Survival Differences in High-Risk Prostate Cancer by Age

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Purpose: Age is an established determining factor in survival in low-risk prostate cancer (PC), being this evidence weaker in high-risk tumors. Our aim is to evaluate the survival of patients with high-risk PC treated with curative intent and to identify differences across ages at diagnosis.

Methods: We did a retrospective analysis of patients with high-risk PC treated with surgery (RP) or radiotherapy (RDT) excluding N+ patients. We divided patients by age groups: < 60, 60-70, and > 70 years. We performed a comparative survival analysis. A multivariate analysis adjusted for clinically relevant variables and initial treatment received was performed.

Results: Of a total of 2383 patients, 378 met the selection criteria with a median follow-up of 8.9 years: 38 (10.1%) < 60 years, 175 (46.3%) between 60-70 years, and 165 (43.6%) >70 years. Initial treatment with surgery was predominant in the younger group (RP:63.2%, RDT:36.8%), and with radiotherapy in the older group (RP:17%, RDT:83%) (p = 0.001). In the survival analysis, significant differences were observed in overall survival, with better results for the younger group. However, these results were reversed in biochemical recurrence-free survival, with patients < 60 years presenting a higher rate of biochemical recurrence at 10 years. In the multivariate analysis, age behaved as an independent risk variable only for overall survival, with a HR of 2.8 in the group >70 years (95%CI: 1.22-6.5; p = 0.015).

Conclusion: In our series, age appeared to be an independent prognostic factor for overall survival, with no differences in the rest of the survival rates.

Keywords: high-risk prostate cancer; age groups; survival differences

INTRODUCTION

Prostate cancer (PC) is the most commonly diagnosed solid organ neoplasm in men in Europe and its incidence increases with age, with 60% of cases being detected in men over 65 years of age.[1]

The incidence of high-risk tumors is 15-20% according to American studies. In the Swedish registry, out of a total of 57187 patients with PC, 24% were classified as high risk.[2,3] In Spain, according to data from the 2010 National Prostate Cancer Registry, 89.4% of patients had localized disease, and of these, 28.8% had high-risk tumors according to the D'Amico classification.[4]

While there is evidence that in low-risk tumors age is a determinant of survival[5], there are not many studies that identify the impact of age on survival in high-risk tumors.

Our aim is to evaluate the survival of patients with high-risk PC treated with curative intent and to identify possible differences according to age at diagnosis.

MATERIAL AND METHODS

We performed a retrospective analysis of all patients with prostate cancer, prospectively included in our hospital database from 1998 to 2016, to reach a minimum follow-up of 5 years.

Review and approval by our hospital's ethics committee did not apply to this study due to the retrospective nature of the study. We selected those patients who met the D'Amico criteria for high-risk disease (stage T2, PSA > 20 ng/mL or Gleason ≥ 8) and who had been treated with curative intent by radical prostatectomy and pelvic lymphadenectomy (RP + LFDN) or radiotherapy with neo and adjuvant hormone therapy for 2 years (RDT + HT). N+ patients were excluded.

All radical prostatectomies from 2004 onward were performed laparoscopically. The approach was extraperitoneal until 2009, and from that moment on the procedure was performed transperitoneally with an extended lymph node dissection.

Until 2013, radiotherapy treatment was administered with radical intent with classic fractionation using IMRT (54.6 Gy on lymph node chains, 62.4 Gy on seminal vesicles and 78 Gy on the prostate) and IGRT daily. From 2013 onwards, treatment was administered with moderate hypofractionation (50.4 Gy on lymph node chains, 56 Gy on seminal vesicles and 70 Gy on the prostate that corresponds to EQD2 81Gy).

We divided the subjects according to age into three groups: under 60, between 60 and 70, and over 70 years of age.

We performed a descriptive analysis of the demograph-

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Received July 2022 & Accepted December 2022

Table 1. Clinical characteristics and treatment received at diagnosis by age group

		Age: N (%) < 60 years(N = 38)	60-70 years (N = 175)	> 70 years (N = 165)	*p*
PSA (ng/mL) [a]		24.49	24.58	22.73	0.036
Grade Group (ISUP)	1	6 (15.8%)	21 (12%)	14 (8.5%)	0.287
	2	8 (21.1%)	22 (12.6%)	18 (10.9%)	
	3	2 (5.3%)	14 (8%)	15 (9.1%)	
	4	11 (28.9%)	84 (48%)	77 (46.7%)	
	5	11 (28.9%)	33 (18.9%)	41 (24.8%)	
T stage	T1-T2b	28 (73.7%)	127 (72.6%)	114 (69.1%)	0.810
	T2c	3 (7.9%)	8 (4.6%)	11 (6.7%)	
	T3-T4	7 (18.4%)	40 (22.9%)	40 (24.2%)	
Treatment at diagnosis	PR + LFDN	24 (63.2%)	85 (48.6%)	28 (17%)	0.001
	RDT + HT	14 (36.8%)	90 (51.4%)	137 (83%)	

