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ARTICLE

Comparative effectiveness of radical cystectomy and radiotherapy without chemotherapy in frail patients with bladder cancer

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ABSTRACT

Objectives: To evaluate cancer-specific (CSS) and overall survival (OS) in a group of frail patients who were treated with RT without chemotherapy and to compare them with a matched cohort of patients treated with RC.

Methods: This study identified 71 patients treated with RT only for high-risk bladder cancer. Patients with metastatic (cN + or cM+) or non-resectable tumors (cT4) and those who received any form of chemotherapy were excluded. Patients where matched 1:1 using propensity scores which adjusted for the effects of age, clinical stage and age-adjusted Charlson comorbidity index (CCI). OS and CSS were evaluated using the Cox proportional hazards regression model and the Fine and Gray competing risk model.

Results: In the overall population, RT was associated with worse OS (HR = 1.78, 95% CI = 1.15–2.77, $p = 0.01$) compared to RC, but not with CSS (HR 1.1, $p = 0.74$). In the matched cohort, RT was neither associated with OS nor CSS ($p > 0.05$) compared to RC. In the competing risk analyses no statistically significant association of any of the treatments was observed in the total or in the matched data set ($p > 0.05$).

Conclusion: The use of RT may be an alternative option in well selected patients with limited disease who are considered unfit for systemic chemotherapy and RC. Future research should focus on improving patient selection and assess the quality-of-life as well as the need for reintervention in patients treated with RT.

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Bladder cancer; bladder sparing; frail; cystectomy; radiotherapy

Introduction

Radical cystectomy (RC) with lymph node dissection is the recommended treatment for muscle-invasive bladder cancer (MIBC) and very high-risk non-muscle-invasive bladder cancer (NMIBC) [1,2]. However, RC is associated with significant morbidity and mortality in this elderly population with comorbidities [3,4]. To improve patients' outcomes by minimizing complications, alternative bladder sparing therapies are increasingly being considered such as trimodal therapy based on maximal trans-urethral resection (TUR), systemic effective combination chemotherapy and modern radiotherapy (RT). Trimodal therapy has shown, in non-comparative single-arm series, comparable oncologic outcomes to RC [5,6] and is therefore suggested by current guidelines as an alternative treatment option in highly selected patients [1,2].

However, no RCT has been conducted and current retrospective series suffer from population and treatment heterogeneity, showing, therefore, conflicting results regarding outcomes [5,7–11]. Moreover, due to comorbidities such as poor renal function, chemotherapy can often not be administered, limiting treatment efficacy significantly [10]. There is limited knowledge on the efficacy of maximal TUR followed by RT in patients unfit for systemic chemotherapy.

To fill this gap, we sought to investigate the cancer-specific survival (CSS) and overall survival (OS) in a cohort of patients with limited disease considered unfit for trimodal therapy or RC and compare it to a matched cohort of patients treated with RC without chemotherapy. We hypothesized that the survival outcomes, both OS and CSS, of patients treated with RC would be superior to those treated with radical TUR followed by RT.

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Supplemental data for this article can be accessed here.

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Materials and methods

Patient selection

Following institutional review board approval (IRB Nr 2196/2018), we reviewed our institutional bladder cancer (BCa) databases to identify patients treated at the Medical University of Vienna between 2004 and 2018. Patients treated with clinically non-resectable disease (cT4 and/or N + and/or M+) were not included in the study. A flow diagram showing the enrollment of subjects is depicted in Supplementary Figure S1.

Patients were considered unfit both for RC and systemic chemotherapy and, consequently, allocated to bladder sparing treatment based on anesthesiology and internal medicine evaluation.

Intervention and pathological analysis

Patients were treated with RC with lymph node dissection according to guidelines recommendations at the time. In the RT cohort, TURB war performed as radical as possible. A re-TURB was performed within 8 weeks based on clinic-pathologic features and at physician discretion. Patients typically received a dose of 60–66 Gy (39.6–50.4 Gy delivered to the bladder and pelvic lymph nodes with a sequential tumor boost) given in daily fractions of 1.8–2.0 Gy.

All surgical specimens were processed according to standard pathologic procedures and staged according to the 1998 TNM classification. All tumors were high grade. Specimens were analysed by two dedicated genitourinary pathologists.

Follow-up

Due to the retrospective nature of the study, the follow-up was not standardized. In general patients underwent physical examination, ultrasonography, whole body imaging and laboratory testing according to guidelines at the time and at physician discretion. In addition, patients treated with a bladder sparing approach were evaluated with cystoscopy.

