*=51)	1.28 (0.83-1.97) (*N*=150)		1.0 (*N*=404)		0.50 (0.34-0.74) (*N*=549)		0.15 (0.06-0.38) (*N*=218)		No data
			5y-BIS	0.80 (0.54-1.18) (*N*=51)	0.96 (0.76-1.22) (*N*=150)		1.0 (*N*=404)		1.12 (0.96-1.31) (*N*=549)		1.24 (1.02-1.50) (*N*=218)		No data

CRT chemoradiotherapy, *RT* radiotherapy, *y* year, *BI* blader intact, *BP* bladder preservation, *BIS* bladder intact survival

Table 7 Reported rate toxicity per age and per study

Author	N	Treatment	Measure unit	Age									p-value
				<50	50-54	55-59	60-64	65-69	70-74	75-79	80-84	≥85	
Christodoulou [8]	167	CRT	1y Grade 3	GU: 2.6% (*N*=76) GI: 1.3% (*N*=77)						GU: 0% (*N*=32) GI: 0% (*N*=31)			NS

CRT chemoradiotherapy, *GU* genitourinary, *GI* gastrointestinal, *y* year, *NS* not significant

was shown to be a useful choice for elderly patients with MIBC with a G8 score ≥ 12.

Comparison of the results and AEs for different treatment methods

An analysis of 9270 cases of T2–4 bladder cancer from the Surveillance, Epidemiology, and End Results) database for patients aged ≥ 80 years showed that the OS of those treated with chemoradiotherapy was comparable to that of the patients treated by surgery alone and that chemoradiotherapy was better than radiotherapy alone or chemotherapy alone [20]. Concerning irradiation techniques, in a study that used three-dimensional conformal radiotherapy or IMRT with a total dose of 55–60 Gy for T2-4N0-1M0 MIBC in patients median age 80 years (range: 41–95 years) who were unsuitable for surgery and chemotherapy, the rate of acute urinary-tract disorders of grade ≥ 3 was 22% with 3D conformal radiotherapy versus only 2% with IMRT ($P = 0.02$), although there was no significant difference in the OS rates among the treatment methods [21]. Similarly, the late GI AE rate was 20% with 3D conformal radiotherapy versus 5% with IMRT ($P = 0.05$) [21].

Discussion

Treatment approaches for nonmetastatic MIBC, including surgery, differ between younger and elderly patients. The risk of treatment-induced complications and reduction in life expectancy due to deterioration of the general condition of elderly patients are the main reasons why aggressive therapeutic approaches are not applied to this age group. However, a systematic literature review raises doubts about the justification of weakening treatment in elderly patients. In particular, chemoradiotherapy have improved, and it is now possible to treat elderly patients with fewer complications. Therefore, our review needed to determine if treatment methods, including radiotherapy, for elderly patients with MIBC, could be recommended in the same treatment strategy as younger patients with MIBC. Our systematic review examined the outcomes of elderly patients with MIBC who received definitive therapy and compared them with those of younger patients in an overview of reported outcomes for elderly patients receiving curative therapy for nonmetastatic MIBC.

The OS rate was poorer in elderly patients than in younger patients [6, 7, 12]. Shorter life expectancy may be a contributing factor, but the OS rates reported across studies were heterogeneous, suggesting that multiple factors are involved. The complications, medical histories, health statuses, and nutritional statuses of elderly patients determine life expectancy, but few articles have reported these details. It is difficult to accurately compare OS rates because the general condition of each elderly patient is different and treatment techniques and regimens vary significantly between studies. Future studies should take into account these elderly-specific factors that affect OS.

In contrast, differences in PFS/RFS and DSS/CSS were not observed between younger and elderly patients [6, 8, 9, 12, 14]. Therefore, treatment methods that include radiotherapy appear to be effective in elderly and younger patients. However, in these comparative studies, the cutoff values for defining the elderly varied, and there was a tendency for the treatment results to differ depending on the cutoff values. Many reports in this systematic review used an age of 70 years to distinguish between elderly and younger patients [7, 9, 10, 14]. Given the aging population and age at diagnosis of MIBC, it seems reasonable to use age 70 as the cutoff for defining elderly patients. However, age stratification differed in some articles selected for this systematic review. Some articles that evaluated treatment methods that included radiotherapy defined elderly patients as ≥ 75 years old [5, 6, 8, 11, 12], reflecting the inevitable inclusion of elderly patients. Furthermore, super-aging societies, such as Japan, are concerned that age bias will be significant when comparing results with those of other countries with different demographics.

The preferable survival results in this review article were mainly associated with TMT with concurrent chemotherapy [5–8, 12, 13]; therefore, chemotherapy tolerability is required. Elderly patients are more likely to have complications and are prone to deterioration of general condition than younger patients. Furthermore, treatment-related AEs in elderly patients are more likely to last longer than younger patients. Radiotherapy for elderly MIBC patients with poor general conditions has a poor prognosis, and the treatment interruption rate is also high. Careful evaluation of indications for chemoradiotherapy and treatment intensity on a case-by-case basis that uses indices, such as PS, Society of Geriatric Oncology, and G8 score, is required [18, 19]. It should be noted that previously reported studies have used different radiotherapy methods for patients with MIBC. The previous reports differed in fractional dose, total dose, radiation field, and use of IMRT and these differences might make the accuracy of treatment results uncertain. In particular, AEs can be reduced by using IMRT combined with image-guided radiotherapy [21] and increasing the dose relative to that used in the era of three-dimensional conformal radiotherapy for bladder cancer in elderly patients may lead to improved treatment outcomes. Similarly, the type and combination of chemotherapy, timing of administration, and number of courses to be administered have varied and might not have been described in detail in reports; therefore, we should pay a careful attention to compare literature sources.

A previous report did not examine QOL, which limits the ability to make recommendations regarding appropriate treatment intensity, including chemotherapy and radiotherapy, and highlights the importance of including QOL outcomes in future studies.

Conclusion

The lack of a difference in PFS/RFS and CSS/DSS between elderly and younger patients indicated that curative chemoradiotherapy is effective for elderly patients. Still, treatment tolerability, including chemotherapy, is required. Individualized treatment decisions based on the patient's health status are needed. With advances in treatment, further prospective studies are needed to optimize the management of MIBC in elderly patients.

Abbreviations

MIBC	Muscle-invasive bladder cancer
RC	Radical cystectomy
QOL	Quality of life
TMT	Trimodality therapy
AEs	Adverse events
OS	Overall survival
RFS	Relapse-free survival
PFS	Progression-free survival
DFS	Disease-free survival
DSS	Disease-specific survival
CSS	Cancer-specific survival
CR	Complete response
GI	Gastrointestinal
GU	Genitourinary
G8	Geriatric-8 score
IMRT	Intensity-modulated radiation therapy
PS	Performance status

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Authors' contributions
Conception and design; MS, TM, YS, HI, Data collection; HI, data analysis and interpretation; MS, TM, YS, HI, Drafting of the article; MS, HI, Critical revision of the article for important intellectual content; MS, TM, YS, HI, Final approval of the article; MS, TM, YS, HI.

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Data availability
The data that support the findings of this study are available from the corresponding author, M.Sakaguchi, upon reasonable request.

Declarations

Ethics approval and consent to participate
All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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