

Age above 70 years and Charlson Comorbidity Index higher than 3 are associated with reduced survival probabilities after radical cystectomy for bladder cancer. Data from a contemporary series of 334 consecutive patients

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Summary *Objective: To assess the joint effect of age and comorbidities on clinical outcomes of radical cystectomy (RC).*

Methods: 334 consecutive patients undergoing open RC for bladder cancer (BC) during the years 2005-2015 were analyzed. Pre-, peri- and post-operative parameters, including age at RC (ARC) and Charlson Comorbidity Index (CCI), were evaluated. Overall and cancer-specific survivals (OS, CSS) were assessed by univariate and multivariate modelling. Furthermore, a three-knot restricted cubic spline (RCS) was fitted to survival data to detect dependency between death-rate ratio (HR) and ARC.

Results: Median follow-up time was 3.8 years (IQR = 1.3-7.5) while median OS was 5.9 years (95%CL = 3.8-9.1). Globally, 180 patients died in our cohort (53.8%), 112 of which (62.2%) from BC and 68 patients (37.8%) for unrelated causes. After adjusting for preoperative, pathological and perioperative parameters, patients with CCI > 3 showed significantly higher death rates (HR = 1.61; p = 0.022). The highest death rate was recorded in ARC = 71-76 years (HR = 2.25; p = 0.034). After fitting an RCS to both OS and CSS rates, two overlapping non-linear trends, with common highest risk values included in ARC = 70-75 years, were observed.

Conclusions: Age over 70 years and CCI > 3 were significant factors limiting the survival of RC and should both be considered when comparing current RC outcomes.

KEY WORDS: Radical cystectomy; Comorbidity; Age; Frail patient; Elderly.

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INTRODUCTION

Bladder cancer is one of the most common urological neoplasms and often requires multiple surgical treatment, as well as radical and invasive therapies (1-3).

Surgery in the form of Radical Cystectomy (RC) represents the mainstay treatment for organ-confined and locally advanced muscle-invasive BC (MIBC). Reference studies of RC showed long-term survival rates around 60% and 40% at 5 and 10 years, respectively (4-6). Such

results published in the first years of this century were obtained in patients treated in a time period spanning from 1995 to 2003, with a median age of 65 to 67 years, and no mention with regards to the presence of co-morbidities is available. In recent years, however, global life expectancy has increased in both sexes causing an expansion of the elderly segment of the population.

Ageing is one of the reasons for increase in cancer incidence worldwide and, with regards specifically to BC, a 1.5-fold rise has been observed in subjects of 70 years of age and beyond (7). In the ageing population systemic diseases are concurrently diagnosed, namely, cardio-vascular, respiratory, metabolic, etc., therefore the need for chronic medications often represents the norm rather than the exception (8-9). The present study was aimed at documenting the association of advanced age together with the presence of co-morbidities on clinical outcomes of RC.

MATERIALS AND METHODS

Study design and patient population

The study population consisted of 334 patients submitted consecutively to RC from 01/01/2005 to 31/12/2015 at our tertiary care center and teaching institution, the University of Genova, Italy. All the charts were examined and data were extracted with regards to pre-, intra-, and post-operative parameters. Follow-up records and life status were retrieved from the internal follow-up database of our Institute, the Liguria Hospitalization Records, the Regional Mortality Registry, and the Genova Cancer Registry. Patients who received neo-adjuvant or adjuvant chemotherapy were excluded from analysis, whereas patients who received salvage (post-RC) chemotherapy and/or radiotherapy were included.

Patients' characteristics

The recorded baseline patients' characteristics were: age at RC (ARC), gender, full medical history, 12 channel Serum Multiple Analysis Compound (SMAC), physical examination, self-reported comorbidities and chronic

need for medications, ECG and cardiologic assessment, anesthesiology assessment and *American Society of Anesthesiology* (ASA) score, and clinical stage of disease. In addition, the *Charlson comorbidity index* (CCI) score was assigned based on the recorded data.

Clinical staging was based on the pathology report of staging trans-urethral resection and by chest and abdomen CT scan. Additional tests (i.e. bone scans) were requested at the discretion of the treating physician.

