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RESEARCH ARTICLE

Curative radiation therapy for very elderly bladder cancer patients with localized disease

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Abstract
Purpose To report the outcomes of a cohort of very elderly muscle-invasive bladder cancer (MIBC) patients treated with contemporary 3D-conformal radiation therapy (3D-CRT) with or without concurrent chemotherapy, after transurethral resection of bladder tumor (TURBT).
Methods From February 2010 to January 2014, a total of 41 patients older than 75 years, with T2-3 N0-1 high-grade MIBC, a Karnofsky index (KI) of at least 90% and/or a Barthel scale score of at least 95, were treated with TURBT followed by radiotherapy (RT) with or without chemotherapy, and were prospectively followed-up.
Results The mean age of patients was 82 years (range 76–88). Median follow-up was 47 months for surviving patients. Mean Charlson Comorbidity Index (CCI) score was 5 points. 28 patients (68.29%) were T2N0. All received 3D-CRT to a mean dose of 60 Gy (range 48.6–66 Gy), and chemotherapy was delivered to 34 patients (83%). Cause-specific survival (CSS) was 86 and 78.8% at 1 and 5 years, respectively. Patients achieving a complete response lived longer (48 vs 14 m, $p = 0.036$) than those with a progressive disease, who were more likely to die from cancer than from other causes (HR 3.865, IC95% 1.562–9.562). Dead patients had a longest treatment time (mean 56.78 vs 48.91 days, $p = 0.019$) than survivors.
Conclusion RT with contemporary 3D-CRT techniques after TURBT for MIBC in elderly patients is feasible and well-tolerated. Achieving a maximal response and shortening the total radiation treatment time may improve outcomes and quality of life.

Keywords Bladder cancer · Elderly · Radiotherapy · Trimodality

Introduction

Due to the aging population, there is an increasing incidence of cancers, particularly for those with a long latency period, such as urothelial bladder carcinoma. In developed countries, such as the United States or Europe, people aged 65 and over will almost double over the next 50 years [1, 2]. Bladder cancer, therefore, is expected to become a huge challenge in the years ahead.

Data obtained from the California Cancer Registry reveals that the peak incidence of urothelial bladder cancer is at 85 years of age [3]. However, evidence-based practice guidelines of urothelial carcinoma of the bladder do not usually reflect on this much older population. In addition, it is inappropriate to extrapolate the best treatment approaches based on studies of younger populations because of their physiological, psychological and social differences [4].

The original version of this article was revised: In the original version of this article the figure captions of Figs. 1 and 2 were interchanged. The correct captions of Figs. 1 and 2 are listed below.

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Radical cystectomy (RC) with lymphadenectomy is known as the gold standard treatment for muscle-invasive bladder cancer. However, the morbidity and mortality of RC are not negligible [5]. Complications such as urolithiasis, wound complications and renal function impairment are common after urinary diversion and continue to occur over 5 years postoperatively [6]. In addition, patients older than 70 years are more likely to receive incontinent forms of urinary diversion [7] and to develop these types of complications.

Trimodality therapy is indicated as the first curative treatment for elderly patients who are in good general health, as an alternative to radical cystectomy [8–11].

A review of trimodality treatments in older bladder cancer patients was recently carried out in some selected retrospective, prospective and phase II studies of patients aged = or $>$ 70 years. The review showed that curative intent for bladder preservation in elderly patients is feasible and well-tolerated. In addition, it seems to lead to equivalent outcomes to RC. However, published series of bladder cancer patients aged more than 75 years are often about more locally advanced tumors, treated in more than one institution, and with old RT techniques [12].

Therefore, we wanted to describe the outcomes of a cohort of very elderly bladder cancer patients ($>$ 75 years old) who were otherwise in good general health, treated with trimodality at our institution with contemporary RT techniques.

Methods

From February 2010 to January 2014, consecutive patients at least 76 years old presenting with T2-3 N0-1 high-grade urothelial bladder cancers, and in good general health represented by a Karnofsky index of at least 90% and/or a Barthel scale score of at least 95, were treated and then prospectively followed-up. All patients provided written informed consent. CCI scoring age was also calculated using the online calculator midcalc.org [13], but it did not affect the treatment decision.

