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ORIGINAL ARTICLE

Older patients with low Charlson score and high-risk prostate cancer benefit from radical prostatectomy

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Abstract
Introduction The aim of the study was to identify the appropriate level of Charlson comorbidity index (CCI) in older patients (>70 years) with high-risk prostate cancer (PCa) to achieve survival benefit following radical prostatectomy (RP).
Methods We retrospectively analyzed 1008 older patients (>70 years) who underwent RP with pelvic lymph node dissection for high-risk prostate cancer (preoperative prostate-specific antigen >20 ng/mL or clinical stage ≥T2c or Gleason ≥8) from 14 tertiary institutions between 1988 and 2014. The study population was further grouped into CCI < 2 and ≥2 for analysis. Survival rate for each group was estimated with Kaplan–Meier method and competitive risk Fine-Gray regression to estimate the best explanatory multivariable model. Area under the curve (AUC) and Akaike information criterion were used to identify ideal 'Cut off' for CCI.
Results The clinical and cancer characteristics were similar between the two groups. Comparison of the survival analysis using the Kaplan–Meier curve between two groups for non-cancer death and survival estimations for 5 and 10 years shows significant worst outcomes for patients with CCI ≥ 2. In multivariate model to decide the appropriate CCI cut-off point, we found CCI 2 has better AUC and *p* value in log rank test.
Conclusion Older patients with fewer comorbidities harboring high-risk PCa appears to benefit from RP. Sicker patients are more likely to die due to non-prostate cancer-related causes and are less likely to benefit from RP.

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Keywords High-risk prostate cancer · Radical prostatectomy · Charlson comorbidity index · Survival benefit

Introduction

Radical prostatectomy (RP) is the treatment of choice for localized prostate cancer (PCa) with superior survival advantage [1]. Improved experience with the RP surgical technique and introduction of robots for surgical assistance has enabled surgeons around the world to achieve better long-term surgical outcomes and simultaneously reduce the adverse effects of the surgery [2]. This improvement in the overall surgical performance of RP resulted in extending the indications of RP, which is continuously evolving with innovative treatment options [3, 4]. Several experienced centers have evaluated the feasibility of RP in localized high-risk PCa and reported positive outcomes. However, evaluation of the survival benefit offered by RP in this cohort of patients is often difficult since majority of these patients are often offered non-operative treatment and many patients die of causes not related to cancer even with the presence of high-risk disease [5–16].

Charlson score is an index for comorbidity (CCI), which is a commonly utilized parameter to assess comorbidities. It is centrally calculated with computer software and is assigned to each patient depending on number of comorbidities present at the time of surgery. Briganti et al. [17] demonstrated using CCI, in high-risk PCa, RP is likely to benefit younger and healthier patients, while older and sicker patients with multiple comorbidities are more likely to die of other causes. The ideal cut off of CCI in older patients is often arbitrary and decided based on the surgeons' experience. In the present study, we retrospectively evaluated the

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multicenter EMPacT database on older patients (>70 years) with high-risk PCa to identify the appropriate level of CCI to achieve survival benefit from RP.

Materials and methods

Study population

We retrospectively analyzed 7651 patients with PCa treated with RP from 14 tertiary institutions from 1988 to 2014. We selected patients aged 70 or more, with high-risk PCa according to EAU (European Association of Urology) risk stratification criteria (preoperative prostate-specific antigen (PSA) >20 ng/mL or clinical stage ≥T2c or Gleason ≥8) for the analysis. Out of 1912 patients fulfilling the above criteria, 904 patients without Charlson comorbidity index (CCI) data were excluded leaving 1008 patients for final analysis.

Patient and tumor characteristics

Preoperative data include age, PSA at surgery, CCI, Gleason at biopsy and clinical stage. The study population was further grouped into CCI < 1 or ≥1 versus <2 and ≥2 for analysis. All the patients had RP—open/laparoscopic/robotic with bilateral pelvic lymph node dissection. The template used for the lymph node dissection was in accordance with then existing recommendation along the study period (1988–2014). Postoperative data include pathological Gleason score, stage, margin status, number or nodes removed, number of positive nodes and cancer volume/prostate volume (%). Cause of death was verified by physician correspondence and/or death certificates.

