



Identification of Prognostic Parameters of the Patient with Prostate Cancer Treated by Robotic Radical Prostatectomy

Loizaga-Iriarte A^{1,2,3*}, Ugalde-Olano A¹, Lacasa-Viscasillas I¹, Rey-Gonzalez S¹, Santos-Martin A¹, Gonzalo-Aparicio D^{1,2}, Carracedo A^{1,2,3} and Miguel Unda^{1,2,3}

¹Department of Urology, Basurto University Hospital, Spain

²Traslational Prostate Cancer Research Lab, CIC bioGUNE-Basurto, Spain

³Centro de Investigación Biomedica en Red de Cáncer, Spain

Abstract

Studying the prognostic factors of Prostate Cancer (PC) is one of the pillars of current research in order to know which patients we should or should not treat. Environmental, epidemiologic, clinical, analytical and pathological factors, and the surgical technique, are going to influence the prognosis of our patients. The literature regarding the prognostic factors is extensive and very often contradictory. The majority of the papers published are related to tumour characteristics. Those associated with the patient, have not been widely studied and in general, they are studied as individual factors and have controversial results, despite the fact that the 60 to 80 year-old population has the greatest incidence of PC, an age group that presents in turn a higher number of comorbidities. Hypercholesterolemia, obesity, diabetes and their respective treatments very often coexist in the population with PC. Knowing the implications of these pathologies and their treatments in the progression of the cancer is another factor to study.

As far as we are aware, this is the first paper that combines all the patient factors that have been studied individually.

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*Correspondence:

Ana Loizaga-Iriarte, Department of Urology, Basurto University Hospital, Avenida Montevideo, 18-48013-Bilbao, Spain, Tel: 34-944006160; E-mail: ana.loizagairiarte@osakidetza.eu

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Subjects and Methods

Disease-Free Survival (DFS) and Metastasis-Free Survival (MFS) are examined through a retrospective study. A total of 1,148 patients operated on by Robotic Radical Prostatectomy (RRP) between January 2009 and December 2019 were reviewed. All with acceptance and signed a written consent for collecting prospective clinical data in accordance with the Helsinki Declaration for this type of studies. The study was approved by Basurto University Hospital Clinical Research Ethics Committee.

All the patients with histological diagnoses of PC, estimated life expectancy >10 years and minimum follow-up of 5 years were included. Those who received any neoadjuvant, adjuvant or rescue treatment were excluded.

As possible prognostic factors of the patient we analyzed age, family history of PC, abdominal and prostate surgical history, toxic habits such as tobacco, Body Mass Index (BMI), diseases such as dyslipidemia, hypertension, diabetes and the treatments for them.

We made single variable comparisons of survival by means of the Kaplan-Meier estimate and long-rank tests conducted to see if there were significant differences among the groups. The significance level for multiple comparisons was established by means of the False Discovery Rate (FDR), obtaining adjusted p values (padj). Once the general test was conducted for each variable, paired survival comparisons were also made the Kaplan-Meier estimate and long-rank tests to check pairs or levels that have significant differences. Also in this case, the level of significance for multiple comparisons was established by FDR adjustment.

Results

We defined our study cohort as 667 patients with a median age of 64.4 years (43 to 77) and a median follow-up of 69 months (59 to 91) (Table 1).

None of the previous factors, the patient's characteristics, or their diseases or treatments such as statins, Metformin or antihypertensive drugs turned out to be prognostic in a significant manner

Table 1: Features of cohort (n=667).

Characteristics		
Continuous	Median	SD
Patient age, yr	63.4	6.2
BMI	27.2	3.4
Prostate weight, g	41.5	21.2
Surgery volume	217.3	37.5
	Median (IQR)	
Preoperative PSA, ngr/ml	6.38	5.12-9
Follow-up length, mo	69	59-91

