# Survival analysis of patients with biochemical relapse after radical prostatectomy treated with androgen deprivation: Castration-resistance influential factors

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## Abstract

**Introduction:** We evaluate the prognosis of patients with biochemical recurrence (BCR) treated with androgen deprivation therapy (ADT) and to determine the influential factors to castration resistance (CR) and death.

**Methods:** From a series of 1310 patients with T1-T2 prostate cancer treated with radical prostatectomy between 1989 and 2012, 371 had BCR. Patients with lymph node involvement were excluded. We analyzed only the 159 treated with salvage ADT. At the end of the study, 77 (48%) had developed CR.

**Results:** The median follow-up to CR was 9.2 years. The CR-resistant free survival (RFS) was 76 ± 3%, 62 ± 3% and 43 ± 9% in 5, 10 and 15 years, respectively. The RFS median time was 14 years. In the multivariate study, the prostate-specific antigen (PSA) doubling time (PSA-DT) was <6 months ($p$ = 0.01) (hazard ratio [HR] 3; 95% confidence interval [CI] 1.4-6.8, $p$ = 0.007); seminal vesicle involvement (HR 3.1; 95% CI 1.5-6.2, $p$ = 0.01) and PSA velocity in ng/mL/year (HR 1.3; 95% CI 1.1-1.5, $p$ = 0.002) with better cut-off points of 0.84 ng/mL/year ($p$ = 0.04) (HR 4; 95% CI 1.7-9.4, $p$ = 0.001) were influential variables. Specific survival (SS) at 5, 10 and 15 years since surgery was 96 ± 1, 85 ± 2 and 76 ± 4, respectively. The time of CR to death was 30 ± 6% at 5 years, with the median at 3.2 years. In the multivariate only Ki 67 (HR 1.04; 95% CI 1.005-1.08, $p$ = 0.02) had an independent influence.

**Conclusions:** In BCR patients treated with ADT, the median to CR was 14 years. PSA-DT <6 months, PSA velocity (ng/mL/year) and seminal vesicle involvement were influential variables. From the CR, the median time to death was 3.2 years. Ki-67 marker was an independent influence.

## Introduction

In patients treated with radical prostatectomy, 15% to 40% of them have biochemical recurrence (BCR).[1-6] Of these, at least 40% to 60% are treated with androgen deprivation therapy (ADT). ADT is a palliative treatment already called castration, and in some cases patients develop castration resistance (CR).[7] New therapeutic options have been developed, however, once CR has developed death is unavoidable.[8,9]

It is important to know the clinic-pathological predictive factors of time to CR and time to death. The therapeutic attitude in prostatectomized patients with BCR depends on these factors. There are several studies about the time to death or time until evidence of metastasis in patients with BCR that were treated with deferred ADT.[1,10,11] There are also studies about the influence of the BCR time on overall survival,[12] about the factors of influence on disease-specific survival (SS),[13,14] and about its comparison with the SS in patients without recurrence.[2]

We studied the clinic-pathological factors of influence in time to CR and time to death in 159 patients (from a series of 1310 patients treated with radical prostatectomy) with subsequent BCR treated with immediate complete ADT.

## Methods

We retrospectively analyzed a series of 1310 patients with prostate cancer qualified as T1-T2 according to the TNM criteria and treated with radical prostatectomy between January 1989 and December 2012.

From the whole series, 371 showed BCR. Subsequently, patients with lymph node involvement were excluded. In total, 313 (23.9%) were part of the study. All patients were treated with radical therapy. Of the 313, 91 (29.1%) received radical radiotherapy, 63 (20.1%) radical radiotherapy and concomitant ADT and 159 (50.8%) received ADT. We only analyzed the 159 treated with ADT in rescue scheme, 77 of whom developed CR.

The selection of a rescue-specific treatment depended on the personal decision of each physician.

CR occurs when patients undergo ADT despite their pro-

gressive elevation of serum prostate-specific antigen (PSA) levels. As per the 2013 Canadian Urological Association guidelines criteria,[15] castration-resistant prostate cancer (CRPC) is defined by disease progression despite ADT and may present as either a continuous rise in serum PSA levels, the progression of pre-existing disease, and/or the appearance of new metastases.

