Chemoradiotherapy in octogenarians as primary treatment for muscle-invasive bladder cancer

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Abstract

Introduction: While radical cystectomy is the gold standard for muscle-invasive bladder cancer (MIBC), in octogenarians cystectomy results in a higher perioperative mortality rate (6.8–11.1%) than in younger patients (2.2%). Trimodality therapy is a bladder-sparing regimen composed of transurethral resection of bladder tumour (TURBT) and chemoradiotherapy, with intent for salvage cystectomy, and has a 62.5–90% initial complete response rate. In this study, we evaluate TURBT and chemoradiotherapy without salvage cystectomy in medically inoperable octogenarian patients.
Methods: We identified a retrospective cohort of patients aged 80–89 years with invasive urothelial carcinoma who received combination chemoradiotherapy between 2008 and June 2014. Outcomes were evaluated by Kaplan-Meier (KM) and Cox regression.
Results: In 40 patients, the mean age was 84.5 years (interquartile range [IQR] 83–86). Seventeen patients received hypofractionated, low-dose radiotherapy (LD) (37.5–40 Gy), while 23 received conventionally fractionated radiotherapy (high-dose [HD]) (50–65 Gy). Mean overall survival (OS) was 20.7 months (IQR 12.75–23.25), while mean recurrence-free survival (RFS) was 13.75 months (IQR 3.75–16.5). Patients receiving HD radiotherapy showed improved OS and local RFS (LRFS) without significant differences in Grade 3–4 toxicities. Univariate Cox regression identified hydronephrosis as a predictor of worse OS and local recurrence and HD radiotherapy as a predictor of improved OS and local recurrence rates. Multivariate Cox regression identified hydronephrosis to be a significant predictor of LRFS.
Conclusions: Primary chemoradiotherapy for inoperable patients with MIBC resulted in a three-year OS of 54.9% (comparable to cystectomy) and three-year RFS of 42.3%. Superior outcomes were associated with more aggressive chemoradiotherapy treatment. The results of the local control subanalyses in this study are hypothesis-generating due to the limited patient numbers in the cohort.

Introduction

Approximately 70 000 people are diagnosed with bladder cancer in the U.S. each year[1] and 90% of these are urothelial carcinomas (UC).[2] The gold standard therapy for muscle-invasive UC is radical cystectomy; however, cystectomy bears a Grade 3–5 complication rate of 13%[3] and a perioperative mortality of 2.5–5.2%.[3-6] Additionally, perioperative mortality increases with age, increasing from 4.7% in patients in their 60s, to 6.8–11.1% in octogenarians.[5,7] Even with the additional risks of surgery, population-based evidence suggests local therapy delivered with curative intent improves overall survival (OS) and cancer-specific survival (CSS) in octogenarians.[8]

Trimodality therapy (TMT) is an alternative to cystectomy comprised of transurethral resection of bladder tumour (TURBT), followed by combination chemoradiotherapy, with the intention to have the patient undergo salvage cystectomy if there is local treatment failure. The benefit of combination chemotherapy added to TMT remain unproven, so it typically is not included in this treatment approach.[9] TMT initial complete response (CR) rates vary from approximately 60–90%,[10-17] with five-year bladder intact survival in these studies at 40–45%,[18] and an approximate acute Grade 3/4 toxicity rate of 36–46%[14,17] and 15.7% during long-term followup.[17]

At the London Regional Cancer Program, combination chemoradiotherapy has been offered to medically inoperable patients for nearly 20 years. This retrospective study sought to evaluate the outcomes of medically inoperable octogenarians treated with TMT alone at London Health Sciences Centre (LHSC).

Methods

A comprehensive review of electronic patient charts was completed for patients aged 80–89 year who were deemed

medically unsuitable to undergo cystectomy for muscle-invasive bladder cancer (MIBC) and thus underwent combination chemoradiotherapy as primary therapy for their disease. In our centre, with few exceptions, medically inoperable patients are treated primarily with chemoradiotherapy regimens. The selection of the chemotherapy is typically based upon the patient comorbidities to allow for drug tolerance. Low-dose (LD) and high-dose (HD) radiotherapy regimens are applied with life-prolonging intent, with both protocols having been seen to be able to produce durable treatment effects in our centre; we have previously published on durable treatment responses using the LD regimen.[18] The selection of radiotherapy regimen is performed on a case-by-case basis at the discretion of the treating physician and often takes patient general health status into consideration. Radiotherapy is applied to the bladder alone, however, in cases where there are suspicious lymph nodes on imaging, these nodes may be included in the radiation target zone at the discretion of the treating physician and on a case-by-case basis.