Cause of death was recorded based on chart and/or death certificate review [12].

Follow-up time was calculated from the date of RC or start of RT.

Statistical analyses

Due to uneven distributions between treatment groups, a propensity score was calculated. The score was generated from a multiple logistic regression analysis with the binary endpoint treatment RT vs RC and the covariates age, age-adjusted Charlson comorbidity index [13] (CCI), clinical T-stage and gender. The two treatment groups were matched 1:1 with covariate propensity score applying the nearest neighbor method. Histograms of the propensity score of the total data set and of the matched data set were plotted for each treatment group (Supplementary Figure S4) and standardized mean differences were computed.

To describe the data for each treatment group, mean and standard deviation (SD) for continuous variables and absolute and percentage frequencies for binary and ordinal variables were reported. Group comparisons were performed (*t*-tests for age, age-adjusted CCI and P-score, χ^2 test for gender, Fisher exact test for cT stage) and standardized mean differences (smd) were calculated. We investigated difference in OS and CSS using the matched data set as well as the total data set. Kaplan Meier curves were plotted for the two treatment groups and Cox regression for the covariate treatment were calculated. A competing risk analysis with 'dead of disease' as event of interest and 'death from other cause' as competing risk was computed to analyse the influence of treatment for the matched as well as the total data set. A multiple analysis with additional covariables age, age-adjusted CCI comorbidity index and clinical T-stage was performed. Cumulative incidence functions for the total and the matched sample were plotted. Due to the exploratory character of the study, statistical significance was considered at $p < 0.05$, but not in a confirmatory manner. Therefore, no adjustment for multiplicity was performed. Statistical analyses were performed using R (R project, Vienna, Austria).

Results

Clinicopathologic features stratified by treatment modality before and after propensity score adjustments are shown in Table 1. Of the 169 patients included in the analysis, 137 (81%) were male and 32 (19%) were female. Median age was 73 years (SD = 11.2). Overall, 98 patients (58%) were treated with RC and 71 patients (42%) were treated with RT. A total of 24 patients in the RT cohort underwent re-TURB before starting treatment. Mean dose delivered to the bladder was 52,4 Gy (SD = 7,81 Gy). Before matching, age, age-adjusted CCI and clinical T stage were significantly different between the two groups ($p < 0.05$). Patients treated with RT were more likely to be older, have more comorbidities and higher rates of clinical T2 stage. After RT treatment a total of six (8.4%) patients had clinically a local disease progression and 11 (15.5%) residual disease. In the overall population, within a median follow-up for alive patients of 10.9 months (IQR = 3.6–38.9), 82 patients died and 43 died of their bladder cancer. The 2-year and 5-year OS were 58% and 34%, respectively. On univariable analyses, RT was associated with shorter OS compared to RC. The 2-years and 5-years OS were 66% and 42% in patients treated with RC and 49% and 25% in patients treated with RT, respectively, corresponding to a HR of 1.78 (95% CI = 1.15–2.77, $p = 0.01$ (Supplementary Figure S2). There was no difference between RC and RT with regards to CSS. The 2-year and 5-year CSS were 70% and 57% in patients treated with RC and 71% and 56% in patients treated with RT, respectively, corresponding to a HR of 1.1 (95% CI = 0.60–2.03, $p = 0.74$, Supplementary Figure S2).

Using propensity scoring, a total of 46 patients treated with RT were matched 1:1 with the subgroup of patients treated with RC. After matching, the two groups did not differ in preoperative clinicopathologic features anymore (Table 1). Within a median follow-up for alive patients in the matched

Table 1. Clinicopathologic features of patients with high-risk bladder cancer stratified by treatment before and after propensity-score matching.