TREATMENT

All patients underwent RC with bilateral pelvic lymphadenectomy with the standard technique (4; 5; 6). Briefly, in the male patient the bladder, prostate, and seminal vesicles, and in the female patient the bladder, uterus, ovaries and anterior wall of the vagina, were removed en bloc. Pelvic lymphadenectomy included all the tissue overlaying the major pelvic vessels from the crossing of the ureter over the iliac vessels proximally to the internal inguinal ring distally, and from the genito-femoral nerve laterally to the obturator fossa medially. A form of urinary diversion (i.e. orthotopic reservoirs, ileal conduits, and uretero-cutaneostomy) was selected based on disease stage, ARC, co-morbidities, and the surgeon's preferences. Additional data searched included pathological stage and grade, *post-operative mortality* (POM), 90-day post-operative incidence of complications using the Clavien-Dindo scale (10), and length of hospitalization.

Follow-up data comprised evidence of local and/or distant recurrence, need for further treatment, vital status, and cause of death.

Outcomes

Two survival outcomes were considered: OS when all deceased patients were assumed to die from BC regardless of the certified cause of death, and CSS when patients died from causes other than BC were considered as censored at the date of death. Patients' characteristics taken into consideration for analysis were: ARC, gender, CCI score, baseline *hemoglobin* (Hb) and *creatinine* (Cr) levels, tumor size, lymph-node involvement, histotype, type of urinary diversion and complications.

Statistical analysis

Patients and disease-related prognostic factors were explored using descriptive statistics. Continuous variables were described using median values and ranges of variation (min-max) and categorized according to statistically or clinically meaningful thresholds, namely quintiles for ARC and a level of 10.0 g/dL, and 1.2 mg/dL for Hb and serum Cr, respectively. A CCI score of 3 was used as a cut-off in order to separate lower from higher comorbid patients. All categorical factors were finally expressed in terms of absolute and relative frequencies. Univariate survival comparisons were carried out using the Kaplan-Meier method and the statistical significance of each comparison was assessed by the log-rank test. The association of ARC and CCI score with survival probability was estimated using the Cox regression modelling and expressed as death rate ratio (HR) and corresponding 95% confidence limits (95% CL). For each prognostic factor the Cox regression allows to obtain an HR value adjusted

for the potential confounding effect of other variables entered the same equation. The likelihood ratio test was applied to evaluate the statistical significance of each prognostic variable included in the Cox model (11).

In order to point out a non-linear dose-response relationship between ARC and death rates, potentially blurred by the categorization process, a three-knot *restricted cubic spline* (RCS) was fitted to survival data with the Cox regression equation. RCS is a flexible fitting procedure that allows the observed data to determine a smoothed functional form of dependency between the death rate (i.e., response) and a continuous prognostic variable (i.e., dose) (12). A two-tailed p-value < 0.05 was considered as significant. All analyses were performed using *Stata* (*Stata Corp. Statistical Software, release 14. Statistical Software. College Station, TX: StataCorp LP, 2015*).

Table 1.

Frequency distribution of patients' baseline characteristics.

Patients' characteristics	No.	%
Age (yrs) at radical cystectomy (median, range)	71, 46-87	-
46-65	66	19.8
66-70	68	20.4
71-76	66	19.8
77-80	67	20.0
81-87	67	20.0
Gender		
Male	288	86.2
Female	46	13.8
Raw Charlson comorbidity index		
≤ 3	269	80.5
> 3	59	17.7
Missing	6	1.8
Tumor stage		
T0-T1	203	60.8
T2-T3	93	27.8
T4	38	11.4
Histotype		
Urothelial	263	78.7
Non urothelial/rare variant	71	21.3
Lymph node involvement		
N0	227	68.0
N1-N3	73	21.9
NX	34	10.2
Preoperative hemoglobin		
≤ 10.0 g/dL	10	3.0
> 10.0 g/dL	302	90.4
Missing	22	6.6
Preoperative creatinine		
≤ 1.2 mg/dL	247	74.0
> 1.2 mg/dL	65	19.5
Missing	22	6.6
Early complications		
No	289	86.5
Yes	45	13.5
Late complications		
No	289	86.5
Yes	45	13.5
Urinary diversion		
Ureterocutaneostomy/ileal conduit	203	60.8
Orthotopic neobladder	131	39.2
Days of hospitalization (median, range)	18, 2-80	-
2-13	88	26.4
14-17	73	21.9
18-23	94	28.1
24-80	79	23.7
Whole sample	334	100.0

Table 2.