[a] Variable expressed as mean (SD)

ic characteristics of the patients including age and comorbidity measured according to the Charlson index, as well as the characteristics referring to prostate cancer: PSA, T stage, Gleason at diagnosis and type of treatment received (RP + LFDN vs RDT + HT).

The analysis of the surgical specimen was analyzed by the uropathologists of our center using TNM staging system according to European recommendations and Gleason according to the 2005 classification. Samples from patients prior to that date were reclassified according to these criteria.

The rates of biochemical recurrence and disease progression to metastasis recorded in each group (defined according to the criteria of the European guidelines) were analyzed, and the differences in survival were analyzed in terms of overall survival, cancer-specific survival, survival free of biochemical recurrence and survival free of progression to metastasis. A multivariate analysis adjusted for clinically relevant variables (age and D'Amico high-risk criteria) as well as initial treatment received was performed.

Statistical analysis

The distribution of quantitative data is presented by mean and standard deviation or median and interquartile range, according to data distribution. Univariate analysis was performed to compare the distribution of clinical variables according to age groups: the chi-square test or Fisher's exact test in case of small sample size for qualitative variables, and the one-way ANOVA F test or the nonparametric Kruskal–Wallis test to compare quantitative variables, depending on the distribution data.

Overall survival time is defined as the time from the date of treatment to the date of death from any cause or to the date of end of follow-up in the case of censored data. Reason for censoring is loss of follow-up. In the case of recurrence-free survival and progression-free survival, the recurrence event was considered to be biochemical recurrence (defined according to EAU guidelines criteria) after treatment with curative intent, and the progression event was considered to be the development of metastases during follow-up. Reason for censoring includes loss of follow-up and death without previous event. The Kaplan-Meier method was used to estimate the survival curves and the log-rank test was calculated to compare groups according to age: under 60, between 60 and 70, and over 70 years of age.

Cox proportional hazards regression models were used to estimate hazard ratios (HR) according to age groups without adjustment and adjusting for other clinical variables of interest (D'Amico criteria and initial treatment received). Cox proportional hazard (PH) assumption and was evaluated testing linear nonzero slope of the residuals and linearity for age was assessed with a link test for model specification. The variables that no compliance PH assumption were including in the models with time-varying coefficients.

All tests were considered bilateral and p-values less than 0.05 were considered statistically significant. Statistical analysis was performed using SPSS 17 and STATA 14 data analysis packages.

RESULTS

Of the 2383 patients included in our institutional prostate cancer database, 378 met the selection criteria. Of these, 38 patients (10.1%) were younger than 60 years,

Table 2. Events recorded during the follow-up period and results of survival at 10 years

	Age: N (%) < 60 years (N = 38)	60-70 years (N = 175)	> 70 years (N = 165)	*p*
		Events recorded during the follow-up		
Biochemical recurrence	20 (52.6%)	69 (39.4%)	44 (26.7%)	0.003
Progression to metastasis	9 (23.7%)	18 (16%)	21 (12.7%)	0.227
Death from any cause	7 (18.4%)	28 (16%)	53 (32.1%)	0.002
Cancer-specific death	3 (7.9%)	5 (2.9%)	11 (6.7%)	0.191
		Estimated survival at 10 years		
Overall Survival	85% (95% CI: 16.3 – 21.0)	88% (95% CI: 16.7 – 18.7)	71% (95% CI: 11.7 – 14.1)	< 0.001
Cancer-specific survival	93% (95% CI: 18.9 – 22.3)	97% (95% CI: 19.6 – 20.7)	95% (95% CI: 16.3 – 18.7)	0.049
Biochemical recurrence-free survival	44% (95% CI: 7.9 – 13.6)	59% (95% CI: 11.6 – 14.3)	62% (95% CI: 11.4 – 13.8)	0.019
Metastasis progression-free survival	74% (95% CI: 14.6 – 20.0)	86% (95% CI: 16.6 – 18.7)	84% (95% CI: 15.7 – 17.9)	0.583

Table 3. The results of multivariate regression Cox models.