Patients evaluated were those who underwent therapy between 2008 and June 2014. These dates were chosen to ensure complete electronic records at the beginning of the period and to allow approximately 12 months of followup data. Treatment-related toxicities were retrospectively assigned according to Common Terminology Criteria for Adverse Events (CTCAE) v4.03. Patients with a small-cell component were excluded, as were patients who underwent salvage cystectomy. Patient survival was censored at recorded date of death or last followup. Recurrence was defined as the date of first imaging or clinical evidence of either local or systemic recurrence. Survival figures are recorded from time of diagnosis, while recurrence figures are recorded from the date of first treatment administration. Statistical analysis was completed using the Medcalc software package (MedCalc Software bvba, Belgium).

Results

Patient demographics

Forty patients met the inclusion criteria and their baseline characteristics are summarized in Table 1. The mean age of patients was 84.5 year (interquartile range [IQR] 83–86), with 28 males and 12 females. Thirty-five patients had T2 disease, four had T3, and one had T4 disease, while three were node-positive. Thirty-one patients were deemed not to be cystectomy candidates due to comorbidity status, while others underwent combination therapy due to advanced age, patient preference, locally advanced disease, and performance status. All patients underwent a TURBT as both a therapeutic and diagnostic procedure, however, only 16 of 37 patients that had clear documentation as to the extent of resection underwent a complete resection.

Table 1. Patient and therapy characteristics

Characteristic or treatment	Number of patients
Patient total	40
Mean age	84.5 (IQR 83–86)
Sex	
M	28
F	12
Clinical stage	
2	35 (87.5%)
3	4 (10%)
4	1 (2.5%)
N+	3 (7.5%)
Standard urothelial cell carcinoma	34 (85%)
Urothelial cell carcinoma variant	6 (15%)
Micropapillary	2
Signet ring	1
Squamous differentiation	1
Mixed	2
ECOG	
0	5 (12.5%)
1	25 (62.5%)
2	5 (12.5%)
3	5 (12.5%)
Reason for no cystectomy	
Comorbidities	31
Advanced age	3
Locally advanced	1
Patient preference	4
Performance status	1
Radiation dose	
37.5–40 Gy	17 (42.5%)
50–65 Gy	23 (57.5%)
Chemotherapy received	
Carboplatin	30 (75%)
5-FU + MMC	7 (17.5%)
Cisplatin	3 (7.5)
Complete TUR	
Complete	16/37 (43.2%)
Incomplete	21/37 (56.8%)
Not recorded	3/40
Hydronephrosis	
Present	12/37 (32.4%)
Not present	25/37 (67.6%)
Not recorded	3/40
Baseline comorbidities	
Cerebrovascular	9
Cardiovascular	19
Respiratory	10
Chronic kidney disease	4
Diabetes	8
Peripheral vascular disease	2

ECOG: Eastern Cooperative Oncology Group; FU: fluorouracil; IQR: interquartile range; MMC: mitomycin; TUR: transurethral resection.

Patients received one of several treatment regimens, encompassing either hypofractionated, LD radiotherapy (n=17; 37.5–40 Gy, 15 fractions, biologically effective dose [BED]10=47–51, BED3=69–76) or conventionally fraction-

ated radiotherapy (HD) (n=23; 50–65 Gy, 20–33 fractions, BED10=63–77, BED3=92–105). One of three sensitizing chemotherapy regimens were used; carboplatin alone, cisplatin alone, or 5-fluorouracil (5-FU) and mitomycin C (MMC). Given the fact that the hypofractionated regimens were associated with a lower BED, we refer to these regimens as low-dose (LD), and the conventionally fractionated regimens as high-dose (HD). A commonly employed strategy was LD radiotherapy with carboplatin, as our early experience suggested this treatment was well-tolerated and effective in this patient population[19] and 16 patients received this combination.