BMI: Body Mass Index; IQR: Interquartile Range; SD: Standard Deviation

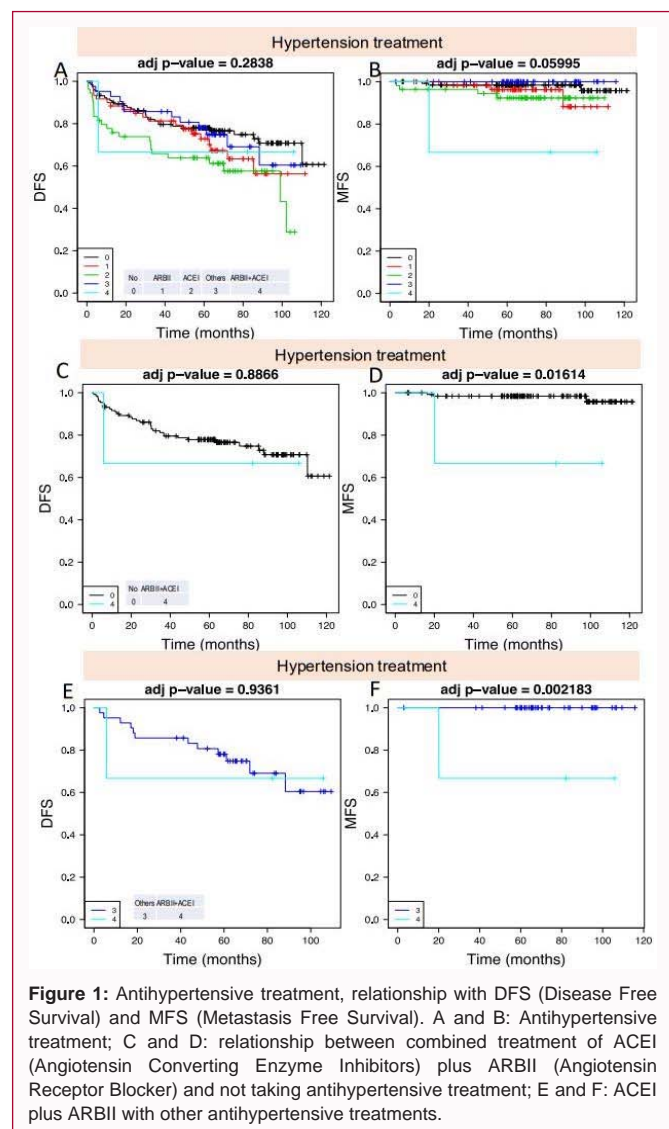


Figure 1: Antihypertensive treatment, relationship with DFS (Disease Free Survival) and MFS (Metastasis Free Survival). A and B: Antihypertensive treatment; C and D: relationship between combined treatment of ACEI (Angiotensin Converting Enzyme Inhibitors) plus ARBII (Angiotensin Receptor Blocker) and not taking antihypertensive treatment; E and F: ACEI plus ARBII with other antihypertensive treatments.

in relation to DFS (Table 2). However, we did find a decrease risk of metastasis-free survival associate to combined antihypertensive treatments of angiotensin-converting enzyme inhibitors and angiotensin receptors blockers II compared to not taking any treatment for hypertension (padj<0.001), or who took treatments other than these (padj=0.001) (Figure 1).

Discussion

The most studied prognostic factors to observe their involvement

Table 2: Variables of the patient: Multiple comparative relation by false discovery rate obtaining p adjusted (adj p) for DFS and MFS.

Patient factors	n	%	DFS adjust p Value	MFS adjust p Value
Age, yr			0.873	0.983
<55	64	10.7		
55-65	266	44.5		
>65	268	44.8		
BMI			0.984	0.828
<25	151	26.3		
25-30	313	54.4		
>30	111	19.3		
Previous surgeries			0.387	0.989
No	469	72.7		
Abd/Abd+Ing	70	10.9		
ing	93	14.4		
Pros	11	1.7		
Pros+ing	2	0.3		
Pros+Abd	0	0		
Medical history			0.734	0.068
No	460	70.1		
Tobacco	129	19.7		
Heart disease	60	9.1		
Tobacco + heart disease	7	1.1		
Other previous tumors			0.137	0.225
No	567	85.1		
Yes	99	14.9		
Prostate cancer family history			0.527	0.949
No	606	96.2		
1° grade, 1° grade+2° grade	19	3		
2° grade	5	0.8		
Hypertension (HT)			0.999	0.761
No	389	58.5		
Yes	276	41.5		
HT Treatment			0.283	0.059
No treatment	118	42.8		
ARBII	59	21.4		
ACEI	51	18.5		
Otros	44	15.9		
ARAI+IECA	4	1.4		
Diabetes			0.77	0.983
No	592	89.7		
Yes	68	10.3		
Diabetes treatment			0.503	0.976
No Metformin	42	61.8		
Yes Metformin	26	38.2		
Dyslipidemia			0.802	0.6
No	372	56.1		
Yes	291	43.9		
Dyslipidemia Treatment			0.897	0.983
No treatment	174	59.9		
No stain	5	1.6		
Yes stain	112	38.5		