Before surgery, a detailed medical history with a physical examination (including rectal examination), PSA and prostate biopsy were performed in every patient. The study was completed with a computed tomography (CT) scan until July 2000. After that point, a magnetic resonance image (MRI) was taken with no special criteria due to the fact that the initial target was to manage MRI diagnostic effectiveness (n = 729 patients).

Up until 2000, a bone gammagraphy was done in all patients. Since that time, it was only used in patients with a PSA higher than 20 ng/mL or Gleason score >6. In every case, a modified retropubic radical prostatectomy, according to the technique described by Walsh in 1982,[16] was performed and was completed systematically with bilateral ilio-obturator node dissection until 2007. As of 2007, the modified retropubic radical prostatectomy was only done in patients with a PSA >15 ng/mL, clinical Gleason score ≥7, or clinical stage T2b. The laparoscopic approach was performed at our center for the first time in 2005.

Two urological sub-specialized pathologists examined the retrieved specimens according to the technique described by True.[17] We also studied the Ki-67 expression.

In 2000,[18] we found that Ki-67 was associated with a worse prognosis and worse cancer stage in operated patients. We now want to assess whether this trend is confirmed in patients with CR. Since 2000, the determination of Ki-67 was made in 99 patients (from the 159 with CR). All immunohistochemical analyses were performed in sections of 4 microns, fixed in formalin and obtained from the primary tumour, which was included in paraffin. Immunohistochemistry was performed with an automatic inmunohistainer (Techmate 500; Dako, Copenhagen, Denmark) with the Envision and System Dako, in which the secondary antibody is coupled to a dextran polymer linked to peroxidase molecules. Endogenous peroxidase activity was neutralized with 5% hydrogen peroxide, in methanol solution for 30 minutes at room temperature. Antigen retrieval was performed with a microwave treatment for 20 minutes at 800 watts. Rabbit serum was phase-locked. The primary antibody was applied for 120 minutes at room temperature; sections were then washed with a washing buffer. The next step was to add the reagents with the Envision and System and incubate them for 30 minutes. The plates were washed with a wash buffer and treated with a 0.05% diaminobencina hydrochloride solution and 0.1% hydrogen peroxide 0.05 mL/L of TRIS buffer saline at pH 7.4 at room temperature, for 5 minutes. After the distilled water wash for 3 minutes, preparations were stained with hematoxylin Harris modified solution, dehydrated and mounted. Lamb normal serum was used for the negative control instead of the primary antibody (MIB1, Zymed). The result was expressed in a percentage of stained cells.

Analytics tracking was performed using PSA determinations at 3, 6 and 12 months after surgery. Then, every 6 months for a total of 3 years, and subsequently, every year. Following the recommendations of the Prostate Cancer Clinical Trials Working Group (PCWG2), BCR was defined as the determination of PSA ≥0.4 ng/mL[19] (Hybritech, Tandem) obtained at least 30 days after surgery and later confirmed with an equal or greater value.

For the PSA doubling time calculation (PSA-DT in months), a minimum of 2 PSA (ng/mL) determinations were obtained after BCR and it was calculated by the following formula: Ln 2 × DT/Log PSA2 - Log PSA1. With these values the growth of PSA velocity is also computed in ng/mL/year (Velocity = PSA1 + 21/DT).

Our goals for this study were twofold: (1) to assess the time from surgery to CR and the clinic-pathological factors of influence; and (2) to study the time from CR to death and the factors of influence.

Chi-square or Fisher exact F testing and contingency tables were used to compare qualitative variables. The normality distribution of quantitative continuous variables was determined using Kolmogorov-Smirnov and Shapiro-Wilk tests. Quantitative variables (age [years], PSA [ng/mL]) and Ki-67) did not follow a normal distribution and non-parametric tests were used for comparison (Mann Whitney U test).

The receiver operating characteristic (ROC) were used to pursue ideal cut points in continuous variables. To assess the actuarial survival, we used the Kaplan-Meier method; to compare survival curves, we used the log-Rank test.

A Cox regression analysis was used to determine survival influential variables (univariate and multivariate study). Statistical significance and hazard ratio *p* values with their respective confidence intervals were calculated and estimated respectively by the Bootstrapping technique with 1000 replications.