Treatment-related toxicities and delayed hematuria

Retrospectively assessed treatment-related acute toxicities are summarized in Table 2. Nine Grade 3–5 toxicities in patients were recorded — four of these were related to pain and one to cellulitis, none of which were life-threatening. Life-threatening toxicities included one patient who died of sepsis while on therapy and one patient who had a myocardial infarction. There were only three Grade 3-4 genitourinary (GU) toxicities and no gastrointestinal (GI) toxicities. The most common late toxicity documented was hematuria (n=13), with the majority being associated with local recurrence (n=11), and nine of these being Grade 3–4 (Supplementary Table 1; available at *www.cuaj.ca*). Of the two patients with late bleeding without recurrence (and thus likely attributable to the radiotherapy), the toxicity were Grades 1 and 3, respectively.

Overall patient outcomes

Objective complete response to therapy, as defined by no visible tumour seen on cystoscopy, was seen in 24 of the 31 (77.4%) patients who underwent a surveillance cystoscopy within four months of therapy completion. Imaging studies were completed at the discretion of the clinical team. Patient outcomes are summarized in Figs.1, 2, 3. The three-year OS was 54.9% (Fig. 1) and 11/14 patients died of their disease. The three-year recurrence-free survival (RFS) was 42.3% (Supplementary Fig. 1; available at *www.cuaj.ca*), while the three-year local RFS (LRFS) was 48.7% (Fig. 2). Disease relapse was typically managed with palliative chemotherapy or supportive measures; salvage cystectomy was not performed.

Subgroup analysis

Chemotherapy regimens were divided into carboplatin and "non-carbo (NC)" chemotherapies, which included cisplatin and 5-FU and MMC. There was no difference in complete response rates between chemotherapy regimens (Supplementary Table 2; available at *www.cuaj.ca*; Fisher exact test [FET]). Using Kaplan-Meier survival analysis, NC chemotherapy regimens were found to be associated with improved OS by log-rank test (Fig. 3; p=0.0425). NC chemotherapies also showed a non-significant trend towards improvement in LRFS (Supplementary Fig. 2; available at *www.cuaj.ca*; p=0.1119). Finally, there was a non-significant trend towards higher rates of Grade 1–2 and 3–5 toxicities in patients who received carboplatin (Supplementary Table 3; available at *www.cuaj.ca*).

Radiation therapy was divided into LD radiotherapy (37.5–40 Gy) and HD radiotherapy (50–65 Gy). There was no difference in complete response rates between radiotherapy regimens (Supplementary Table 2). HD radiotherapy was found to show an improvement in both OS (p=0.0348) and LRFS (p=0.0367) by log-rank test (Figs. 4, 5). The HD radiotherapy group did show a higher rate (20/23 vs. 7/17) of Grade 1–2 toxicities vs. the LD radiotherapy group (Table 3), however, there were no significant differences in the rates of local regional GI or GU Grade 3–4 toxicities or in the overall rate of delayed hematuria (Table 3).

Finally, outcomes were analyzed by chemoradiotherapy regimen. Although limited by the small numbers in each group, the HD, NC group showed a non-significant trend towards improved OS (Fig. 6) and LRFS (Supplementary Fig. 3; available at *www.cuaj.ca*) when compared with the HD and carboplatin, LD and carboplatin, and LD NC groups.

Cox regression analysis

Univariate Cox regression analysis was completed to evaluate the contribution of clinical factors to OS and LRFS.

Table 2. Acute toxicities assessed by Common Terminology Criteria for Adverse Events (CTCAE), version 4.03

Grade	GI	GU	Cardiovascular	Infectious	Respiratory	Renal	Other	Total
1	15	15	2	0	1	1	4	38
2	1	4	0	0	0	0	5	11
3	0	3	1	1	0	0	2	6
4	0	0	1	0	0	0	0	1
5	0	0	0	1	0	0	0	1
Total	16	22	4	2	1	1	11	58
Total Grade 3–5	0	3	2	2	0	0	2	9

GI: gastrointestinal; GU: genitourinary.

