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RESEARCH ARTICLE

Spanish validation of Charlson index applied to prostate cancer

F. Casas Duran[1] · I. Valduvieco[1] · G. Oses[1] · K. S. Cortés[1] · T. D. Barreto[1] · D. Muñoz-Guglielmetti[1] · F. Ferrer[2]

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Abstract

Purpose Comorbidity assessment is essential in the triage of care for men with prostate cancer (PC). The aim of this study was to validate the Spanish version of the revised Charlson index (RCI) in PC.

Materials and methods 731 PC patients diagnosed from 1993 to 2008 were referred to our Radiation Oncology Department. The RCI classified patients into four categories RCI 0, RCI 1–2, RCI 3–4, and RCI 5 and higher. The Kaplan–Meier method and Cox proportional hazards modeling were used. We also analyzed the median age of patients who remained alive at the last control and those who died due to non-prostate cancer comorbidities.

Results 636 patients were included median age: 70 years (44–85). The mean follow-up was 153.62 months, (6–288 months). Distribution of the D'Amico risk classification was 21%, 38.2%, and 40.8% for low, intermediate, and high risk, respectively. The RCI distribution categories were: 303 (46.7%) RCI 0, 102 (16%) RCI 1–2, 131 (20.6%) RCI 3–4, and 100 (15.7%) RCI 5 and higher. The probability of non-cause-specific mortality at 5 and 10 years was 2. 4% and 11.25% RCI 0, 3 and 14.1% RCI 1–2, 5.7% and 22.1% RCI 3–4, and 47% and 92% (RCI 5 and higher). The median age in the last control in patients alive or who had died by non-PC causes was 82.81 years (55.27–102).

Discussion The RCI may be used to aid medical decision making in older Spanish men with PC, especially in those with a high RCI 5 and higher.

Keywords Prostate cancer · Life expectancy · Charlson index · Non-cause-specific mortality · Comorbidities

Introduction

Evaluation of comorbidity is a main factor in management decision making in patients with prostate cancer (PC). The survival benefits of radical treatment in low and intermediate risk are effective at 8–10 years after definitive therapy [1], and patients with major comorbidities (CO) may not live long enough to benefit from any radical treatment. In these cases, clinical guidelines recommend conservative management to avoid possible secondary effects [2], but the use of population-based measures such as life tables to estimate life expectancy (more than 10 years), fail to account for individual health status.

The Charlson comorbidity index (ChI) is the comorbidity index most commonly used [3]. It was based on a study of 559 medical inpatients in 1985. CO were determined along hospitalization, and the risk of 1-year mortality was associated with each comorbidity weight determined. This index was validated for estimating overall and non-PC survival of men with PC [4].

Nonetheless, the ChI may not be optimized for the prediction of the real long-term mortality in men with PC. In a study carried out in 2011, Daskivich et al. proposed the use of a ChI applied to PC patients to improve the prediction of long-term, non-cause-specific mortality (NCSM) in PC [5]. They determined the long-term risks of NCSM associated with specific CO in a sample of 1598 men with newly diagnosed PC at 2 Veterans Affairs Medical Centers. They repeated the original study design of the ChI to determine if the risk of comorbidity would differ in a contemporary PC population with a long-term follow-up. Then they determined if the ChI could be reweighted to improve the prediction of long-term NCSM. A multivariate logistic regression model predicting NCSM verified that the revised ChI (RCI)

✉ F. Casas Duran
fcasas@clinic.cat

[1] Radiation Oncology Department, Hospital Clínic, Barcelona, Spain

[2] Departament de Ciències Clíniques, Radiation Oncology Department, Institut Català d'Oncologia, IDIBELL, Universitat de Barcelona, Barcelona, Spain

was a stronger predictor of other-cause mortality in those at highest risk. This new reweighting of ChI CO is shown in Table 1. This initiative by Daskivich et al. has very recently been externally validated by an observational study including 181,009 PC patients [6].