	Overall population				Matched population			
	RT	RC	*p* value	SMD	RT	RC	*p* value	SMD
n (%)	71	98			46	46		
Age, mean (SD)	80.3 (8.3)	67.7 (10.1)	<0.001	1.356	77.3 (7.9)	74.6 (7.5)	0.1	0.342
Male gender, *n* (%)	59 (83.1)	78 (79.6)	0.7	0.09	38 (82.6)	38 (82.6)	1	<0.001
Age adjusted CCI, mean (SD)	8.4 (2.6)	6.3 (2.6)	<0.001	0.467	7.8 (2.2)	7.6 (2.3)	0.7	0.077
Clinical T stage, *n* (%)			0.01	0.467			1	0.091
NMIBC	7 (9.9)	27 (27.6)			6 (13)	7 (15.2)		
T2	59 (83.1)	66 (67.3)			35 (76.1)	35 (76.1)		
T3	5 (7)	5 (5.1)			5 (10.9)	4 (8.7)		
P-score, mean (SD)	0.38 (0.23)	0.73 (0.24)	<0.001	1.495	0.47 (0.23)	0.55 (0.23)	0.07	0.378
Pathological T stage at 2nd look TURB, *n* (%)								
T0	6 (25)	–			2 (12.5)	–		
Tis	2 (8.3)	–			2 (12.5)	–		
T1	3 (12.5)	–			3 (18.7)	–		
T2	13 (54.2)	–			9 (56.3)	–		
Pathological T stage, *n* (%)*								
T0	–	4 (4.1)			–	2 (4.3)		
NMIBC	–	25 (25.5)			–	7 (15.2)		
T2	–	27 (27.6)			–	13 (28.3)		
T3	–	31 (31.6)			–	19 (41.3)		
T4	–	11 (11.2)			–	5 (10.9)		

RC: Radical cystectomy; RT: Radiotherapy; CCI: Charlson comorbidity index; NMIBC: non-muscle-invasive bladder cancer; SD: standard deviation; SMD: standardized mean difference.
*After radical cystectomy.

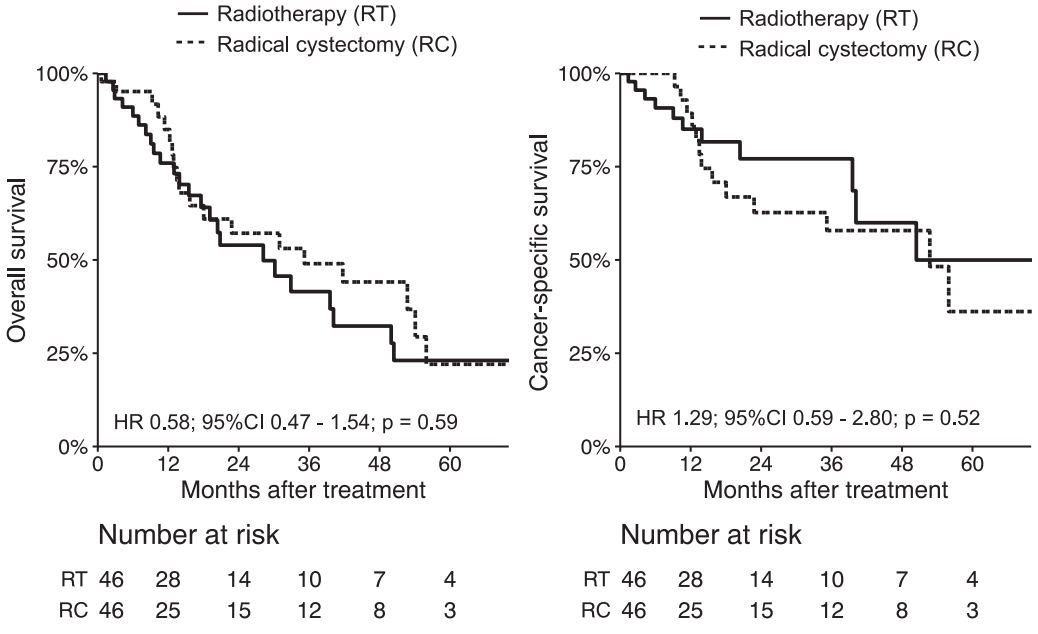

Figure 1. Overall survival and cancer-specific survival of 92 patients with high-risk bladder cancer after propensity-score matching, stratified by treatment.

population of 10.8 months (IQR = 3.79–27.7), 46 patients died and 26 patients died of their bladder cancer. On univariable analyses, RT was neither associated with OS (HR = 0.85, 95% CI = 0.47–1.54, $p = 0.59$) nor CSS (HR = 1.29, 95% CI = 0.59–2.8, $p = 0.5$) compared to RC. The 2-year and 5-year OS were 57% and 22% in patients treated with RC and 54% and 23% in patients treated with RT, respectively. The 2-year and 5-year CSS were 63% and 36% in patients treated with RC and 77% and 50% in patients treated with RT, respectively (Figure 1).