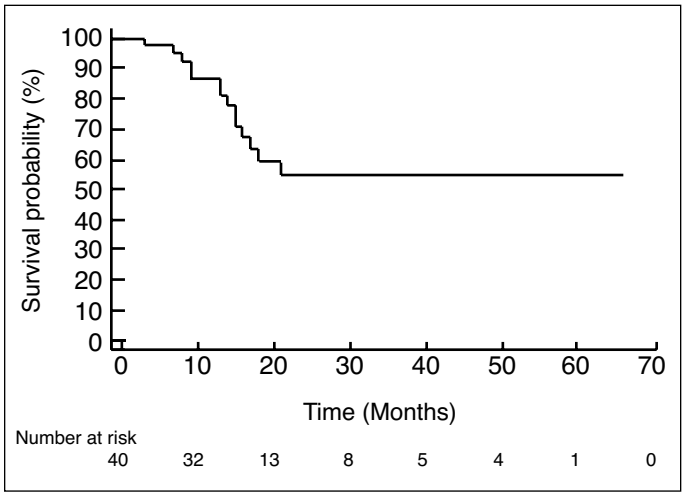

Fig. 1. Overall cohort: Kaplan-Meier overall survival.

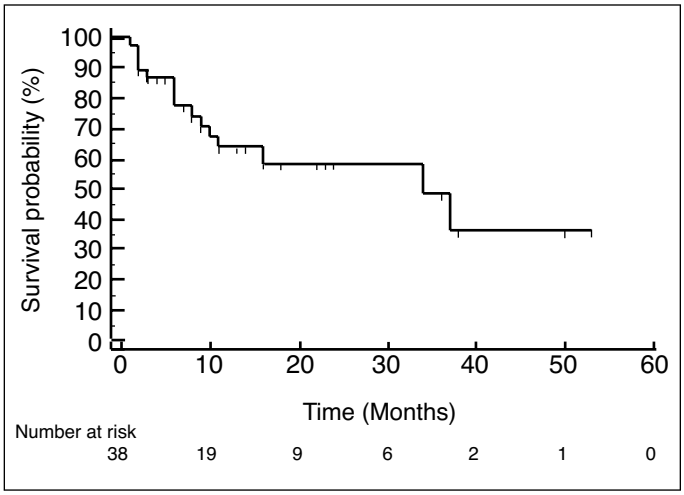

Fig. 2. Overall cohort: Kaplan-Meier local recurrence-free survival.

Hydronephrosis (hazard ratio [HR] 3.13, 95% confidence interval [CI] 1.10–8.92) and HD radiotherapy (HR 0.34, 95% CI 0.12–0.97) were significant predictors of OS (Table 4), while hydronephrosis (HR 4.67, 95% CI 1.53–14.31) and HD radiotherapy (HR 0.35, 95% CI 0.13–0.99) were significant predictors of LRFS (Table 5).

Multivariate Cox regression was also completed using the variables that were found to be statistically significant on univariate analysis. This found only a trend towards significance for both hydronephrosis and HD radiotherapy in OS (Table 4), while hydronephrosis (HR 3.95, 95% CI 1.29–12.1) was a predictor of LRFS (Table 5).

Discussion

In this retrospective review of 40 patients aged 80–89 years (mean 84.5) who were medically inoperable for MIBC and treated with chemoradiotherapy, the three-year OS, RFS, and LRFS were 54.9%, 42.3%, and 48.7%, respectively. The historical results of radical cystectomy, indicate five-year OS and LRFS figures of 40–60% and 80–90%, respectively.[18] Octogenarians have a median survival of only 3.3 years following radical cystectomy, compared with 7.7 years for their younger counterparts, and have a 42.3% five-year cumulative death rate from other causes.[5] Thus, our three-year OS outcomes are comparable for reported survival for octogenarians undergoing cystectomy and the requirements