The main end point of our study was to validate this contemporary RCI applied to PC in the public health system of Spain, which is different from the predominantly private health system in the USA. The objective of this study was to determine whether the RCI is useful in decision making in the treatment of PC in Spain in terms of life expectancy and/or CO which differ between Spain and the USA.

Materials and methods

The participants in our study included men diagnosed with PC from 1993 to 2008 who were referred to the Radiation Oncology Department of the Hospital Clinic of Barcelona for clinical assessment. After obtaining board approval, patient records were reviewed.

CO were determined at diagnosis by reviewing patient records from the year of the diagnosis of PC. This review was conducted by the study coordinator (FC). CO were categorized by the RCI according to the new numerical weight of each CO in each subject. PC tumors were risk stratified by the D'Amico criteria as low, intermediate or high risk. Of the initial group of 731 consecutive cases of PC (204 treated post-operatively [7] and the remaining cases underwent radical external beam radiotherapy (REBRT) with or without androgen deprivation therapy), two patients were lost to follow-up, and 83 patients died due to PC during follow-up and were excluded from the study. The RCI classified the patients into four categories: RCI 0, RCI 1–2, RCI 3–4, and RCI 5 and higher, and these were compared with the results of Daskivich et al. Survival was measured from the date of diagnosis to the date of death. The date and cause of death were determined from the hospital medical records and the electronic records from general practice.

Death by PC was based on control reports by the Palliative Unit for PC, increased PSA values despite treatment (including new hormonal therapy such as abiraterone, enzalutamide, chemotherapy, etc.) or death as a result of metastatic PC. Non-prostate cancer mortality (NPCM) was defined as death by other-causes. If the cause of death could not be determined, the subjects were considered to have died of other causes if PSA values had remained stable for less than 1 year after the last visit. We compared the characteristics of our PC patients across the four RCI groups using Chi-square and Fisher's exact tests. We used Cox proportional hazards modeling to assess the risk of NPCM associated with each comorbidity. We also analyzed the median age in the last control in patients alive or who had died by non-PC COM to make a preliminary estimation of the life expectancy of our patients.

Table 1 Distribution of RCI score categories in relation to age groups

RCI score categories	0	1–2	3–4	5 and more	Total
Age (years)					
(44–64)	92	20	19	15	146
(65–69)	76	24	32	18	150
(70–74)	73	31	49	38	191
(75–85)	62	27	31	29	149
Total	304	102	131	100	636

Results

A total of 636 patients with a median age at diagnosis of 70 years (44–85) were included in the analysis. The mean follow-up was 153.62 months, (6–288). The D'Amico risk distribution was 21%, 38.2%, and 40.8% for low, medium, and high risk, respectively. The distribution of the RCI categories was as follows: 303 (46.7%) RCI 0, 102 (16%) RCI 1–2, 131 (20,6%) RCI 3–4, and 100 (15.7%) RCI 5 and higher. The distribution of RCI categories by age groups is shown in Table 2.

The survival probability analysis showed statistically significant differences between RCI 0 and the other 3 groups, RCI 1–2 and RCI 3–4, and RCI 5 or more ($p < 0.01$). We did not find statistically significant differences between the RCI 1–2 and RCI 3–4 groups ($p = 0.09$) to identify patients at risk of death by other causes within 5 and 10 years after diagnosis. The odds ratios of 5 and 10 years for the probability of NPCM were 2.4% and 11.3% RCI 0; 3% and 14.1% RCI 1–2; 4.6% and 22.1% RCI 3–4 and 47% and 92% RCI 5 and higher (Fig. 1). In our Spanish comparative comorbidity model the highest risk (greater than or equal to a RCI of 5) of NPCM probability was most frequently associated with moderate to severe liver, renal and pulmonary disease compared to other CO with a lower risk such as arrhythmia and/or mild chronic obstructive pulmonary disease (COPD) and/or neurological diseases.

The median age of the patients alive in the last control or in those who had died by non-PC causes was 82.81 years (55.27–102), with an age distribution of 10% ≥ 90 years old, 25% ≥ 86.82 years old and 75% ≥ 76.89 years of age.