Statistical analysis

We performed *T* test, Ji^2 test and log rank to compare means, proportions and survival, respectively. Survival rate was estimated using the Kaplan–Meier method in each Charlson cutoff group and competitive risk Fine-Gray regression to estimate the best explanatory multivariable model. We performed area under the curve (AUC) and Akaike information criterion (AIC) to compare Charlson score cutoff of 2 and 1. All the statistical analysis was performed using Stata® v13.1 for Mac.

Results

Global data

The global population (1912 patients) had mean age of 72.83 ± 2.5 years and mean preoperative PSA of 22.97 ± 5.3 ng/mL. The distribution of clinical T-stage was T2 (36.63 %) and T3 626 (35.83 %), and Gleason score in prostate biopsy was 8–10 in 1027 cases (54.69 %). Postoperatively, the final pathological T-stage was pT3b-T4 (755, 40.74 %) and pathological Gleason 7 (893, 48.74 %). The median global survival was 64.77 ± 5.47 months.

Analysis of study population

A total of 1008 patients were included for the final analysis (Table 1). As expected we found more patients in the CCI < 2 group, 936 (93 %), while CCI ≥ 2 had only 72 (7 %). However, both the groups were comparable in terms of mean age (73.31 vs 73.31 years) and all the other tumor variables with comorbidities being their main difference (Table 1). Comparison of the survival analysis using the Kaplan–Meier curve between two groups for non-cancer death and survival estimations for 5 and 10 years shows significant worst outcomes for patients with CCI ≥ 2 (Fig. 1). Since there were no cancer deaths in CCI ≥ 2 group, Kaplan–Meier curve and survival estimates for cancer deaths are shown only for CCI < 2 group (Fig. 1). Finally, the competing-risks regression model (Fine-Gray) coefficients and global significance in Charlson 2 cutoff are shown in Table 2, main event considered was cancer death.

In our multivariate model to decide the appropriate CCI cut-off point, we found CCI ≥ 2 had equal area under the curve (AUC) ($p = 0.1073$) and Akaike information criterion (AIC) than ≥1 (Fig. 2). But there were no deaths from prostate cancer in CCI ≥ 2 group, while up to 30 (6.7 %) cancer deaths in CCI ≥ 1 group; consequently CSM estimates in CCI ≥ 2 were statistically significant ($p < 0.02$) between both groups, whereas CSM estimates in CCI ≥ 1 were not ($p = 0.8$; Fig. 2).

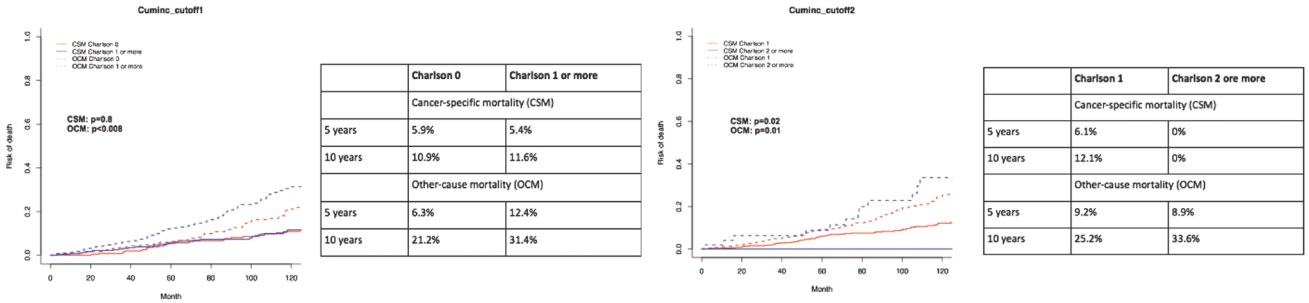
Discussion

Radical prostatectomy for clinically localized high-risk prostate cancer has evolved into a more acceptable treatment option worldwide with better understanding of the heterogeneity in these groups of patients. With longer RP learning experience, assistance with versatility of surgical robots and availability of multimodal treatment, we tend to extend the surgical indications to hrPCa. Though RP offers excellent cancer control in hrPCa, the benefits are not uniform with several factors affecting the outcomes.