All statistical analyses were performed using SPSS expanded version 22.0 (SPSS Inc., Chicago, IL). All data were presented as mean ± standard deviation or number (%). A *p* value of less than 0.05 was required to determine the statistical significance.

## Results

The mean and median time to BCR of patients treated with AD was 27 and 14 months, respectively. The median follow-up of the entire group (159 patients) was 9.2 years. For the 82 patients in BCR without CR, it was 9.2 years; for the 77 patients with CR, it was 7.7 years. We tallied the

clinico-pathological characteristics of our study patients (Table 1).

## Time to CR study

At the end of the study, 77 patients (48%) had developed CR. CR resistance-free survival (RFS) is 76 ± 3%, 62 ± 3% and 43 ± 9% at 5, 10 and 15 years, respectively (patients at risk 93, 39, 5). Median RFS was 14 years (95% confidence interval [CI] 11-17 years) (Fig. 1).

In the univariate study (Cox model), the RFS influential factors were seminal vesicle involvement, pathological Gleason 8-10, having been operated among the first 500 patients in the series (1989-1999), PSA doubling time

**Table 1. Clinico-pathological characteristics of prostatectomized patients in treatment with ADT by BCR, with and without castration-resistance***

| BCR patients | No. | No CR | CR | *p* value† |
|---|---|---|---|---|
| N | 159 (100%) | 82 (51.6%) | 77 (48.4%) | |
| **Clinical variables** | | | | |
| *Age (years)* | | | | |
| 64.4 ± 6.1 | | 64.6 ± 5.8 | 63.4 ± 6.7 | ≤0.1 |
| *Initial PSA (ng/mL)* | | | | |
| 18.8 ± 15.5 | | 18.2 ± 15.3 | 20.2 ± 16.7 | ≤0.3 |
| *BMI (kg/m²)* | | | | |
| 28.1 ± 4 | | 27.8 ± 3.7 | 28.2 ± 4.6 | ≤0.8 |
| *Abnormal rectal examination* | | | | |
| 90 (56.6) | | 40 (48.7) | 50 (65) | ≤0.09 |
| *Biopsy diagnostic (T1c)* | | | | |
| 60 (37.7) | | 32 (39) | 28 (36.3) | ≤0.4 |
| *Gleason score* | | | | |
| 2-6 | 88 (55.3) | 39 (47.6) | 49 (63.6) | |
| 7 | 35 (22) | 25 (30.5) | 10 (13) | |
| 8-10 | 36 (22.6) | 18 (21.9) | 18 (23.4) | ≤0.09 |
| *Clinical stage* | | | | |
| T1a-c | 56 (35.2) | 34 (41.5) | 22 (28.6) | |
| T2a-b | 62 (38.9) | 35 (42.7) | 27 (35) | |
| T2c | 41 (25.8) | 13 (15.8) | 28 (36.3) | 0.000 |
| *High-risk D´Amico* | 93 (58.5) | 45 (54.8) | 48 (62.3) | ≤0.2 |
| **Pathological variables** | | | | |
| *Pathological stage* | | | | |
| pT2 | 45 (28.3) | 29 (35.3) | 16 (20.7) | |
| pT3 | 55 (34.6) | 33 (40.2) | 22 (28.6) | |
| pT3b | 59 (37.1) | 20 (24.4) | 39 (50.6) | ≤0.003 |
| *Positive surgical margins* | 97 (61) | 52 (63.4) | 45 (58.4) | ≤0.8 |
| *Pathological Gleason* | | | | |
| 2–6 | 54 (33.9) | 22 (26.8) | 32 (41.5) | |
| 7 | 49 (30.8) | 34 (41.4) | 15 (19.4) | |
| 8–10 | 56 (35.2) | 26 (31.7) | 30 (39) | ≤0.04 |
| *Ki-67 marker* | 8.3 ± 10.5 | 8.5 ± 11.7 | 7.8 ± 7.6 | ≤0.7 |
| *State* | | | | |
| Live in progression | 101 (63.5) | 77 (93.9) | 24 (31.2) | |
| Dead of prostate cancer | 47 (29.5) | 0 (0) | 47 (61) | |
| Died of other causes | 11 (7) | 5 (6.1) | 6 (7.8) | 0.000 |
| *Follow-up (years)* | | | | |
| Mean | 9.4 ± 4.2 | 9.4 ± 4 | 8.6 ± 4.2 | |
| Median | 9.2 (0.2-19.5) | 9.2 (0.9-19.5) | 7.7 (0.2-17.5) | |