Discussion

In patients with low and intermediate risk PC, treating specialists (radiation oncologists and urologists) commonly use a 10-year life expectancy as the benchmark for defining

Table 2 New assigned weights to comorbidities in the Charlson index applied to prostate cancer

Comorbidities	New assigned weights
Leukemia	6
Lymphoma	
Metastatic solid tumor	
Moderate-severe liver disease	
Congestive heart failure	3
Hemiplegia	
Dementia	
Moderate-severe renal disease	
Moderate-severe COPD	
Peptic ulcer disease	2
Inflammatory bowel disease	
Gastrointestinal bleed	
Connective tissue disease	
Heart valves disease	
Arrhthymia	
Mild COPD	
Angina	
Mild renal disease	
Other neurological disease	
Peripheral artery disease	
Mild liver disease	
Diabetes with end-organ damage	1
Any other tumor	
Cerebrovascular disease	

or not overtreatment of PC. This value is used because of the results of randomized controlled trials suggesting that significant differences in survival between watchful waiting and aggressive treatment do not develop until 10 years after treatment, and guidelines universally agree that men with life expectancies < 10 years should not receive any radical/aggressive treatment [8].

Although guidelines advocate the use of population-based measures such as life tables to estimate life expectancy, these measures fail to account for individual health status and may overestimate or underestimate life expectancy [9]. The most promising tools for estimating life expectancy incorporate individual health status using a comorbidity index. The classical ChI has been very useful along these last three decades, but is no longer adequate taking into account the advances in the control of diseases and CO since the 1980s. A good example of this is HIV/AIDS which had a weight of 6 in the classical ChI and with the current RCI its weight is 0 because of the high probability of survival at 5 or 10 years. It is also of note that in the RCI the impact of diabetes is only negative if secondary organ damage is also present. The same occurs at the cardiac level with myocardial infarction, which was classified as detrimental in the classical ChI but now in the RCI only important cardiac CO such as angina and/or congestive heart failure,but not myocardial infarction, are considered. All these examples reflect important changes in disease treatments in this century.

The Daskivich RCI groups of CO cannot be directly compared with our RCI groups in the Spanish validation