Specific to older patients with hrPCa, do these patients need to be treated at all? Currently, this question has no clear answer and neither answer exists for ideal therapeutically option, if one decides to treat. Therefore, radiation or any other modalities can be offered to this cohort of patients; but in our multiinstitutional experience, a subset

Table 1 Comparison of patient characteristics

Variable	Charlson < 2	Charlson ≥ 2	*p* value
Number of patients	936 (93 %)	72 (7 %)	
Average age (mean)	73.31 ± 2.80	73.31 ± 2.15	0.832
Clinical stage	cT1 = 134 (15.12 %)	cT1 = 10 (14.49 %)	0.140
	cT2 = 237 (26.75 %)	cT2 = 27 (39.13 %)	
	cT3-T4 = 515 (58.13 %)	cT3-T4 = 32 (46.38 %)	
Gleason Biopsy	6 = 271 (29.78 %)	6 = 20 (28.17 %)	0.402
	7 = 226 (24.84 %)	7 = 17 (23.94 %)	
	8–10 = 413 (45.38 %)	8–10 = 34 (47.89 %)	
Preoperative PSA	23.39 ± 64.90	14.80 ± 16.94	0.26
Pathological T-stage	pT2 = 290 (32.19 %)	pT2 = 27 (39.71 %)	0.280
	pT3a = 249 (27.64 %)	pT2 = 20 (29.41 %)	
	pT3b-T4 = 362 (40.18 %)	pT3-T4 = 21 (30.88 %)	
Pathologic Gleason	6 = 196 (24.45 %)	6 = 18 (25.35 %)	0.365
	7 = 345 (39.52 %)	7 = 22 (31 %)	
	8–10 = 332 (38.03 %)	8–10 = 31 (43.66 %)	
Positive nodes	222 (23.82 %)	14 (19.72 %)	0.164
Number of nodes removed (mean)	15.24 ± 8.84	12.79 ± 7.33	0.112
R+	397 (42.5 %)	31 (43.7 %)	0.849
Tumor volume/prostate volume (mean)	21.82 % ± 27.24	11.88 % ± 6.11	0.253
CSM	74 (8.61 %)	0	0.001
OCM	175 (20.37 %)	28 (40.70 %)	0.003
Median survival (months)	186 (1–260)	159 (1–206)	



	Charlson 0	Charlson 1 or more
	Cancer-specific mortality (CSM)	
5 years	5.9%	5.4%
10 years	10.9%	11.6%
	Other-cause mortality (OCM)	
5 years	6.3%	12.4%
10 years	21.2%	31.4%

	Charlson 1	Charlson 2 ore more
	Cancer-specific mortality (CSM)	
5 years	6.1%	0%
10 years	12.1%	0%
	Other-cause mortality (OCM)	
5 years	9.2%	8.9%
10 years	25.2%	33.6%

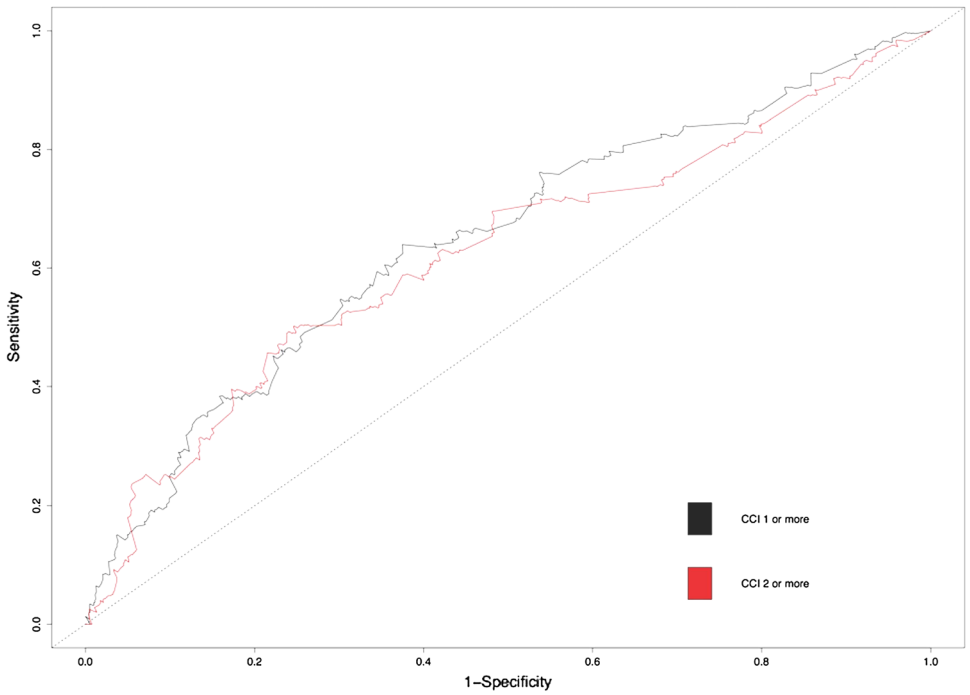
Fig. 1 Comparison of CSM and OCM with CCI cut off of 1 and 2