Data presented as mean ± DS or number (%).
*n=159 prostatectomized with AD by BP; †$p < 0.05$; PSA: prostate-specific antigen; BMI: body mass index; ADT: androgen deprivation therapy; BCR: biochemical recurrence; CR: castration resistant.

(PSA-DT) <6 months, PSA velocity in ng/mL/year, and PSA velocity with the best cut-off point as 0.84 ng/mL/year, and the stained cells percentage for Ki-67 (Table 2).

In the multivariate study, the influential variables were PSA-DT <6 months, PSA velocity in ng/mL/year, PSA velocity with the best cut-off point as 0.84 ng/mL/year, and seminal vesicle involvement (Table 2).

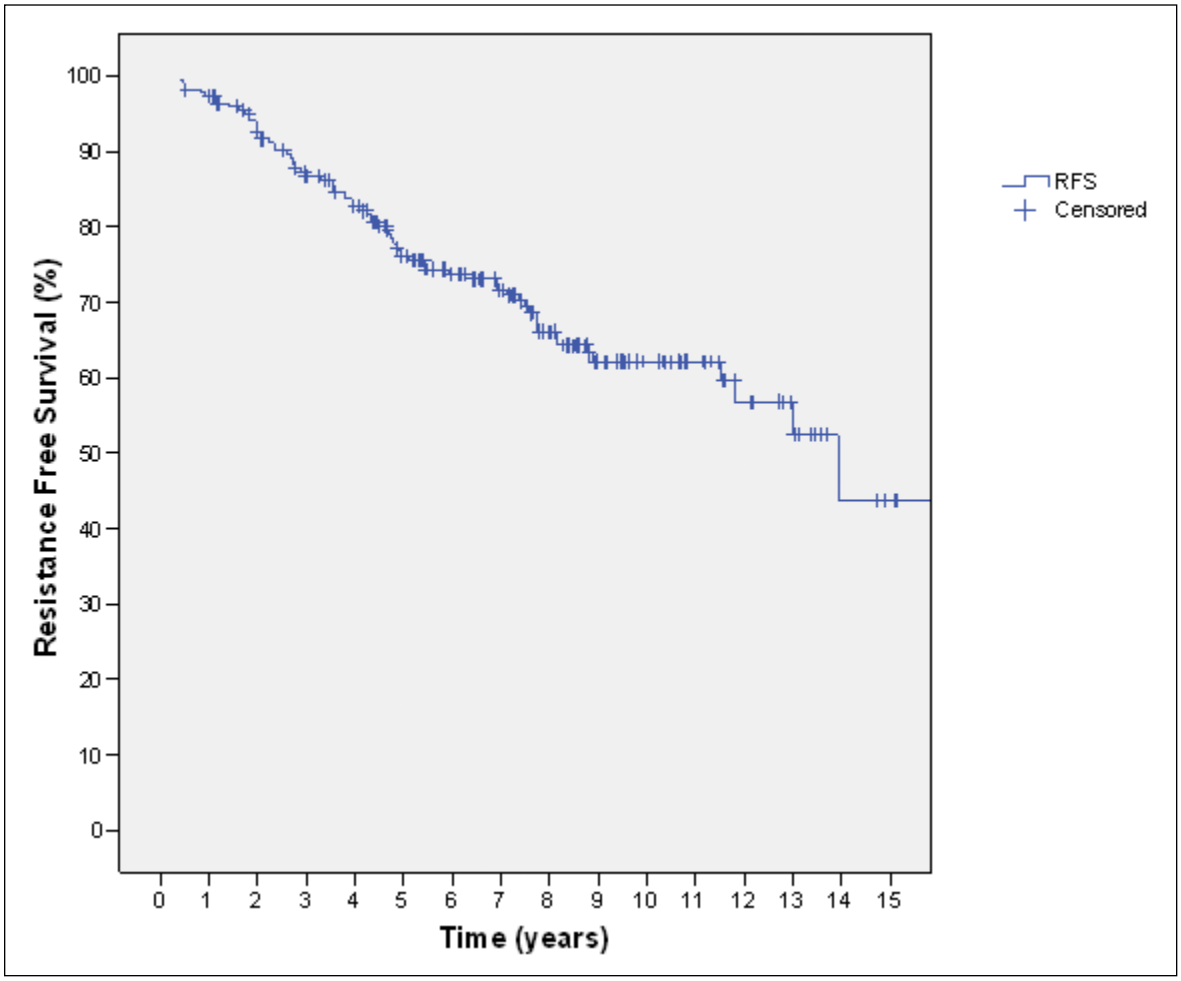
PT3b patients had a RFS of 65 ± 6% and 45 ± 7% at 5 and 10 years, respectively. The median time to CR was 8 years (95% CI 5-11 years). In patients without seminal vesicle involvement, the RFS was 82 ± 3% and 72 ± 4% at 5 and 10 years, respectively ($p < 0.000$).