In the competing risk analysis with 'death from other cause' as competing risk, no statistically significant association of treatment type (RC vs RT) was observed in the total (HR = 1.26, 95% CI = 0.52–3.01, $p = 0.6$) or in the matched (HR = 1.34, 95% CI = 0.56–3.19, $p = 0.5$) data set. On multivariable competing risk analyses, treatment was not associated with survival outcomes. In the matched cohort, clinical stage had to be removed from the multiple model due to convergence problems (Supplementary Table S1 and Table 2). The cumulative incidence functions for the overall and the matched population are plotted in Supplementary Figure S3 and Figure 2, respectively.

Discussion

Patients diagnosed with MIBC are generally frail because of their advanced age, comorbidities and poor performance

status [14]. This frailty is often prohibitive of a radical surgery and systemic therapy, leaving RT as the only option. However, the efficacy of RT in this frail patient population has not been elucidated.

Using propensity score with stringent criteria, we generated two comparable treatment groups. We found that RT was associated with improved CSS but not OS compared to RC. However, these results must be interpreted within the study design and the treated population. Indeed, in the overall population, RC was associated with longer OS. This finding was consistent with those reported by previous studies. Indeed, three retrospective analyses of the National Cancer Database showed a significant longer OS and CSS in patients treated with RC compared to those treated with trimodal therapy [15–17]. Analogous to our study, similar statistical methods were used. However, patients included were in general healthier and the effect of RT alone was not investigated. In another single-center retrospective analysis with one third of patients having a CCI $>$ 4, there was no difference in OS and CSS between TMT and RC using propensity score matching. However, patients ineligible for cisplatin-based chemotherapy were excluded from the analysis [11]. A recent analysis on 3,309 patients from 'The bladder cancer data base Sweden' investigated the survival of patients treated with RT and RC using a population theoretically eligible for inclusion in a trial comparing these two therapies. Using instrumental variable analysis, the authors found no statistically significant difference in OS and CSS between groups [18].

To our knowledge, this is the first study investigating the effect of RT in a cohort of patients considered unfit for extirpative surgery and systemic chemotherapy and comparing it to a matched cohort of patients treated with RC.

Given the number of comorbidities and the high probability of death of other cause in the elderly bladder cancer patient cohort, we further analysed the data using competing risk analysis. The results expanded upon those obtained by conventional methods for survival analysis. In a matched cohort of patients, RT was independently associated with longer survival from bladder cancer. Moreover, the adjusted sub-distribution hazard model showed the frailty of the patients in the RT cohort, having significantly more patients dying from other causes in the RT compared to RC in the overall as well as in the matched population. Moreover, the 2-years OS of patients treated with RT in our series is slightly shorter to that reported in other series [10,19], reflecting the frailty of the patients included in our analysis. This clearly differentiates our population from that of other studies [9,11], suggesting a need for better patient selection prior to definitive treatment [20].

Incorrect staging due to inappropriate clinical judgment and limitations inherent to imaging modalities represents a challenge for all clinicians [21]. Compared to the current literature, upstaging rates in our RC cohort is within the lower bound, reflecting an acceptable clinical staging. Indeed, previous reports have shown an upstaging at RC in up to 50% of the cases [22], while, in our cohort, it was $\sim$ 30% and with almost no change in the matched cohort. However, one must be aware that patients with lower tumor burden may have been selected for RT in concert with the recommendations of current guidelines [1,2]. This could partially explain

Table 2. Multivariable proportional hazards regression model assessing the effect of covariates on the sub-distribution of death from bladder cancer with death from other causes as a competing risks event in the matched population of 92 patients.

	HR	95% CI	*p* value
RC vs RT	1.34	0.56–3.19	0.5
Age	0.98	0.91–1.05	0.6
Age adjusted CCI	0.82	0.68–0.99	0.04

RT: radiotherapy; RC: Radical cystectomy; CCI: Charlson comorbidity index; HR: Hazard ratio; CI: Confidence interval.