Table 2 Competing regression model coefficients (Fine-Gray)

Variable	Coefficient	95 % CI	*p* value
Age	0.07	(0.02 to 0.13)	0.013
Clinical stage			
T2	0.44	(−0.17 to 1.04)	0.154
T3–T4	0.66	(0.08 to 1.24)	0.025
Biopsy Gleason			
7	0.11	(−0.25 to 0.48)	0.547
8–10	0.03	(−0.31 to 0.37)	0.857
Charlson ≥ 2	0.69	(0.31 to 1.08)	<0.001

of these patients received surgical treatment and aim of the present work is to provide readers with a variable that could help in decision making for RP in older patients with hrPCa.

Briganti et al., in a retrospective analysis of multiinstitutional data showed the influence of age and CCI in hrPCa. Younger and healthier patients with higher CSM are more likely to benefit from RP than older and sicker patients with higher OCM [17]. In the present multiinstitutional study involving 14 tertiary care institutions around the world, we performed a subgroups analysis of 1000 patients older than 70-year harboring hrPCa. We analyzed the influence of CCI



Test	Charlson 2	Charlson 1
AUC	0.623*	0.648*
AIC	924	923
* *p* value AUC comparison = 0.1073		

Fig. 2 ROC curve and comparison of AUC and AIC with CCI cut off of 1 and 2

on CSM and OCM on this subgroup and noted CCI $\geq$ 2 appears to be better cut off for deciding RP in this group of sub-group of patients.

In patients more than 70 years with hrPCa undergoing RP, CSM and OCM increase with higher CCI, but the 10-year difference between CSM and OCM also widened indicating that most of these deaths were not related to prostate cancer. We analyzed the cut-off CCI for achieving optimal outcomes and patients with CCI < 2 had 10-year difference between CSM and OCM of 10 %, which was comparable to the RP outcomes of younger and healthier patients with hrPCa. When patients had CCI $\geq$ 2, all the recorded deaths in the present study (40.7 %) were not related to PCa. This transition point was further proved statistically in the competing-risks regression model.

The findings of the present study have important clinical implications. First, older patients harboring hrPCa should receive treatment with curative intent. Akre et al. [18] had shown the 10-year CSM can be as high as 52 % in high-risk patients treated with non-curative intent versus 8.6 % in older patients in the present series. Though the untreated sicker patients were not included, they were less likely to be benefitted from RP since we noted no CSM in patients with CCI $\geq$ 2. Second, though there is certain reluctance in offering RP for older patients with hrPCa, our multicenter data suggest that the CSM rates of this subgroup of patients were comparable to younger and healthier patients published in literature. Third, the 10-year difference between CSM and OCM widened progressively with increasing comorbidities. But difference is similar up to CCI $\geq$ 2 beyond which patients were more likely to die of other causes than of prostate cancer. Hence, older patients with CCI $\leq$ 2 and most CCI $\leq$ 1 can be treated as aggressively as the younger patients. However, our findings do not exclude the cancer control offered by RP in older patients with CCI $\geq$ 2, but these patients are at higher risk of dying from other causes.