Overall survival	**Coefficient**	**HR**	**CI 95%**		***p***
Age at diagnosis (/10 years)	0.09	1.09	0.50	2.38	0.820
High risk Gleason	0.23	1.26	0.77	2.06	0.367
High risk PSA	0.08	1.08	0.69	1.71	0.730
High risk T stage	0.35	1.43	0.87	2.33	0.155
Treatment at diagnosis:					
RP + LNFD		1			
RDT	0.04	1.04	0.60	1.82	0.878
Time varying coefficients					
Age at diagnosis (/10 years)	0.10	1.10	1.01	1.20	0.035
Recurrence-free survival	**Coefficient**	**HR**	**CI 95%**		***p***
Age at diagnosis (/10 years)	-0.21	0.81	0.61	1.08	0.143
High risk Gleason	0.65	1.92	1.24	2.97	0.003
High risk PSA	0.51	1.66	1.13	2.44	0.010
High risk T stage	0.71	2.02	1.31	3.14	0.002
Treatment at diagnosis:					
RP + LNFD		1			
RDT	-1.83	0.16	0.08	0.30	< 0.001
Time varying coefficients					
RDT	0.19	1.21	1.07	1.37	0.002
Progression-free survival	**Coefficient**	**HR**	**CI 95%**		***p***
Age at diagnosis (/10 years)	-0.39	0.68	0.43	1.06	0.088
High risk Gleason	0.92	2.50	1.29	4.84	0.007
High risk PSA	0.07	1.07	0.60	1.89	0.820
High risk T stage	.05	2.86	1.52	5.36	0.001
Treatment at diagnosis					
RP + LNFD		1			
RDT	-0.29	0.75	0.39	1.43	0.384

175 (46.3%) were between 60 and 70 years, and 165 (43.6%) were older than 70 years.

The mean age of each group was 55.8 (SD: 2.9), 65.7 (SD: 2.6) and 74.3 years (SD: 3.1) respectively.

The median follow-up of the series was 8.9 years (IQR: 5.5-13.2). In those patients who were < 60 years-old and between 60 and 70 years it reached 10 years (10.6 and 10.4 respectively), however, in the group > 70 years-old it was slightly lower (7.5 years), being the difference statistically significant (p < 0.001).

Patients > 70 years had higher Charlson Index scores than the other two groups. Specifically, 48 patients (29.1%) > 70 years had a score > 2, while in the 60-70 years group there were 29 (16.6%) and in the younger group only 5 (13.2%) (p = 0.03).

The characteristics of the disease at diagnosis by age group are shown in Table 1.

In patients who underwent surgery, we found no differences between age groups in the pathologic findings of the prostatectomy specimen. The patients who associated LFDN were: 20 (83.4%), 68 (80%) and 19 (67.9%) respectively, with no differences in the rate of positive nodes.

The mean overall survival of the total series is 16.8 years (95% CI: 15.8 - 17.7). The events recorded during the follow-up, defined as biochemical recurrence,