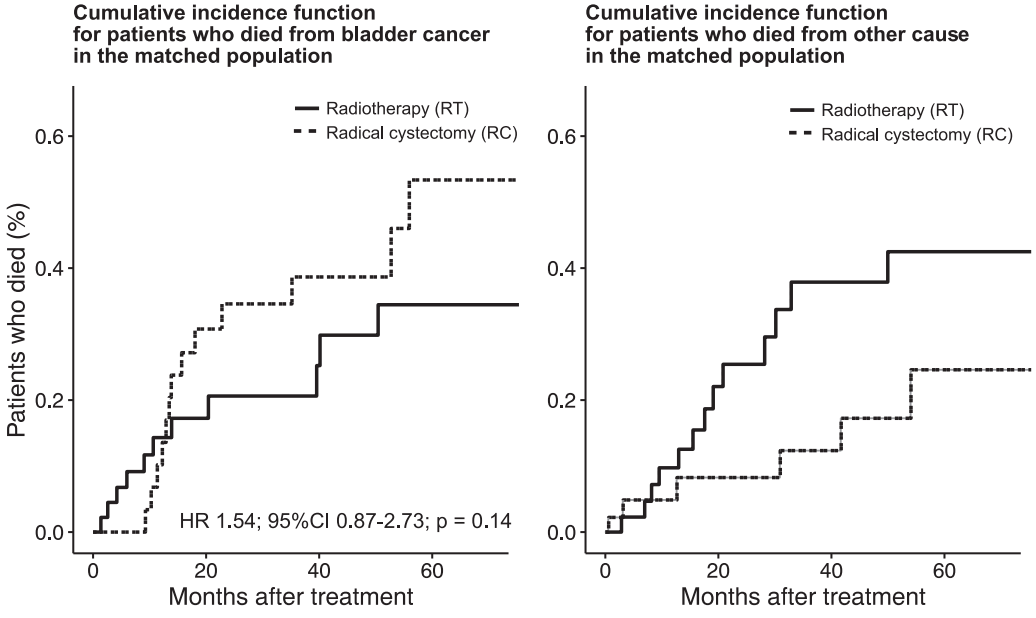

Figure 2. Competing risk with death from other cause as competing risk in 92 patients with high-risk bladder cancer after propensity-score matching, stratified by treatment.

the different results in survival outcomes between the overall and the matched population.

There are limitations to our analyses that deserve particular attention and are inherent to the retrospective design with a relatively small sample size. We had no pathological re-review of the specimens. Therefore, we could not account for some prognostic relevant pathologic features like concomitant CIS, lymphovascular invasion or variant histology [19–21]. Indeed, some variants are thought to have a better response to RT and others rather to extirpative surgery [23]. Despite matched pair analysis, there is still a clinically relevant selection bias due to population heterogeneity and unknown confounders which we could not account for [24]. Indeed, the two treatment groups, RT and RC, in the original data set are very different concerning age, age-adjusted CCI and clinical stage. Thus, the matching algorithm only selected a small number of patients to generate two homogenous samples. There was no assessment of reinterventions, complications or quality-of-life for either of the two populations. Finally, the decision of unfit patients was based on clinical evaluation by the treating physician and was not standardized.

The results of our analysis generate the hypothesis that RT may be an alternative option in well selected patients with limited disease who are considered unfit for systemic chemotherapy or RC. Future research should focus on improving patient selection and assess the quality-of-life as well as the need for reintervention in patients treated with RT.

Informed consent

Due to the retrospective nature of the study, no informed consent was needed

Disclosure statement

Dr. D'Andrea has nothing to disclose; Dr. Soria has nothing to disclose; Dr. Zehetmayer has nothing to disclose; Dr. Stangl-Kremser has nothing to disclose; Dr. Grubmüller has nothing to disclose; Dr. Abufaraj has nothing to disclose; Dr. Gust reports personal fees from Advisory Board: Cepheid, Ferring, Roche and MSD, personal fees from Speaker: Astellas, Astra Zeneca, BMS, Ipsen, Janssen, MSD and Roche, other from Meeting/travel expenses: Allergan, Astellas, Astra Zeneca, Bayer, BMS, Janssen, MSD, Novartis, Pfizer, Pierre Fabre and Roche, outside the submitted work; Dr. Kimura has nothing to disclose; Dr. Babjuk has nothing to disclose; Dr. Goldner has nothing to disclose; Dr. Shariat reports personal fees from Nucleix (Rehovot, Israel) during the conduct of the study; other from Method to determine prognosis after therapy for prostate cancer; Granted 2002-09-06, other from Method to determine prognosis after therapy for bladder cancer; Granted 2003-06-19, other from Prognostic methods for patients with prostatic disease; Granted 2004-08-05, other from Soluble Fas urinary marker for the detection of bladder transitional cell carcinoma; Granted 2010-07-20, other from Astellas, Astra Zeneca, Bayer, BMS, Cepheid, Ferring, Ipsen, Janssen, Lilly, MSD, Olympus, Pfizer, Pierre Fabre, Roche, Sanochemia, Sanofi and Wolff, outside the submitted work

Research involving human participants and/or animals

This retrospective study was approved by the ethics committee of Medical University of Vienna (IRB Nr 2196/2018). This article does not contain any studies with animals performed by any of the authors.

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