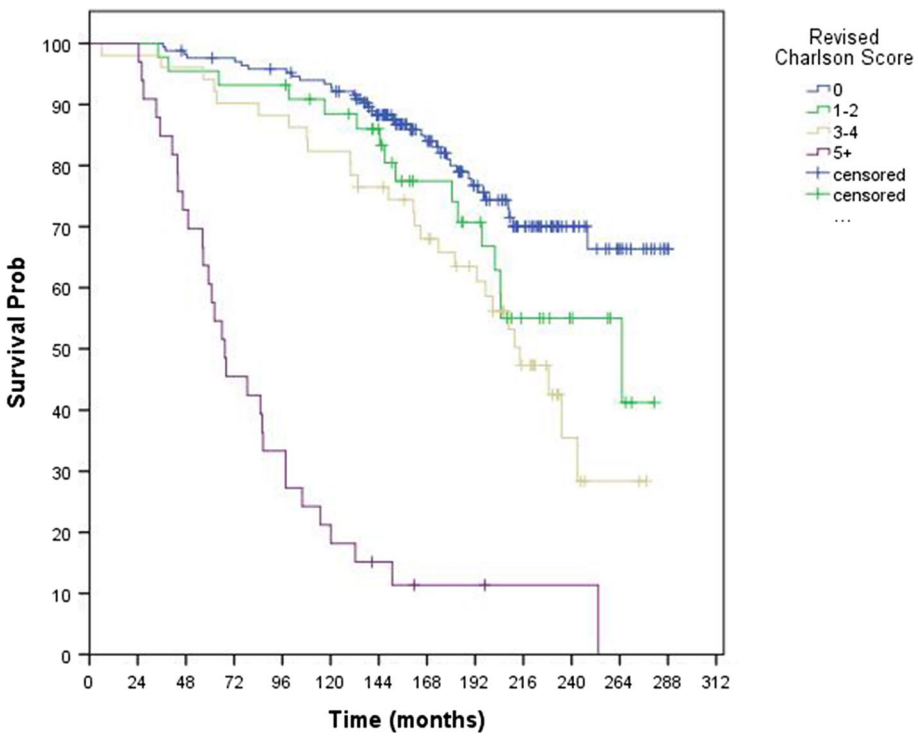


Fig. 1 Survival probability curves for non-prostate cancer mortality

of the revised index. In the original trial by Daskivich et al., reweighting of the CO was performed to develop a revised index for application in PC, and the median follow-up of their large cohort of 1598 patients was 5.8 years (range 0–13.3). In the present study, their index was applied in 636 PC patients with a very long follow-up of more than 150 months. It may also be important to consider the difference in life expectancy of 82.9 years versus 78.9 years between Spain and the USA, respectively [10], likely related to several aspects such as different life styles (Mediterranean diet in Spain) and different health systems.

However, there was an evident correlation between the groups of patients (original RCI group and Spanish validation group) distributed by RCI CO and survival probability to establish the probability of NPCM (Fig. 1). For example, in the RCI seminal trial, the RCI group categorized as six or more had a greater than 90% probability of NPCM within 10 years. In our validation group of RCI of five and more, the NPCM at 10 years was very similar (92%). The same was observed for low levels of RCI, with a NCPM probability of 3.9% at 5 years in the seminal RCI of 1 versus 3% in the Spanish validation RCI 1–2 group. Comparison of similar rates with the other RCI groups is difficult because the groups categorized in the original RCI were RCI 0, RCI 1–2, RCI 3–5, RCI 6–8, and RCI 9 and more, while to ensure a more balanced distribution of groups with fewer patients in our validation study, the groups were categorized as RCI 0, RCI 1–2, RCI 3–4 and RCI 5, and more. In the RCI of Daskivich et al. there was a significant difference between NPCM among the RCI groups ($p < 0.001$), with the exception of 0 and 1 ($p = 0.4$). In our validation group, this difference in odds ratio NPCM probability was observed among all the groups ($p < 0.001$) except between RCI 1–2 and RCI 3–4 ($p = 0.09$). As in the original RCI, in our validation study the RCI was found to be very useful to discriminate CO in the RCI group of five and more to avoid radical treatment in PC patients with a low and intermediate risk of PC, since the probability of patients remaining alive at 10 years and benefitting from radical treatment is very low. For example, a study [11] found that up to 54% of patients with low risk PC and significant CO were treated radically with surgery or REBRT despite a 70% probability of other-cause mortality at 8 years after diagnosis.

In the original RCI study the highest risk of long-term probability of NPCM was associated with the presence of severe liver disease (as in our comparative group) but not with metastatic solid tumor or hematologic malignancies (lymphoma and leukemia) reported in the original RCI. A possible explanation for this may be that our analysis only included patients referred for REBRT management and patients with solid metastatic or hematologic tumors were likely not referred for irradiation.

The distribution of RCI categories by age groups (Table 2) showed a good balance between the different groups (44–64 years, 65–69 years, 70–74 years, 75–78 years). In spite of the arbitrary distribution of age groups, we observed a progressive increase of group of RCI comorbidity when we increase the age from group 44–64 to 75–85 CO in the RCI groups when age increased from 44–64 to 75–85. These last results are in apparent concordance with another study [12] which proposed an age-adjusted comorbidity index that predicts other cause mortality in men with PC. They used a complex analysis with a competing risks regression in testing and validation cohorts to determine the risk of non-PC-related mortality associated with age at diagnosis and CO score. In their results they showed that each 6-year increase in age at diagnosis of greater than 60 was equivalent to one additional point of CO. Following the Spanish validation of the RCI (main objective of this trial) a confirmatory analysis of this last article could also be of interest.