Treatment

A previous TURBT had been carried out on all patients, to note that resection was not always up to the fatty tissue according to the urologist criteria. Tumor size was reported by urologists as "small" (less than 1 cm) or "big" (more than 3 cm) with regard to the resector head size. In addition, the tumor size was measured and classified by ultrasonography and/or on the computed tomography as "less than 5 cm" for one group and "more than or equal to 5 cm" for the other group. Tumors were staged according to the AJCC cancer staging 7th edition [14]. To dichotomize tumor stage and size equal to or less than T2N0 was considered as a cut-off. Doubtful T2-3 or N0-1 was considered as T3 or N1 for analysis. "Small" tumors were grouped with those smaller than 5 cm, and "big", bifocal or multiple tumors were grouped with those bigger than 5 cm size.

Afterwards, all patients received 3D-CRT with high energy photons. All patients provided written informed consent. Patients were simulated with a computed tomography in a supine position using an adaptive-like approach: first with a filled bladder and then with an empty bladder to estimate the internal target volume (ITV) of the tumor bed. Concurrent chemotherapy was preferred, although a neoadjuvant or concurrent regimen was delivered according to the Medical Oncologist criteria. Cisplatin was discarded for unfit patients who met at least one of these Galsky criteria [15]: an Eastern Cooperative Oncology Group performance status of 2, creatinine clearance of less than 60 mL/min, grade $\geq$ 2 hearing loss, grade $\geq$ 2 neuropathy, and/or New York Heart Association Class III heart failure. Schemes and doses of concurrent chemotherapy were: carboplatin AUC 2.5 mg weekly or cisplatin 40 mg/m^2 weekly. In the neoadjuvant setting, the doses were: carboplatin AUC 3 plus gemcitabine 2000 mg/m^2/15 day or cisplatin 50 mg/m^2 plus gemcitabine 2500 mg/m/15 day.

Endpoints

Local progression was defined as having signs of disease restricted to the bladder. Regional progression was defined as presenting signs of disease outside the bladder, limited to the pelvis. Overall survival (OS) was measured from the date of the end of RT until death from any cause. For cancer-specific survival, patients who died from other causes were censored at the time of death.

Acute and late toxicity was recorded using the CTC_AE v 4.0 scale.

Statistics

Categorical variables were correlated using the Chi square test. Time-to-event distributions were estimated using the Kaplan–Meier curves, and survival functions were compared with the Mantel-Cox test. A Cox proportional hazards regression was performed to analyze competing risks. A level of 5% was used to denote statistical significance.

The SPSS software was used for statistical analysis (SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.). Competing risk analysis was performed using the R package cmprsk [16], and regression parameters were estimated with the Fine and Gray proportional subdistribution hazards model.

Results

41 patients met the eligibility criteria. The mean age of patients was 82 years (range 76–88). Only 5 patients (12%) were female. Median follow-up was 29 months (range 3–78) for the entire cohort and 47 months (range, 12–74) for the survivors. The median score on the CCI was 5 points (range 4–9). Table 1 shows baseline patient, tumor and treatment characteristics. TURBT was maximal in 15 patients (36.5%), flattened in 14 (43.1%), and not well-detailed in 12 (29.2%). Eight patients with a previously flattened or unknown resection (30%) were treated with a repeated TURBT before RT. Besides TURBT, random bladder biopsies (RBB) were performed on 14 patients (35%).

All patients received RT to a median dose of 60 Gy (48.6–66 Gy) at 1.8–2 Gy in 7–7.5 weeks. The majority of patients (80%) received a prophylactic 45–46 Gy to the pelvic lymph nodes, followed by a boost of 14–20 Gy to the whole, or affected hemibladder. Chemotherapy was delivered to 34 patients (83%) and 7 patients (17%) were treated with RT alone. Chemotherapy was delivered in different schemes: concurrent carboplatin in 19 (56%), neoadjuvant cisplatin–gemcitabine followed by concurrent carboplatin in 10 (29%), neoadjuvant chemotherapy only in 4 (12%) and concurrent cisplatin in 1 (3%). Only one patient did not complete his RT treatment, which was stopped at 40 Gy secondary to a G3 haematuria.

By the final follow-up, three patients had been lost to the study. Eleven patients (28.9%) were still alive, 3 of them (27.3%) with signs of tumor progression. Nineteen of the 27 patients (70%) who had died also had a tumor progression. Recurrences had a locoregional component in 12 (63%), and were only distant in 4 (15.3%). The main metastatic location was lung, followed by bone and liver. Figure 1 shows the main patterns of progression.

The Chi square and Mantel–Cox analysis for qualitative variables did not find statistical differences, except for patients achieving a complete response, who lived longer (48 vs 14 m, $p = 0.036$) (Table 2). For quantitative variables, only the mean duration of RT was statistically significant: living patients were treated within 48.91 days (SD = 4.3) in comparison to those who died, treated with a mean of 56.78 days (SD = 14.42, Mann–Whitney U test, $p = 0.019$). The mean days of treatment for the entire cohort was 54.4 (SD = 12.350).