RFS at 5 and 10 years was 53 ± 10 and 47 ± 11, respectively, for the PSA-DT <6 months group (26.8%) and 89 ± 4 and 73 ± 6, respectively for the PSA-DT >6 months group (73.2%) ($p = 0.002$).

Patients with a PSA velocity >0.84 ng/mL/year had a RFS at 5 and 10 years of 52 ± 10% and 45 ± 10%, respectively, versus 92 ± 3% and 75 ±7% in patients with a PSA velocity <0.84 ng/mL/year ($p = 0.001$).

Specific survival (SS) in patients with BCR treated with ADT at 5, 10 and 15 years after surgery was 96 ± 1%, 85 ± 2%, and 76 ± 4%, respectively (patients at risk=147, 85 and 31). SS at a median follow-up of 9.2 years was not available. In 17.4 years, the SS was 61 ± 8, with 9 remaining patients at risk (Fig. 2).

In the multivariate study, only PSA velocity >0.84 ng/mL/year was influential (HR 19.9; 95% CI 12.4-162.2, $p = 0.05$).




| | Failure (%) | RFS to 5 years (%) | RFS to 10 years (%) | Patients at risk to 5 years | Patients at risk to 10 years |
|---|---|---|---|---|---|
| RFS | 48.4 | 76 ± 3 | 62 ± 3 | 93 | 39 |

***Fig. 1.*** Castration resistance free survival (RFS) in patients with biochemical recurrence on treatment with androgen deprivation (N=159). *With a median follow-up of 9.2 years, the RFS median in patients treated with androgen deprivation by biochemical recurrence is 14 years, 95% confidence interval (11-17).

**Table 2. Univariate and multivariate analysis of RFS influencing factors***

| | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| | HR | HR 95% CI | *p* value† | HR | HR 95% CI | *p* value† |
| Initial PSA (ng/mL) | 1.004 | 0.9–1.02 | ≤0.5 | | | NS |
| PSA >20 ng/mL | 1.1 | 0.7–1.9 | ≤0.5 | | | NS |
| BMI (kg/m²) | 1.04 | 0.9–1.1 | ≤0.4 | | | NS |
| T2 vs. T1 | 1.4 | 0.8–2.5 | ≤0.1 | | | NS |
| Unilateral vs bilateral biopsy | 2 | 0.9–4.5 | ≤0.09 | | | NS |
| Gleason score 8–10 | 1.4 | 0.8–2.4 | ≤0.2 | | | NS |
| High-risk D´Amico | 1.5 | 0.8–2.5 | ≤0.1 | | | NS |
| First 500 surgeries 2000-2009 vs. 1989-1999 | 1.9 | 1.01–3.4 | ≤0.04 | | | NS |
| Ki-67 | 1.02 | 1.005–1.04 | ≤0.01 | | | NS |
| Ki-67 >10% | 2.4 | 1.1–5.2 | ≤0.02 | | | NS |
| PSA-DT <6 months | 3 | 1.4–6.8 | ≤0.007 | 3.2 | 1.4–7.2 | ≤0.004 |
| PSA velocity (ng/mL/year) | 1.3 | 1.1–1.6 | ≤0.002 | 1.3 | 1.1–1.5 | ≤0.002 |
| PSA velocity >0.84 ng/mL/year | 4 | 1.7–9.4 | ≤0.001 | 4 | 1.7–9.4 | ≤0.001 |
| Surgical margins | 1.2 | 0.7–1.9 | ≤0.5 | | | NS |
| Pathological Gleason 8–10 | 1.8 | 1.1–2.9 | ≤0.02 | | | NS |
| Seminal vesicle involvement | 2.8 | 1.7–4.6 | 0.000 | 3.1 | 1.5–6.2 | ≤0.001 |