Prost: Prostatesurgery; Abd: Abdominal Surgery; Ing: Inguinal Surgery; ACEI: Angiotensin Converting Enzyme Inhibitors; ARBII: Angiotensin Receptor Blockers; DFS: Disease Free Survival; MFS: Metastasis Free Survival

in the oncological results of the patients treated with RRP for PC are those that are associated with the tumor characteristics prior to surgery, PSA, clinical stage, number of affected cylinders and percentage of tumor, bilaterality or Gleason of the biopsy, as well as those also derived from the anatomopathological analysis of the surgical piece such as stage, Gleason, or surgical margins.

The factors that are associated with the patient are not widely studied and the results are controversial. As far as we know, this is the first paper that combines all the factors that are published in the literature and that have been studied individually.

Age

In our series, this has not been observed to be a prognostic factor for DFS or MFS in line with other authors such as den Broeck et al. [1] who in his systematic review did not associate age as an unfavorable factor for MFS and specific cancer, after a treatment of curative intent. Only in two of all the articles reviewed [2,3] appears a small but statistically significant unfavorable effect with an increase in age.

Family history

In our group, having family members with prostate cancer did not show that the oncological results are going to be worse. Nor did Herkommer et al. [4] find differences in biochemical relapse, specific or global cancer mortality among patients with or without family history, concluding that a family history of PC, although aggressive, did not worsen the results. This datum can help to reinforce the surgical approach of patients who have had family members with PC with poor prognosis.

Tobacco

Tobacco habits have not influenced the prognosis of our patients. Rieken et al. [5] found that tobacco is associated with a higher biochemical relapse risk after a radical prostatectomy in N0 patients. Ngo et al. [6] reported up to twice the possibilities with respect to those who had never smoked, adjusted to the tumor volume, but not to the stage, Gleason, margins or state of the regional nodes. Joshu et al. [7] related it to active smokers at the time of the diagnosis, but not to former smokers, Moreira et al. and Moreira et al. [8,9] did not find any relationship after adjusting for clinicopathological factors in his review of the SEARCH database.

BMI

There are few published data for evaluating the impact of obesity after RRP [10]. In our study we have differentiated three groups following the definition of the World Health Organization [11]: Group 1: Patients with $<25 \text{ Kg/m}^2$, group 2: 25 Kg/m^2 to 30 Kg/m^2 , group 3: $\geq 30 \text{ Kg/m}^2$ and we did not find statistically significant prognostic differences in DFS or MFS among the different groups. Yu et al. [12], in his retrospective paper in which the patients were divided into three groups, $<23 \text{ Kg/m}^2$, 23 Kg/m^2 to 27.5 Kg/m^2 and $>27.5 \text{ Kg/m}^2$, found significant differences in patients on which radical prostatectomy was performed in biochemical relapse-free survival, with the patients with $>27.5 \text{ Kg/m}^2$ being those with less survival. He concluded that having a BMI $>27.5 \text{ Kg/m}^2$ is an independent factor of poor prognosis in DFS. Gozen et al. [13] did not find differences in specific cancer survival or global survival among the three groups of patients, $<25 \text{ Kg/m}^2$, 25 Kg/m^2 to 29.9 Kg/m^2 and $>30 \text{ Kg/m}^2$. Schiffmann et al. [14] in his retrospective study of the Martini-Klinik Prostate Cancer Center database, compared the patients with BMI $<25 \text{ Kg/m}^2$ with $\geq 30 \text{ Kg/m}^2$ and although the obese patients had a greater probability of having advanced cancer, he did not find significant differences in DFS with

eight years of follow-up.