Our results were in concordance with the earlier published data by Briganti et al. However, our subgroup analysis showed the outcomes of patients with CCI—0 were similar to CCI—1 and statistically significant transition occurred at CCI—2. Though their study presented comprehensive results of hrPCa in all age groups stratified to number of risk factors, our results were exclusively on patients $\geq$70 years. This shift in CCI cut off from 0 to 1 will eventually result in additional 20 % of patients in this group benefiting from RP.

Several studies in the past have addressed the influence of comorbidities on the PSM and OCM in PCa patients undergoing RP [18–23]. Majority of these studies

presented the overall PCa data; hence, the number of hrPCa patients was limited and the analyses were diluted. We present a large series of older hrPCa patients operated in 14 large volume cancer centers. The experience of these centers might have influenced to include higher number of high-risk patients; nevertheless, these data are feasible to be translated to clinical practice worldwide.

Our study has few limitations. Retrospective nature of the data analysis has inherent limitations as we do not have information in patients last to follow-up, missing data etc. Patients treated with non-curative intend or refused treatments were not included in the analysis. Inclusion of these data in a prospective randomized model will, however, present more comprehensive information of this sub-group of patients. The number of patients in the CCI $\geq$ 2 group was relatively small, and this may be due to the selection bias in since most centers tend to perform RP in healthier patients. We did not report the complications and procedure-related morbidity. Considering all the high-risk PCa patients will require bilateral lymphadenectomy, this information is essential to weigh the benefits of cancer control over quality of life and cost in the final years of these older patients [24]. Moreover, the distribution of the patient population is over a very long time period (1988–2014). There were changes in the concept of lymphadenectomy for PCa over this time period. The template used was not homogeneous throughout the study population and varied according to the existing guidelines of that particular time period. All the centers involved in the study were experienced high volume cancer centers, and hence, the surgical outcomes should be cautiously translated to regular clinical practice. Finally, the series of patients included in the study are over a longer time frame. Significant medical and surgical advancements in both urological and non-urological field including the development of multidisciplinary approach to prostate cancer have occurred over this time period [25]. Older patients with comorbidities are better controlled than a decade before and the patients tend to live longer. Introduction on robot assistance in RP might have resulted in better surgical outcomes, and hence, the results need to be continually assessed.

In spite of the limitations, our study represents a larger series of older hrPCa patients indicating the advantages of RP in even with minimal comorbidities.

Conclusion

Older patients with fewer comorbidities harboring high-risk prostate cancer appear to benefit from RP as compared to sicker patients. However, although CCI $\geq$ 2 seems to exclude better unfit patients for curative treatment, no clear cutoff election can be made. The results of this study will aid in treatment decision making of RP in high-risk disease.

Author Contributions Sivaraman A, Ordaz Jurado G, Sanchez-Salas R were involved in conception and design; Sivaraman A and Ordaz Jurado G were involved in acquisition of data; Ordaz Jurado G, Sanchez-Salas R, Eric Barret Dell'Oglio P, Joniau S, Bianchi M, Briganti A, Spahn M, Bastian P, Chun J, Chlosta P, Gontero P, Graefen M, Jeffrey Karnes R, Marchioro G, Tombal B, Tosco L, Henk van der Poel H were involved in analysis and Interpretation of Data; Sivaraman A drafted the manuscript; Eric BarretDell'Oglio P, Joniau S, Bianchi M, Briganti A, Spahn M, Bastian P, Chun J, Chlosta P, Gontero P, Graefen M, Jeffrey Karnes R, Marchioro G, Tombal B, Tosco L, Henk van der Poel H critically revised the paper; Ordaz Jurado G and Briganti A performed statistical analysis; and Cathelineau X and Sanchez-Salas R supervised the manuscript.

Compliance with ethical standards

Ethical standards We declare that prior to the start of the study, Independent Ethical Committee (IEC) was obtained. All the patients (or the legal representative) enrolled in the study completed and signed the written informed consent form. The study was conducted in accordance with the Declaration of Helsinki and the EU clinical directive on GPC (2001/20/EC).

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