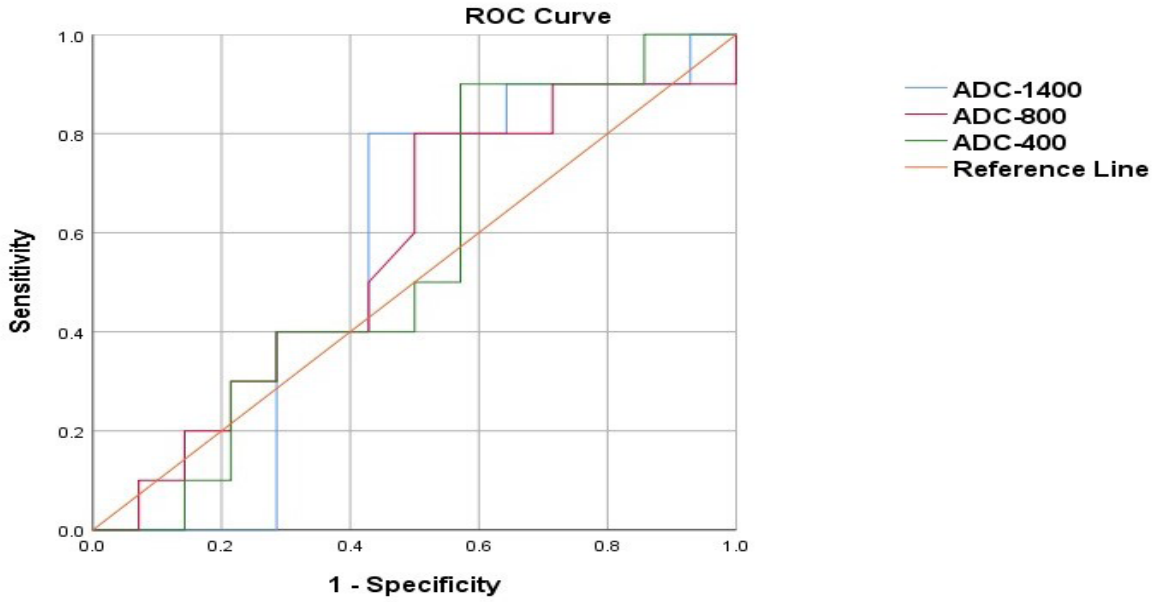

Figure 2. ROC curve analysis of all ADC values including b values for 400, 800, and 1400 to discriminate variant associated pathology.

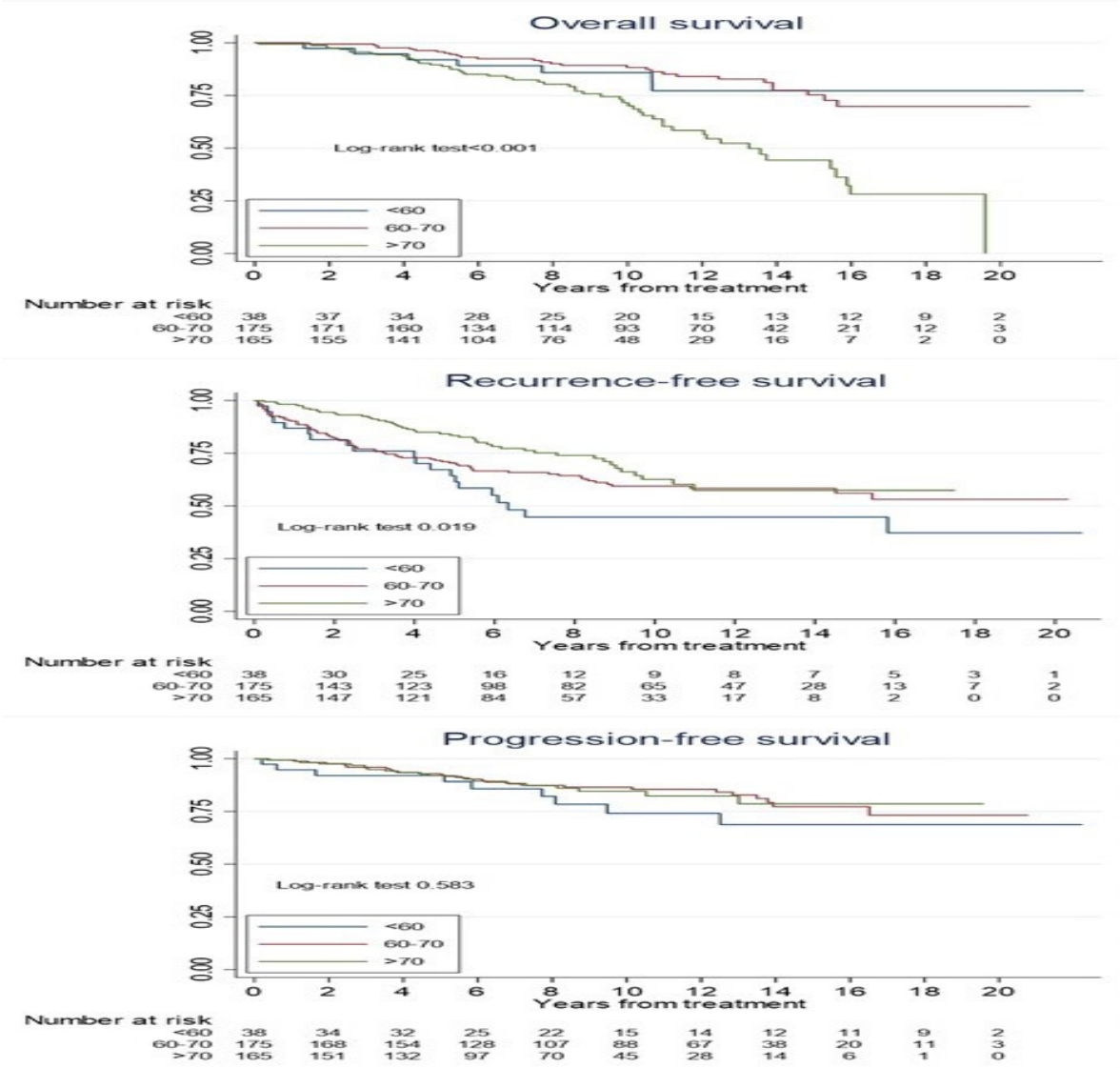

Figure 1. Kaplan-Meier overall, cancer-specific, biochemical recurrence-free and metastasis progression-free survival curves.