Statins and metformin

Neither have we demonstrated statistically significant differences with respect to DFS and MFS between the patients who did not take statins or Metformin or both and those that did take them. Joentausta et al. [15] described the statins as a beneficial prognostic factor for specific and global cancer survival, indicating a lower risk of relapses in patients who were taking them at the time of diagnosis, although, as it was a retrospective study, the causality could not be well established. Joentausta et al. [16] also associated the use of Metformin with greater survival, despite the fact that diabetic patients could have more aggressive pathological factors. Wang et al. [17] and Pennanen et al. [18] suggested in their studies, both *in vitro* and *in vivo*, an additive protector effect between Metformin and statins in PC.

Antihypertensive drugs

Taking antihypertensive drugs worsened metastasis-free survival, especially in those who combined ACE and ARB inhibitors compared to patients who did not take any or who took treatments other than these. In his study, Santala et al. [19] reached the conclusion that the use of antihypertensive drugs is associated to a higher risk of progression. In addition, the risk was associated to the taking of multiple drugs with different action mechanisms and increased if they were already in treatment at diagnosis.

Previous abdominal surgeries: We did not find prognostic differences between patients with previous abdominal surgeries and those who had not had any. Pierro et al. [20] published the first study that focused on the impact of previous abdominal surgery on oncological and functional results after RRP. Upon analyzing DFS in his cohort of patients, neither did he find significant differences between those with previous abdominal surgeries and those who had not had them.

Prostatic surgeries

There were no statistically significant differences as regards the control of cancer after RRP. Nor did Abedali et al. [21] find them among patients who had undergone laser enucleation.

As limitations to our study, we stress that there are no data on the medication dosage, we have not used the date of beginning the exposure to the medication nor has the combination of the treatments been studied except for that of the antihypertensive drugs. As the patients who took the combination of antihypertensive drugs are few and the number of patients that progresses is still limited, even the prognostic value of this combination must be taken with caution.

Conclusion

It can be pointed out that the studied patient factors: age, family history of PC, tobacco, use of statins or Metformin and previous abdominal or prostate surgeries are not prognostic factors that imply better or worse prognosis in our series. Only the combination of antihypertensive drugs (ACE and ARB inhibitors) has demonstrated a significant decrease of metastasis-free survival with respect to the patients who did not take them or took others. Further studies are required over a longer period and with a larger number of patients in order to be able to validate these results.

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Statement of Ethics

This study protocol was reviewed and approved by Basurto University Hospital Clinical Research Ethics Committee, reference number 1801.17CEICHUB, and written informed consent to participate in the study was obtained from all participants in accordance with the Helsinki Declaration for this type of studies.

Author Contributions

Management and coordination responsibility for the research activity planning and execution: Ana Loizaga-Iriarte, Miguel Unda, Arkaitz Carracedo; Conceptualization: Ana Loizaga-Iriarte, Miguel Unda, Arkaitz Carracedo; Methodology: Miguel Unda, Arkaitz Carracedo, Ana Loizaga-Iriarte Isabel Lacasa-Viscasillas; Validation: Arkaitz Carracedo, Ana Loizaga-Iriarte, Miguel Unda; Formal analysis: Ana Loizaga-Iriarte, Aida Santos-Martin, David Gonzalo-Aparicio, Arkaitz Carracedo; Investigation: Ana Loizaga-Iriarte, Sofia Rey-Gonzalez, Aida Santos-Martin, Aitziber Ugalde-Olano; Resources: Miguel Unda, Arkaitz Carracedo, Aitziber Ugalde-Olano; Writing-Original Draft: Ana Loizaga-Iriarte, Miguel Unda; Writing-Review & Editing: Ana Loizaga-Iriarte, Isabel Lacasa-Viscasillas, Sofia Rey-Gonzalez, David Gonzalo-Aparicio, Aitziber Ugalde-Olano, Aida Santos-Martin, Arkaitz Carracedo, Miguel Unda; Supervision: Miguel Unda, Arkaitz Carracedo.

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