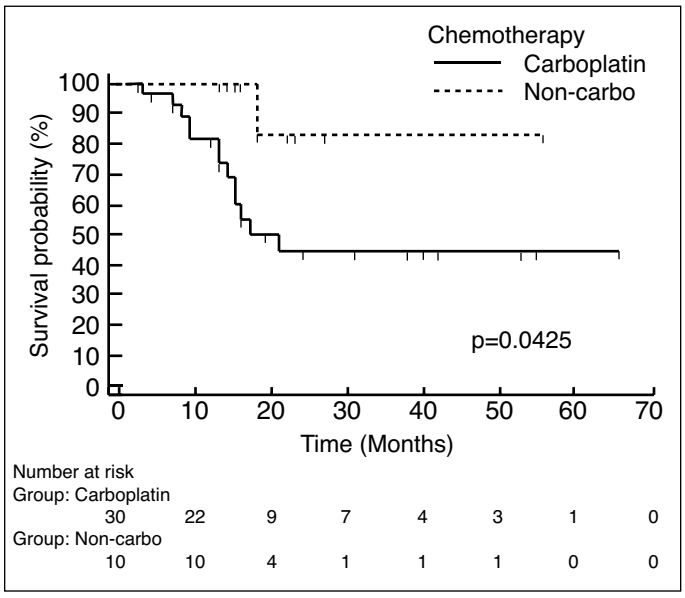

Fig. 3. Kaplan-Meier overall survival analysis by chemotherapy regimen.

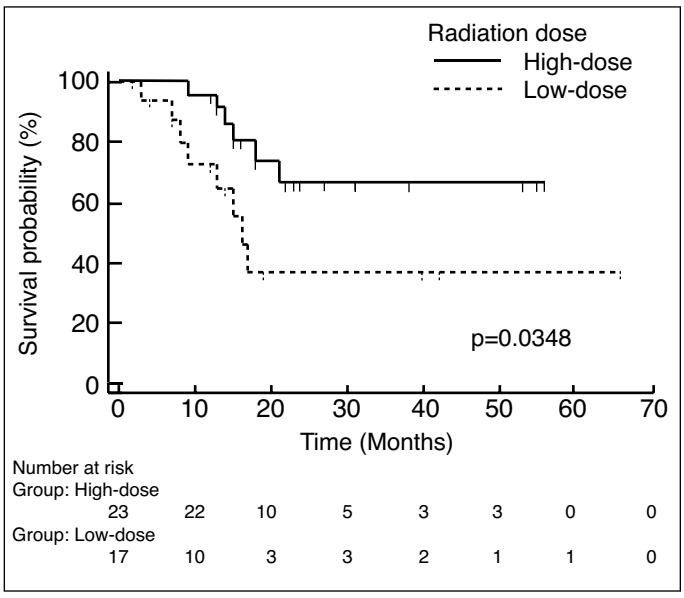

Fig. 4. Kaplan-Meier overall survival analysis by radiotherapy regimen.

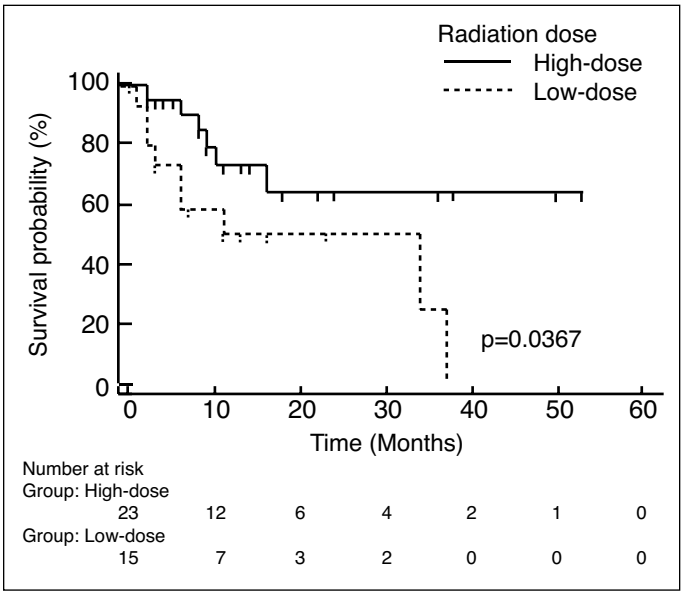

Fig. 5. Kaplan-Meier local recurrence-free survival analysis by radiotherapy regimen.