One-, three- and five-year overall survival probabilities (Pr) estimated through the Kaplan-Meier method according to levels of study prognostic factors.

Patients' characteristics				Follow-up		One-year		Overall survival		Five-year		P-value
	T	D	D%	Med	IQR	Pr	95%CL	Pr	95%CL	Pr	95%CL	
Age at radical cystectomy												
46-65	66	26	39.4	6.8	2.4-10.0	0.89	0.79-0.94	0.71	0.58-0.80	0.66	0.53-0.76	0.006
66-70	68	34	50.0	4.1	1.6-8.3	0.84	0.72-0.90	0.62	0.48-0.71	0.55	0.41-0.65	
71-76	66	38	57.6	3.5	0.9-6.0	0.70	0.57-0.79	0.54	0.41-0.65	0.47	0.34-0.58	
77-80	67	40	59.7	3.3	1.0-6.5	0.75	0.62-0.83	0.58	0.45-0.68	0.47	0.34-0.59	
81-87	67	42	62.7	2.3	0.9-6.2	0.72	0.59-0.80	0.47	0.34-0.58	0.43	0.30-0.54	
Gender												
Male	288	155	53.8	3.7	1.3-7.5	0.78	0.72-0.82	0.58	0.51-0.63	0.52	0.46-0.57	0.882
Female	46	25	54.3	3.9	1.1-7.2	0.76	0.60-0.85	0.63	0.47-0.75	0.50	0.33-0.63	
Raw Charlson comorbidity index												
≤ 3	269	131	48.7	4.4	1.7-8.1	0.82	0.76-0.85	0.63	0.56-0.68	0.57	0.50-0.62	< 0.001
> 3	59	43	72.9	1.6	0.9-5.2	0.66	0.52-0.76	0.44	0.31-0.56	0.33	0.21-0.45	
Missing	6	6	100.0	0.1	0.0-0.2	0.17	0.00-0.51	0.17	0.00-0.51	0.17	0.00-0.51	
Tumor stage												
T0-T1	203	90	44.3	5.2	2.3-8.4	0.85	0.79-0.89	0.72	0.65-0.77	0.65	0.57-0.71	< 0.001
T2-T3	93	63	67.7	1.9	0.9-4.8	0.70	0.59-0.78	0.38	0.28-0.48	0.33	0.23-0.42	
T4	38	27	71.1	1.3	0.4-4.2	0.58	0.40-0.71	0.34	0.19-0.48	0.28	0.14-0.42	
Histotype												
Urothelial	263	137	52.1	4.0	1.5-8.3	0.81	0.75-0.84	0.62	0.55-0.67	0.53	0.46-0.59	0.032
Non urothelial/rare variant	71	43	60.6	2.2	0.5-6.3	0.68	0.55-0.77	0.46	0.33-0.57	0.46	0.33-0.57	
Lymph node involvement												
N0	227	101	44.5	8.4	2.1-8.4	0.85	0.79-0.89	0.70	0.63-0.75	0.63	0.55-0.68	< 0.001
N1+N2	73	53	72.6	4.7	0.8-4.6	0.64	0.52-0.74	0.35	0.24-0.46	0.29	0.19-0.40	
NX	34	26	76.5	5.2	0.4-5.2	0.59	0.40-0.73	0.32	0.17-0.48	0.29	0.15-0.44	
Preoperative hemoglobin												
≤ 10	10	8	80.0	0.4	0.2-1.0	0.40	0.12-0.67	0.20	0.03-0.47	0.20	0.03-0.47	0.002
> 10	302	156	51.7	3.9	1.4-7.4	0.80	0.75-0.84	0.61	0.55-0.66	0.54	0.48-0.59	
Missing	22	16	72.7	1.5	0.2-8.2	0.59	0.36-0.76	0.41	0.20-0.60	0.32	0.14-0.51	
Preoperative creatinine												
≤ 1.2	247	118	47.8	4.4	1.7-7.9	0.83	0.77-0.87	0.65	0.58-0.70	0.58	0.51-0.63	< 0.001
> 1.2	65	46	70.8	1.9	0.6-5.6	0.65	0.51-0.74	0.40	0.27-0.51	0.36	0.24-0.48	
Missing	22	16	72.7	1.5	0.2-8.2	0.59	0.36-0.76	0.41	0.20-0.60	0.32	0.14-0.51	
Early complications												
No	289	151	52.2	4.0	0.7-0.8	0.81	0.75-0.85	0.61	0.55-0.66	0.54	0.47-0.59	0.009
Yes	45	29	64.4	1.7	0.4-0.6	0.58	0.42-0.70	0.42	0.27-0.55	0.40	0.25-0.53	
Late complications												
No	312	167	53.5	3.9	1.3-7.5	0.79	0.73-0.82	0.60	0.54-0.64	0.53	0.46-0.58	0.241
Yes	22	13	59.1	2.1	0.9-4.5	0.68	0.44-0.83	0.41	0.20-0.60	0.41	0.20-0.60	
Urinary diversion												
Ureterocutaneous/ileal conduit	203	124	60.9	2.5	0.9-6.3	0.70	0.64-0.76	0.50	0.43-0.56	0.44	0.37-0.51	< 0.001
Orthotopic neobladder	131	56	42.7	5.2	2.2-8.9	0.89	0.83-0.94	0.72	0.64-0.79	0.65	0.56-0.72	
Whole sample	334	180	53.9	3.8	1.3-7.5	0.78	0.73-0.82	0.58	0.53-0.64	0.52	0.46-0.57	.