†$p < 0.05$. RFS: castration resistance-free survival; NS: not significant, $p > 0.05$; HR: hazard ratio; CI: confidence interval; PSA: prostate-specific antigen; BMI: body mass index; PSA-DT: PSA doubling time; ADT: androgen deprivation therapy; BCR: biochemical recurrence; CR: castration resistance.
*159 prostatectomized patients with AD by BCR. Patients with lymph node involvement were excluded. PSA-DT has been calculated in 123 patients; 33 show a PSA-DT <6 months and 90 a PSADT >6 months. PSA velocity has been calculated in 123 patients; PSA velocity is <0.84 ng/mL/year in 90 patients and >0.84 ng/mL/year in 33 patients. Ki-67 marker staining has performed in 99 patients. 80 have stain (+) <10% and 19 stain (+) >10%.

Patients with a PSA velocity >0.84 ng/mL/year had a SS at 5 and 10 years of 96 ± 3% and 68 ± 10%, respectively, since surgery (28 and 10 at-risk patients, respectively).

In the 77 patients with CR, the SS median time from surgery to death was 10.2 years (range: 6.9-13.5).

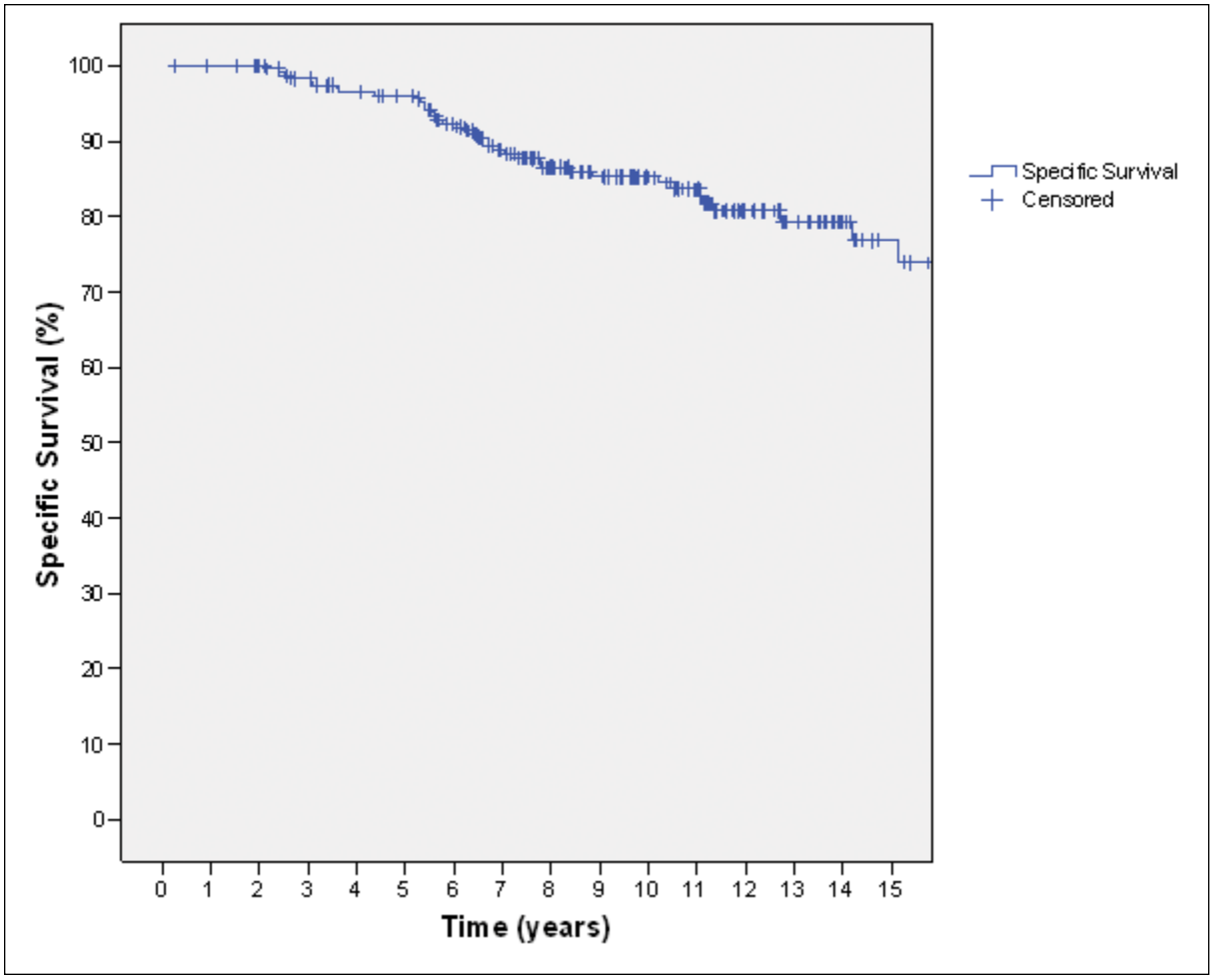
## Time since CR to death

From the 77 patients, 24 (31.2%) are currently living in state of BCR and CR, 6 (7.8%) have died due to other causes and 47 (61%) have died as a result of their prostate cancer. The SS time from CR was 30 ± 6% in 5 years. The SS median time was 3.2 years (95% CI, range: 2.6-3.9) (Fig. 3).

**Table 3. Univariate and multivariate analysis of SS influencing factors in CR patients***

| | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| | HR | HR 95% CI | *p* value† | HR | HR 95% CI | *p* value† |
| Initial PSA (ng/mL) | | | NS | | | NS |