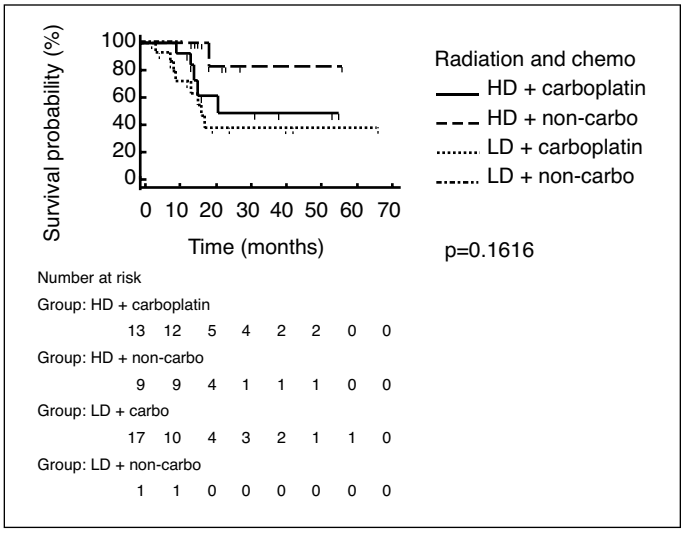

Fig. 6. Kaplan-Meier overall survival analysis by chemoradiotherapy regimen.

for long-term disease control in this patient population is less stringent due to the lower median survival time.

Radical cystectomy bears significant morbidity and mortality, with an overall perioperative complication rate of 28–49%,[3,4] and a Grade 3–5 complication rate of approximately 13%.[3-6] Additionally, perioperative mortality rates rise in octogenarians,[5] and while overall Grade 3–5 complications are similar, one study identified a significant increase in cardiovascular (9.5–19.7%) and neurological (3.9–10.3%) complications.[5] In our study, there were nine Grade 3–5 acute toxicities (22.5%), with one patient who died from sepsis while on treatment (2.5%) and one who suffered a non-fatal myocardial infarction. Acute Grade 1–2 GU (19; 47.5%) and GI (16; 40%) toxicities were common, while severe late toxicities were uncommon, with only two patients experiencing late treatment-related hematuria, of which one patient had Grade 1 toxicity and the other Grade 3 (11 had late bleeding related to tumour recurrence). Therefore, the octogenarian mortality rate in our study was lower than that in the cystectomy literature (2.5% vs. 6.8–11.1%),[5] while there was an increased rate of Grade 3–5 complications; most, however, were non-life-threatening.

In this study, the choice of chemotherapy regimen was associated with improved OS, but not LRFS. Carboplatin may have been given to patients with multiple comorbidities, reduced performance status, and/or impaired renal function precluding the use of cisplatin; therefore, this may represent a selection bias. For example, patients with hydronephrosis, an adverse prognostic factor, may be more likely to receive carboplatin because of impaired renal function. That said, a phase 3 study of 360 patients given 5-FU and MMC showed a 13% improvement in both two-year locoregional disease-free survival (DFS) and in five-year OS

Table 3. Local toxicities by radiation dose

Toxicity	Proportion of patients affected	p (FET)
Grade 1–2 toxicities		
37.5–40 Gy	7/17 (41.2%)	**0.0051***
50–65 Gy	20/23 (87.0%)	
Grade 3–4 toxicities		
37.5–40 Gy	1/17 (5.9%)	0.4250
50–65 Gy	0/23 (0%)	
Delayed hematuria		
37.5–40 Gy	5/17 (29.4%)	0.2499
50–65 Gy	3/23 (13.0%)	
Overall; Grade 3–4+ hematuria		
37.5–40 Gy	5/17 (29.4%)	
50–65 Gy	3/23 (13.0%)	0.2499

FET: Fisher exact test.