OS was 68.4, 35.3 and 21.5% at 1, 3 and 5 years, respectively. CSS at 1 and 5 and years was 86 and 78.8%, respectively. The mean and median survival for the entire cohort was 32.23 and 23 months, respectively.

The cause of death, when not secondary to cancer progression were as follows: complications of a chronic obstructive pulmonary disease in three patients (23%), urinary sepsis in two (15%), bronchoaspiration pneumonia in two (15%), acute pulmonary edema in two (15%), and

Table 1 Patient, disease and treatment characteristics

		N	%
Sex	Male	36	87.80
	Female	5	12.20
Age	Mean (range)	81.95 (76–88)	
	Median	81.50	
Charlson score	Mean (range)	5.51 (4–9)	
	Median	5	
Previous NMIBC	Yes	9	21.95
	no	28	68.29
	Unknown	4	9.76
In situ component	Yes	8	19.51
	No	27	65.85
	Unknown	6	14.63
RBB	Yes	14	34.15
	No	26	63.41
	Unknown	1	2.44
TNM	T2N0	28	68.29
	T3N0	3	7.32
	T2N1	2	4.88
	T3N1	1	2.44
	Doubtful T2-T3 N0	5	12.20
	Doubtful T2 N0-1	2	4.88
Tumor size	< 5 cm	18	43.90
	≥ 5 cm	12	29.27
	Bifocal or multiple	6	14.63
	Unknown	5	12.20
Hydronephrosis	Yes	8	19.51
	No	28	68.29
	Unknown	5	12.20
TURBT	Maximal	15	36.59
	Flattened	14	34.15
	Unknown	12	29.27
Re-TURBT pre-RT	Yes	8	19.51
	No	33	80.49
Chemotherapy	Concurrent only	18	43.90
	Induction + concurrent	10	24.39
	Induction only	4	9.76
	No	4	9.76
RT dose(Gy)	Mean (range)	60.95 (48–66)	
Prophylactic pelvic RT	Yes	33	80.49
	No	8	19.51
Days of RT	Mean (range)	54.33 (35–106)	

NMIBC Non muscle-invasive bladder cancer, *RBB* randomized bladder biopsy, *TURBT* transurethral resection bladder tumor, *RT* radiotherapy

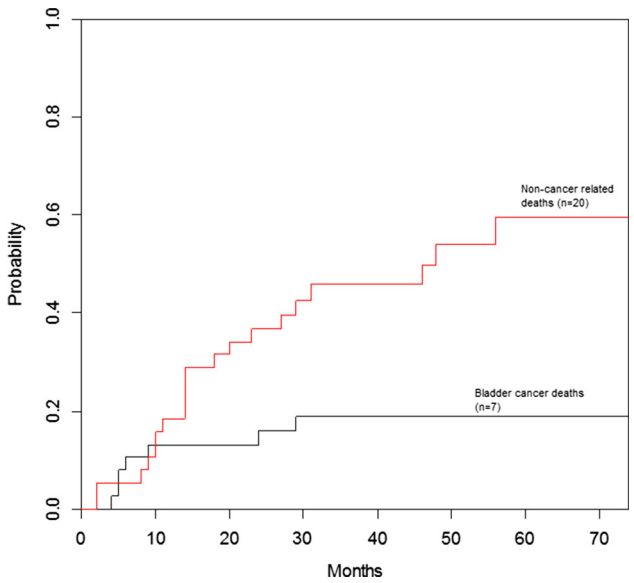

Fig. 1 Cumulative incidence curves for death

deep vein thrombosis, acute ischemic heart disease, renal insufficiency and adrenal dysfunction in four individuals. Cox proportional hazards regression showed that patients with a progressive disease are more likely to die from cancer than from other causes [HR (IC 95%): 3.865 (1.562–9.562)]. The cumulative incidence method used to analyze cause-specific mortality, showed a greater probability of death from other causes at 1 and 5 years than from vesical cancer itself (Fig. 2). The fine and gray regression model did not succeed in finding a statistical significance from any variable. This may be explained by a low number of specific events ($n = 7$).

Acute tolerance was good, with only one G3 haematuria and a patient with hematological toxicity related to chemotherapy, who both needed to interrupt their RT. The main acute toxicities were dysuria (56.1%) followed by pollakiuria (53.7%), and diarrhea (36.6%). 28.6% of women also had symptoms of acute vulvovaginitis. During the follow-up, four patients presented haematuria, documented as radiation-induced in only one of them.