| PSA >20 ng/mL | | | NS | | | NS |
| BMI (kg/m²) | | | NS | | | NS |
| T2 vs T1 | | | NS | | | NS |
| Unilateral vs. bilateral biopsy | | | NS | | | NS |
| Gleason score 8–10 | | | NS | | | NS |
| High-risk D´Amico | | | NS | | | NS |
| First 500 surgeries 2000-2009 vs. 1989-1999 | | | NS | | | NS |
| PSA-DT <6 months | | | NS | | | NS |
| PSA velocity (ng/mL/year) | | | NS | | | NS |
| PSA velocity >0.84 ng/mL/year | | | NS | | | NS |
| Surgical margins | | | NS | | | NS |
| Seminal vesicle involvement | | | NS | | | NS |
| Pathological Gleason 8–10 | 1.9 | 1.04–3.8 | ≤0.03 | | | NS |
| Ki-67 | 1.05 | 1.008–1.09 | ≤0.02 | 1.05 | 1.008–1.09 | ≤0.02 |

†$p < 0.05$; NS: not significance, $p > 0.05$; HR: hazard ratio; CI: confidence interval; PSA: prostate-specific antigen; BMI: body mass index; SS: specifics survival; CR: castration resistance.
*77 prostatectomized patients with androgen deprivation by biochemical recurrence and castration resistant.




| | Failure (%) | SS to 5 years (%) | SS to 10 years (%) | Patients at risk to 5 years | Patients at risk to 10 years |
|---|---|---|---|---|---|
| SS | 29.5 | 96 ± 1 | 85 ± 2 | 147 | 85 |

**Fig. 2.** Specific survival (SS) in patients with biochemical recurrence on treatment with androgen deprivation (N=159). SS median is not available. *With a median follow-up of 9.2 years from surgery to death, we do not have SS median.

In the univariate analysis, the Ki-67 marker and the pathological Gleason score 8-10 were SS influential variables. Nonetheless, in the multivariate analysis only Ki-67 had independent influence (Table 3).