Table 4. Cox regression analysis predicting survival

Variable	Hazard ratio	95% confidence interval	p
Unvariable analysis			
Hydronephrosis	3.13	1.10–8.92	**0.0339***
Complete TUR	0.89	0.31–2.55	0.8256
Cardiovascular disease	2.63	0.91–7.63	0.0749
Respiratory disease	1.54	0.52–4.58	0.4493
Diabetes	0.30	0.04–2.25	0.1644
Nodal disease	1.30	0.17–9.89	0.8106
High-dose radiation	0.34	0.12–0.97	**0.0457***
Non-carbo	0.16	0.02–1.22	0.0786
Multivariable analysis			
Hydronephrosis	2.82	0.98–8.15	0.0569
High-dose radiation	0.41	0.14–1.21	0.1072

*Statistically significant. TUR: transurethral resection.

Table. 5. Cox regression analysis predicting local recurrence-free survival

Variable	Hazard ratio	95% confidence interval	p
Univariable analysis			
Hydronephrosis	4.67	1.53–14.31	**0.0083***
Complete TUR	0.81	0.29–2.29	0.6960
High-dose radiation	0.35	0.13–0.99	**0.0458***
Non-carbo	0.32	0.0723–1.42	0.0906
Multivariable analysis			
Hydronephrosis	3.95	1.29–12.1	**0.0168***
High-dose radiation	0.46	0.16–1.33	0.1562

*Statistically significant. TUR: transurethral resection.

vs. radiotherapy alone[17] and may be a more appropriate alternative to carboplatin when cisplatin regimens are not tolerated. However, the approximate four weeks required to fully deliver this chemotherapy regimen would limit its applicability in patients selected for shorter-term, LD radiotherapy regimens.

LD radiotherapy with platinum chemosensitization has been administered in our centre in order to provide disease control while minimizing toxicity and overall treatment time in frail patients, as previously reported.[19] In this current study, while a reduced low-grade toxicity was noted in the LD radiotherapy group, outcomes in terms of OS and LRFS were inferior, while there was no difference in the number of Grade 3–4 toxicities or hematuria. This corresponds with the result of a 2006 Dutch study, which showed that 10 Gy increments in the final radiotherapy dose increased the local control rate by 50% in three years.[20,21] Notably, while there is evidence regarding the overall radiation dose, studies have shown no effect of the number of fractions or duration of treatment on local control, and thus hypofractionated (55 Gy/20 fractions) gives comparable results to conventionally fractionated (62 Gy/32 fractions) radiotherapy.[21,22]

This study has a number of potential limitations. It is a retrospective analysis with a limited number of heterogeneously treated patients, limiting its statistical power. All outcomes, including adverse events, recurrence, and death were assessed retrospectively, and causality of adverse events was inferred from the available clinical documentation, with variable number of followup visits surrounding therapy. Recurrence and death were determined from imaging tests and clinical notes, and not all patients underwent a post-treatment cystoscopy for assessment of tumour response. Finally, no adjustment was made in the Cox regression analysis to account for multiple comparisons due to the limited sample size of our study. Thus, we acknowledge that the results are primarily hypothesis-generating.

However, the results are consistent with conclusions that chemoradiotherapy is a safe treatment option for MIBC in octogenarians and is associated with three-year OS and RFS rates of 54.9% and 42.3%, respectively in our cohort. Based on our experience and reports of prospective trials, our results with TMT comprised of TURBT followed by hypofractionated HD radiotherapy (55 Gy/20 fractions) with concurrent 5-FU and MMC, as described in the study by James et al in 2012[17] appear to provide an appropriate balance between risk of toxicity and optimizing clinical outcomes in suitable octogenarians.

Competing interests: Dr. Bauman has received clinical trial funding from Sanofi. Dr. Winquist has participated in clinical trials for Roche and Sanofi. Dr. Chin has been an advisor for US HIFU and Profound Medical Inc. Dr. Izawa has received speaker honoraria from Astellas, AstraZeneca, Janssen, and Sanofi. Dr. Ernst has been an advisor for Astellas, BMS, Merck, Novartis, and Roche; a speaker for BMS, Novartis, and Roche; and has participated in clinical trials for Astellas, BMS, Janssen, Merck, Roche, and Tokai. Dr. Ahmad has received honoraria from Ferring and has participated in several radiation studies for prostate, bladder, and kidney cancers for the London Regional Cancer Program. Dr. Power has participated in clinical trials for Argos Therapeutics. The remaining authors report no competing personal or financial interests.

This paper has been peer-reviewed.

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