T: sample size; D/D%: number/percent of deceased patients; Med: median of follow-up time (years); IQR: inter-quartile range (min-max); 95%CL: 95% confidence limits for estimated Pr; P-value: probability level associated with the log-rank test.

RESULTS

Baseline patients' characteristics are listed in Table 1.

The median follow-up time was 3.8 years (IQR = 1.3-7.5 years). During the study period, a total of 180 patients died (53.8%), 68 (62.2%) from all causes whereas the remaining 112 patients (37.8%) from BC. The median OS was 5.9 years (95%CL = 3.9-8.1 years). 288 (86.2%) patients were male whereas 46 (13.8%) patients were female.

Table 2 shows the results of univariate OS analysis. ARC, CCI, tumor stage, histotype, preoperative hemoglobin and creatinine levels, and urinary diversion showed a strong association with OS. A significant decreasing tendency in OS probabilities was found to be associated to an increasing ARC (p-value = 0.006). In addition, comorbid patients with CCI score > 3 showed a twofold increased death rate (p-value < 0.001) when compared to patients with lower CCI score (≤ 3).

The cumulative effect on OS of ARC and CCI score was assessed in a multivariate context by modelling data using the Cox regression. After adjusting for gender, tumor stage, lymph node involvement, preoperative Hb and Cr levels, complications, and urinary diversion the significant association of ARC and CCI score with OS was confirmed (Table 3, Model 1). Specifically, patients with CCI score > 3 showed a death rate excess of about 60% when compared to patients with CCI score ≤ 3 (HR = 1.61; 95%CL

Table 3.

Joint effect of age at radical cystectomy (ARC) and Charlson comorbidity index (CCI) on overall and bladder cancer-specific survival estimated through the Cox regression model.