progression to metastasis and death, and the estimated 10-year survival by age group is shown are presented in **Table 2**.

Kaplan-Meier overall, cancer-specific, biochemical recurrence-free and metastasis progression-free survival curves are presented in **Figure 1**.

The multivariate Cox PH regression model for overall survival showed that age has a time-dependent effect, with a statistically significant estimated time-varying coefficient and an estimated time-dependent HR of 1.1 (95% CI: 1.01-1.2, $p = 0.035$), whereby the HR is not constant over time increasing a 10% for each year during follow-up, therefore the HR is 1.2 in the first year of follow-up raising to 2.8 in the tenth year.

However, in biochemical recurrence-free survival, age was no longer a risk factor, being the treatment received the one that had a significant impact, with effects change over time. The time varying coefficient estimated is statistically significant with HR of 1.2 (95% CI: 1.1-1.4) so RDT had a protect effect in first year with HR= 0.2, but this protect effect decrease over time, with null effect in tenth year of follow up. Tumor-dependent variables (PSA, Gleason and T) were also significantly related to biochemical recurrence-free survival.

Finally, in metastasis progression-free survival, neither age nor initial treatment at diagnosis had an impact on survival. Tumor-dependent variables Gleason and T stage were significantly associated.

DISCUSSION

There are no studies comparing survival outcomes in high-risk prostate cancer by age group, which is the main objective of our study.

We found some studies about active treatment in PC according to the recommendations of the NCCN and EAU guidelines most of them in young patients, without a good representation of older ones.[6] However, it has been confirmed that elderly patients with localized prostate cancer are eligible for radical treatment with curative intent with good oncologic outcomes.[7]

Due the aging population, several studies have empha-

sized the need to change the approach of the disease by prioritizing tumour stage and biology over age, as they appear to have a greater impact on oncological outcomes.[8,9]

All patients included in our series were treated according to the standard of care indicated in the guidelines. We believe that our findings may be interesting because we do not describe only the results in elderly patients, but we compare them with the rest of the patients included in our institutional database and perform a multivariate analysis to find out if age actually influences in the results obtained or if it is a confounding factor.

In general terms, our data on the survival of high-risk PC patients treated with curative intent are similar to those described in the literature.[10] The results obtained in overall survival were more favorable for the younger group, without finding relevant differences in cancer-specific survival between groups. However, as described in the results, there were significant differences in the treatment of the different age groups and because of this, we must take into account that the groups are not completely comparable and the results should be interpreted with some caution.

According to data from the National Registry, RP is the most frequent treatment for PC in our country, followed by RDT.[11] In our study, which only includes high-risk patients, we found a higher percentage of patients treated with radiotherapy than with surgery, since it was not until 2009 that we started to perform RP associated with lymphadenectomy in high-risk patients.

Although there is no age threshold that limits or contraindicates surgery, it seems that patients with a life expectancy > 10 years benefit more from this therapeutic modality than those with a shorter life expectancy.[12] It has been shown that the greater number of comorbidities, the greater likelihood of mortality from other causes unrelated to prostate cancer.[13,14] Based on this, and as we have seen in our results and as described in numerous studies, the patient's characteristics are the main variables to be taken into account when deciding the most appropriate type of treatment in each case. These findings are closely related to the retrospective review by Park et al. investigating the efficacy of the age-adjusted Charlson Comorbidity Index as a prognostic factor after RP in patients with very high-risk prostate cancer, confirming this hypothesis.[15] Post et al. also discussed this topic, confirming in their study that comorbidity was the most important prognostic factor in localized prostate cancer, especially for those under 70 years.[16]

To this date, several meta-analyses comparing RP and RDT treatments have been published. Specifically, Wallis et al., Petrelli et al. and Roach et al. report better overall survival outcomes in patients treated with surgery than in those receiving RDT. The first one describes a higher risk of overall mortality (HR = 1.63, p < 0.001) in the case of RDT, even in the analysis by risk subgroups and radiation regimen (SRT, IMRT, BT). The last two authors attribute this advantage to the different baseline characteristics of the patients, assuming that those undergoing PR present a lower rate of comorbidities.[17,18,19]

In our series, we found no differences in overall survival according to the treatment received in the multivariate analysis. However, age does seem to be a determining factor in the evolution of the patients since, as mentioned above, advanced age is associated with a greater number of comorbidities and, consequently, with a greater probability of all-cause mortality.