Discussion

Populations around the world are aging rapidly. Bladder cancer is an age-associated malignancy, with a median age at diagnosis of 73 years and individuals aged 75–84 years accounting for the largest percentage of new cases [17]. In addition, because of the increase in life expectancy, the fastest growing group of the population is 65 years and older [18]. Reported cohorts of very elderly bladder cancer patients are few, and are often a summary of patients who have been treated at different institutions over a long recruitment period. The strength of our series is that these 41 patients older than 75 years were treated consecutively with RT (with or without chemotherapy) at the same institution over a period of only 4 years. Although the patients' professional history was not recorded in our series, it is known that in our region (the central area of Catalonia, Spain), specific groups of textile workers (such as spinners and winders) had a high risk of bladder cancer due to their working practices [19]. The region had one of the most important textile industries in Spain during the first half of the 20th century, which brought with it a large migratory phenomenon. It is likely that some of these patients would have been working in the regional textile industry.

While surgery is known to be the gold standard treatment for bladder cancer, it has been reported that patients over 80 years of age have high post-RC mortality rates, especially at 90 days after surgery [5]. For example, a cohort of 275 patients over 80 years old in Canada, showed 33% of major postoperative complications, and the mortality rates at 30, 60 and 90 days were 5.8, 9.8 and 13%, respectively, with a 5-year overall survival rate of only 27% [20]. Furthermore, patients with several comorbidities logically have poorer postoperative survival outcomes, both in terms of cancer and non-cancer-specific mortality rates after surgical treatment [21]. In an analysis of 37,288 patients who underwent potentially curative operations from 2007 to 2012, those with a CCI score > 2 were associated with higher cancer-specific mortality rates. In our series of patients with a non-advanced disease and a median CCI age of 5 points, the only factors associated with death were to have a non-responding tumor and the total RT treatment time, in spite of comorbidity factors related to age. In addition, the observed good CSS along with the safety of RT and chemoradiation, would mean a lower treatment-related mortality than radical cystectomy. Thus, it should potentially translate into some OS benefit, especially in the elderly and/or comorbid population.

Numerous prospective studies have shown that trimodality therapy for MIBC results in comparable overall survival rates to contemporary surgical series [8–10, 22, 23]. In addition, a recent systematic review of MIBC in elderly patients suggests that curative intent trimodality bladder preservation is certainly feasible and tolerable in the elderly population [12] In addition, our results have shown a statistical significance favoring patients with a complete pathological response, who are less likely to die from cancer than from other causes, we are encouraged to follow prescribing local RT, regardless of the age of these patients.

Although Villavicencio et al. reported a worse prognosis with bladder preservation strategy in patients with MIBC after the progression of a NIBC [24], we found the trend to

Table 2 Bivariate analysis of qualitative variables

	Events	Censored	p^1	Median survival (months)	p^2
Recurrence of a previous superficial tumor					
No	20	6		14	
Yes	5	4	0.221	56	0.082
Tumor size					
<5 cm or small	11	6		23	
≥ 5 cm or big/multifocal	8	3	0.657	20	0.665
Hydronephrosis					
No	18	8		23	
Yes	5	2	0.911	20	0.715
T*ype of TURBT*					
Maximal	10	4		14	
Flattened	9	4	0.901	27	0.867
Previous re-TURBT					
No/unknown	23	8		24	
Yes	4	3	0.369	23	0.991
Chemotherapy					
No	5	1		20	
Yes	22	10	0.470	23	0.459
Disease					
Complete response	7	7		48	
Progression/unknown	20	4	0.029	14	0.036
Type of progression					
Local component	15	9		14	
Other	12	2	0.128	29	0.219
Regional component	5	0		11	
Other	22	11	0.126	24	0.282
Distant component	6	1		11	
Other	21	10	0.179	29	0.078
Prophylactic RT to the pelvis					
Yes	7	1		24	
No	20	10	0.240	20	0.807
Charlson score					
4	6	1		9	
5	10	7		31	
6	4	1		14	
7	5	1		24	
8	2	1	0.621	29	0.238

p^1 Pearson's Chi square test, p^2 Mantel-Cox test, *TURBT* transurethral resection bladder tumor, *RT* radiotherapy

a better prognosis. Patients in their series were younger (mean age of 61 years) and RT was not included in the preservation strategy. Besides the therapeutic effects of radiation in bladder cancer, we suppose that aged patients who had had a previous superficial tumor may have had a closer follow-up that allowed invasive tumors to be detected at more initial stages.