Regression model	Patients' characteristics	Overall survival Deaths = 164 (52.7%)			Cancer-specific survival Deaths = 101 (32.5%)		
		HR	95%CL	P-value	HR	95%CL	P-value
1	Age at radical cystectomy			0.034			0.750
	46-65	1.00	(Ref.)		1.00	(Ref.)	
	66-70	1.92	1.06-3.47		1.57	0.77-3.16	
	71-76	2.25	1.28-3.94		1.41	0.69-2.84	
	77-80	2.08	1.19-3.64		1.44	0.73-2.84	
	81-87	2.03	1.16-3.57		1.41	0.70-2.81	
	Charlson comorbidity index			0.022			0.253
≤ 3	1.00	(Ref.)		1.00	(Ref.)		
> 3	1.61	1.07-2.41		1.38	0.80-2.38		
2	Age at radical cystectomy			0.155			0.431
	46-69	1.00	(Ref.)		1.00	(Ref.)	
	70-80	1.39	0.97-1.99		1.09	0.70-1.71	
	81-87	1.04	0.59-1.83		0.68	0.31-1.48	
	Charlson comorbidity index			0.054			0.437
≤ 3	1.00	(Ref.)		1.00	(Ref.)		
> 3	1.50	0.98-2.26		1.26	0.72-2.21		

HR: death rate ratio adjusted for gender, tumor size, lymph nodes involvement, pre-operative hemoglobin and creatinine, early and late complications, urinary diversion; 95%CL: 95% confidence limits for HR; Ref.: reference category; P-value: probability level associated with the likelihood ratio test.

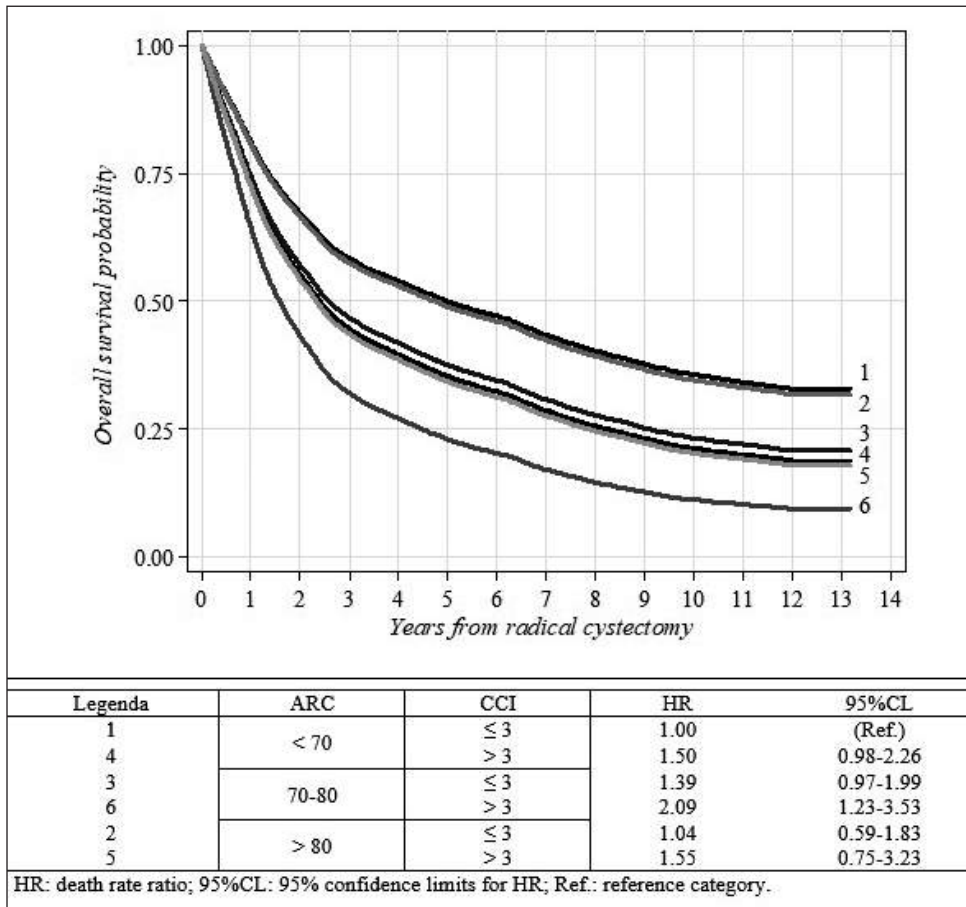


Figure 1. Joint effect of age at radical cystectomy (ARC) and raw Charlson comorbidity index (CCI) on life expectancy estimated through the Cox regression model. Overall survival probabilities are adjusted for gender, tumor size, lymph node involvement, pre-operative hemoglobin and creatinine, early and late complications, urinary diversion.