Therefore, older patients (> 70 years) have a reduced overall survival. However, these results are not reproduced in cancer-specific survival, with the 3 age groups presenting similar survival rates.

In relation to the aforementioned, Hamstra et al. studied the impact of age on overall survival, cancer-specific survival and 10-year metastasis-free survival in patients with high-risk PC. Broadly speaking, they agree on the relationship between age and patient survival, with the older age group ($\leq$ 70 vs >70 years) showing a poorer overall survival (55% vs 41% respectively; $p < 0.001$), although better results in cancer-specific survival (18% vs 14%; $p < 0.001$) and metastasis-free survival (27% vs 20%; $p < 0.001$).[20]

These results contrast with those described by Lin et al. who carried out a cohort study to analyze the possible relationship between age at diagnosis, tumor characteristics and survival in patients with prostate cancer. In their case they divided the patients by age group into 35-44, 45-54, 55-64 and 64-75 years, with the youngest group showing worse results than the rest, both in overall survival and cancer-specific survival, in high-risk tumors.[5]

Our series also reports worse cancer-specific survival results in the younger group. We think that the type of treatment received may act as a confounding factor in the results obtained. As noted in the study by Briganti et al., in high-risk prostate cancer, long-term cancer-specific mortality after radical prostatectomy is the leading cause of death in young and presumably healthy patients. In contrast, older patients (with more associated comorbidities and multiple risk factors) are more at risk of dying from other causes and therefore their cancer-specific mortality is lower although their overall survival will also be poorer.[21]

When we focus on biochemical recurrence-free survival, we assume the premise given by the study of D'Amico et al., who demonstrated that 29% of high-risk patients treated with radical prostatectomy remained free of disease at 10 years.[22]

In our study these figures are relatively higher, 44% in younger patients, 59% in patients between 60 and 70 years of age and 62% in older patients, although we must take into account that our series includes patients treated with adjuvant RDT+ HT, and that the median follow-up for the older group does not reach 10 years, which could partly justify these results.

In addition, it is important to note that, although in the univariate analysis the younger age group is the one that shows the worst results in biochemical recurrence-free survival, in the multivariate analysis it is no longer significant, observing that the variables that are independently related to recurrence-free survival are the treatment received and the characteristics of the tumor. These data contrast with those described by Smith et al., who demonstrate a 10-year biochemical recurrence-free survival close to 60% in patients aged < 60 years. In fact, in younger patients (< 50 years), the results are even better with 10-year survivals around 90% (p = 0.010). After multivariate analysis adjusted for race, clinical and pathologic stage and pretreatment PSA, age remained a significant prognostic factor (p = 0.033).[23]

It should be noted that this study only includes patients treated with RP and not RDT as in our case.
In relation to the previous discussion and according to the results obtained in our series regarding to the possible influence of the treatment received on survival free of biochemical recurrence, we must note that the criteria for biochemical recurrence after prostatectomy and after RDT are different and, therefore, these results must be interpreted with certain caution.
Our study is not free of the limitations inherent to an observational, retrospective, single-center study. In addition, the sample size is somewhat limited, and some of the age groups have a small number of patients. In spite of this, our series has a long follow-up and a non-negligible number of patients. Admiteddly, strong conclusions cannot be drawn but our hypothesis deserves further specifically designed studies.

CONCLUSIONS

In our series, survival of patients with high-risk PC treated with curative intent is similar to that described in the literature. Age only influences in overall survival, with no impact on cancer-specific survival, free of biochemical recurrence or progression to metastasis.

ACKNOWLEDGEMENTS

This study was developed in the Department of Urology, Hospital Universitario Fundación Alcorcón, as a research project. Special thanks to all the authors for their contribution to this manuscript, especially to Dr. Guijarro and Dr. Llorente for their support in the preparation and revision of the manuscript.

CONFLICT OF INTEREST

The authors report no conflict of interest.

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