The optimal treatment schedule after TURBT for elderly patients has not yet been established, but the combination of radiation and chemotherapy might offer better outcomes than RT alone, as demonstrated by the BC2001 trial [25, 26]. In addition, in a recent retrospective cohort of 49 patients, those treated with a combination of RT and chemotherapy had significantly longer CSS compared to

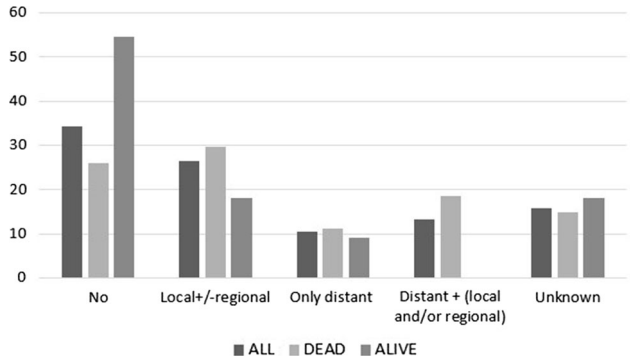

Fig. 2 Main patterns of tumor progression of the cohort

those treated with RT or chemotherapy alone [27]. Surprisingly, we did not find any statistical link with the use of chemotherapy. However, one weakness in our series is that the chemotherapy programmes used were heterogeneous, and cisplatin was not widely used in the cohort (according to the aforementioned Galsky criteria). Since most of the patients were treated before the publication of the BC2001 trial, a regimen consisting in fluorouracil and mitomycin C was not considered in the period. In spite of that, 5-year survival was similar to the series of Bamias et al. (5-year OS of 23%), they with only a 65% of patients aged 75 years old or more.

Delayed radiation treatment times have been linked to poor local control and/or OS in several cancers such as cervix, prostate, lung and head and neck cancers as a consequence of an accelerated re-population of the tumor. In our series, a longer mean treatment time was linked to poorer OS. The causes of the delay were logistical except in the case of two patients, secondary to toxicity. Interruptions were not compensated in this elderly population to avoid any risk of toxicity. Nevertheless, strategies that explore the possibility of shortening total treatment times such as a hypofractionation have been tested by others in elderly patients. Turgeon et al. [28] treated a cohort of 24 patients with a median age of 79 years with T2-3N0M0 MIBC with 3D-CRT to a dose of 50 Gy in 20 fractions. OS and CSS rates at 3 years were of 61 and 71%, respectively. Of the surviving patients, 75% were disease-free with a functioning bladder, which is well-consistent with the disease-free rates observed in our series. Acute grade 3 gastrointestinal or genitourinary toxicities occurred in only 4% of patients and no patient experienced grade 4 gastrointestinal or genitourinary toxicity, which is also consistent with our results, although we used a standard fractionation.

Finally, a selection criteria of our patients was to have a Karnofsky index of at least 90% and/or a Barthel scale score of at least 95 and, despite the fact that only a few of them had a specific geriatric assessment, acute and late tolerances to RT (± chemotherapy) were good. The majority of deaths were related to a progressive disease, which might have been prevented by shortening treatment times. However, we agree that a comprehensive geriatric assessment in this elderly population would help to better balance risks and benefits of bladder cancer therapy [18]. We suspect that some clinicians may have an acquiescent approach to these elderly patients, as can be seen by rates of doubtful cancer staging of 15%, a 36% of patients receiving a maximal TURBT, or again a few patients with a previously flattened or unknown resection being treated with a repeated TURBT before RT. This all means that multidisciplinary efforts are needed to improve the quality of treatment of this elderly population, as it is in younger patients treated with a trimodality approach.

Conclusion

RT (with or without chemotherapy) after TURBT for invasive bladder cancer in very elderly patients who are in good general health is feasible and well-tolerated. We suggest that RT is needed to attain a complete bladder response and is an appropriate therapeutic option for octogenarian patients. The optimal schedule of concurrent chemotherapy needs to be ascertained, although efforts to shorten total radiation treatment times might improve outcomes and the quality of life for elderly patients with invasive bladder cancer.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Research involving human participants and/or animals While the present study is not a clinical trial, both the treatment and follow-up were performed according to the accepted standards of good clinical practice in agreement with the latest version of the Declaration of Helsinki.

Informed consent All patients provided written informed consent. The paper is IRB exempt, given that treatment with radiation in bladder cancer patients is the clinical practice in our institution.

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