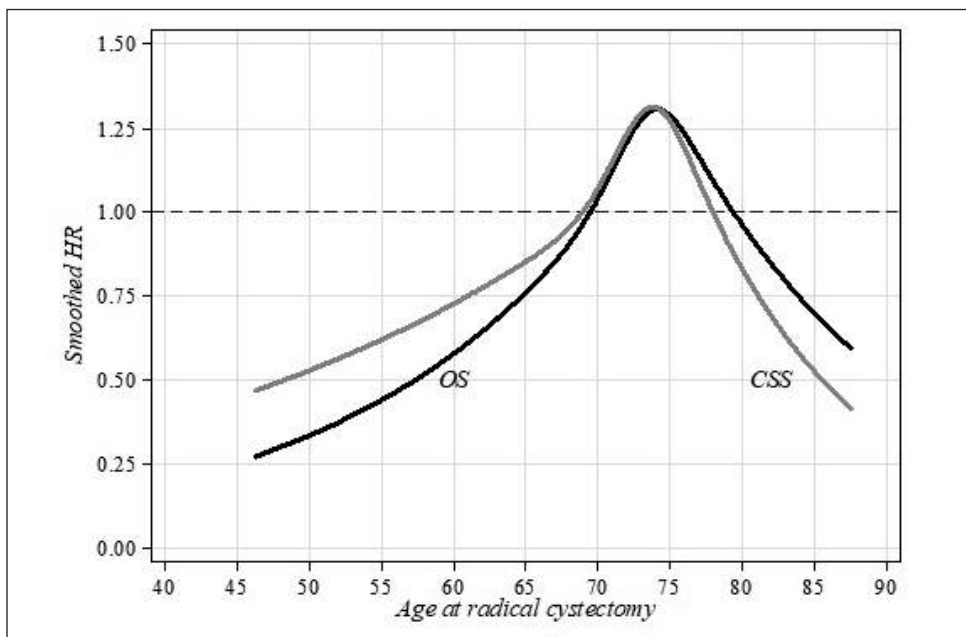


Figure 2. Relationship between overall (OS) and cancer specific (CSS) death rate ratio (HR) and age at radical cystectomy (ARC) estimated using the Cox regression model adjusted for gender, tumor size, lymph node involvement, pre-operative hemoglobin and creatinine, early and late complications, urinary diversion. Smoothed HR point estimates were obtained by fitting three-knot cubic spline functions to OS and CSS data.

= 1.07-2.41; p-value = 0.022). An increase in death rates by ARC was observed although the estimated dose-response relationship appeared to be non-linear. In other words, assuming the death rate of the lowest ARC category (46-65 years) as a reference (HR = 1.00) the highest rate was estimated in the intermediate category 71-76 years (HR = 2.25, 95%CL = 1.28-3.94).

In order to point out better such a non-monotonic tendency, a Cox model was fitted to OS data after rearranging ARC in three categories using 70 and 80 years as threshold values (Table 3, Model 2; Figure 1). In this case, the intermediate category (70-80 years) showed a death rate which was about 40% higher than those in the other two categories (46-69 and 81-87 years), even though a

loss in statistical power was pointed out (p-value = 0.155). In order to assess the influence of death on the relationship between ARC and CCI on survival, all previous analyses were repeated using CS mortality as an outcome. After fitting a three-knot RCS (Figure 2) to both survival data series, two overlapping non-linear trends with common upmost risk values included in the ARC group 70-75 years were pointed out.

DISCUSSION

Multiple systemic diseases known as co-morbidities are diagnosed in the ageing men and women whom, in addition, are also exposed to the risk of developing cancer (8-9). Notably, the presence of multiple systemic diseases necessitating chronic treatment can also undermine the results of cancer treatment.