It is important to point out that the median age of the patients alive in the last control or of patients who had died by non-PC causes in our study was 82.81 years. This it is practically identical to the Spanish life expectancy of 82.9 years. This may represent a positive impact of REBRT ± androgen deprivation (AD) used in our patients to reduce mortality secondary to PC as has been published previously by Bandini et al. [13].This fact is especially significant among the very old people included our study in whom the median age in the last control or of patients who had died by non-PC causes was greater than or equal to 90 years in 10% and greater than or equal to 86.82 years old in 25%. It is important to take these results into account when offering radical treatment to patients over 70–75 years of age with a low RCI 0–4 since the use of AD alone in older patients may increase mortality by causes other than PC [14].

A recent study predicted the life expectancy of all-cause and cause-specific mortality in 250 causes of death from 2016-2020 in 195 countries [15]. In this study the forecast of life expectancy in Spain in 2040 will be the most important around the world, exceeding 85 years for both sexes. These results are in concordance with ours showing a progressive increase in the median age of all-cause death in our patients. In this scenario, our validation of the original RCI could be very useful to decide whether patients 70–75 years of age with PC with low/intermediate risk but with a RCI less than five should be given radical treatment.

National comprehensive cancer network (NCCN) guidelines can be used to predict life expectancy in men with PC, but there may be less heterogeneity in survival in correlation with RCI scores. By analyzing life expectancy with RCI scores, NCCN guidelines misclassified the 10-year life expectancy in 24% and 50% of men less than 65 and 65–69 years of age and the 5-year life expectancy in 18% of men of 70-74 years of age [16].

From our point of view the original RCI only had one limitation for application in Spanish PC patients. The RCI study did not consider men with PC cancer with very important organ insufficiency (RCI more than 5) who received radiotherapy as radical or curative treatment prior to organ transplantation. The article by Daskivich et al. makes no mention of this possibility. Six of our patients were in this situation. Three were on dialysis, two had congestive heart failure and one had severe liver disease and underwent kidney, heart and liver transplantation, respectively, after REBRT. In these six cases all the patients with low and intermediate risk PC remain alive 10 years after radical REBRT. It is important to take into account this limitation of the Daskivich et al. study in a country such as Spain which has been the world leader in organ donation and transplantation for 27 straight years [17]. In these patients the RCI must be applied with caution.

This Spanish validation may have several limitations. First, detailed information about the main causes of non-PC causes of death were not available. Due to the retrospective nature of this study we collected and interpreted the causes of death from hospital chart records and electronic general practitioner charts. Therefore, the probability of misclassification of cause of death may lead to inaccuracy in NCSM. However, this limitation was present in all the studies by Daskivich et al. (more than eight studies). It is of note that none of the studies by this group provide any information of distribution of NCSM by cancer. As in our analysis they classified the patients as death by PC or for other causes alone, with no other details. As we described in the Methods section, it is easier to interpret the cause of death by the tumor in patients with a very advanced phase of PC. Another limitation of our study is also its main objective: validate the RCI for only Spanish patients. From our point of view, validation of the RCI in Spain is a mandatory step to be able to compare our results from a scientific point of view with another more in depth analysis of our author of reference comparing effect of age, tumor risk and COM as competing risk for survival in PC patients [18, 19] and also the impact of age, CO and PSA doubling time in metastatic castration-resistant patients with PC [20]. The last limitation is that our study population was treated in a high-tech university of excellence in Spain. The results may have been different in other hospitals with less experience and technology. This fact may limit the generalizability of our findings. Nonetheless, more than 50% of the patients were referred from other hospitals in which their CO had been treated to receive REBRT, and these results may be very similar within our Spanish public health system.

In conclusion, it may be useful to integrate this Spanish validation of RCI in PC treatment decision making based on both age and CO to calculate life expectancy. It may be especially important in men around 70–75 years of age since these patients comprise the majority of newly diagnosed PC in our country.

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Compliance with ethical standards

Conflict of interest None of the authors have any conflicts of interest.

Research involving human participants and/or animals Research involving human participants and/or animals was not performed, and all the patients provided signed informed consent before radiotherapy.

Informed consent After obtaining board approval, patient records were reviewed.

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