The effect of ARC on the prognosis has been investigated previously. The conclusion reported so far are heterogeneous probably because, among other reasons, an objective threshold for dichotomizing this risk factor is not clearly identifiable and, accordingly, the issue remains controversial. Nevertheless, in several studies increased ARC showed an association with poor prognosis and survival (13-16) and although RC is currently performed in advanced age subjects a systematic review of the literature has outlined a decline in both OS and CSS beginning at the age of 70 years (17).

The association of comorbidities and survival after RC has also been investigated. The Adult Co-morbidity Evaluation 27 instrument (ACE-27) was used retrospectively in some studies (18-19) showing that co-morbidity score and pathologic stage of disease significantly correlated with reduced OS. Moreover, in the severe comorbidity group the number needed to harm was 6, that is, for every 6 patients dying after RC 1 death occurred due to co-morbidity per se.

The CCI score was used also and correlated with the outcomes of RC. *Koppie et al.* classified RC patients with the age-adjusted CCI (AA-CCI) into three groups, namely i) low AA-CCI score ≤ 2 , ii) moderate AA-CCI score of 3 to 5, and iii) a high AA-CCI score > 5 (20). They found a median OS time of 6.3 years, 3.9 years, and 1.7 years in the low, moderate, and high score groups, respectively. *Mayr et al.* compared the ASA score, the ACE 27 instrument, the ECOG scale, and the AA-CCI (21). The Authors found that none of the comorbidity indices were significant predictors for CSS, whereas each index was a significant predictor for cancer-independent mortality. Importantly, based on ARC and comorbidity a weighed prognostic risk model was developed where after 3 years 47% of the patients within the high-risk group died of causes other than BC, compared with 8% of patients within the low-risk group.

In a recently published study, *D'Andrea et al.* analysed a cohort of 46 patients with localized MIBC who were considered unfit for RC or TT, and therefore sent to RT alone (22). Their survival outcomes were compared to an equal number of patients treated with RC. After performing a propensity score analysis CSS and OS of the patients undergoing RT were substantially the same as those who were treated with RC.

The main findings of our study can be summarised as follows. First, after adjusting for known prognostic factors (Table 1), patients in the age group 70-80 years showed the greater mortality risk. Second, after eliminating the competitive risk of death due to causes different from BC, the curves of OS and CSS show a parallel profile, as outlined by the RCS analysis (Figure 2). Finally, in patients with 70-80 years and CCI score > 3 the mortality risk is remarkably higher (HR = 2.09, 95%CL = 1.23-3.53) than all other groups (Figure 1). These findings reproduce closely what reported previously by other authors (21).

Certain limitations of our study are to be acknowledged. Firstly, inherent to the retrospective nature of the investigation (study period: 2005-2015), although the comorbidities were listed at the moment of patient enrolment, the CCI score was retrospectively assigned. Secondly, the CCI score has been commonly used to assess survival for various cancers since it offers a general patient evaluation. However, some particular conditions, i.e., hypertension, lung diseases in the absence of chronic obstructive disease, coronary artery disease in the absence of myocardial infarction, etc., are overlooked. Thirdly, based on our dataset we were unable to address several concurrent factors that may have had an influence on survival such as a delay from symptoms-onset and diagnosis/treatment, nutritional status, and post-operative hospitalization in intensive care units, among others.

On the other hand, the strengths of our study are to be acknowledged as well. Two factors known to influence prognosis are addressed jointly, namely age and co-morbidities, and we were able to confirm their cumulative effect on survival after RC, as previously observed by other researchers. Moreover, the study cohort consists in series of consecutive subjects treated at a single referral, high volume center, offering a homogeneous treatment to all patients, that is, RC alone (with pelvic lymphadenectomy), and no selection was made to exclude from treatment older and sicker patients.

CONCLUSIONS

In conclusion, in the present cohort analysis of BC patients consecutively submitted to RC we were able to identify age 70-80 years and higher CCI score (> 3) as significant factors limiting a better prognosis.

Although in principle we believe that surgery should not be precluded in the presence of advanced age and comorbidities both factors should be attentively considered when comparing outcomes after RC in contemporary series. Implementation of ad hoc trials, focusing on these patients, should be encouraged.

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