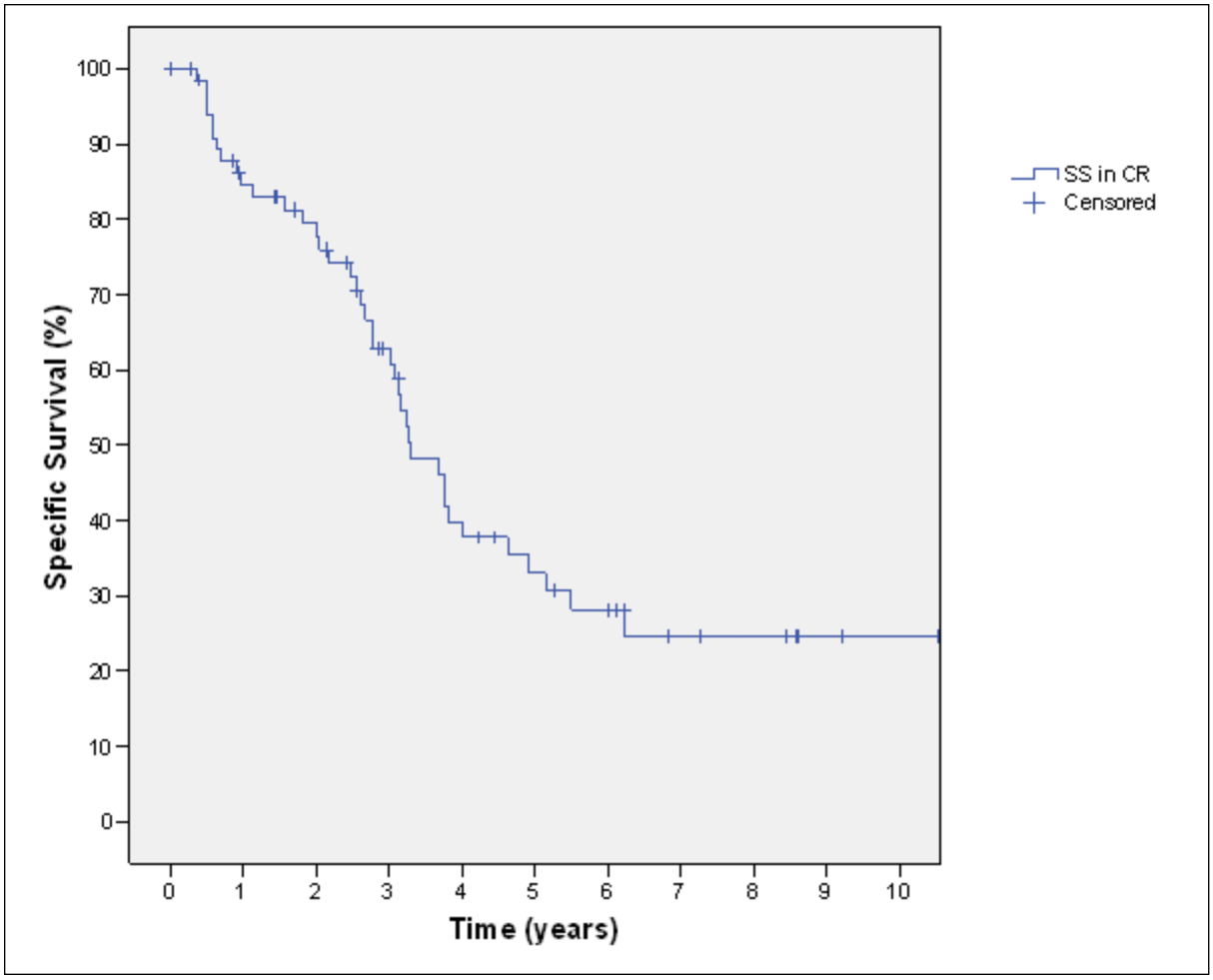
The median time to death of patients with Ki-67 >10% stained cells was 11 months (95% CI, range: 8-15) versus 5.5 years in those with Ki-67 <10% stained cells. The median time to death of patients with Gleason score 8-10 was 2.7 years (95% CI, range: 2.5-4).

## Discussion

Patients with localized prostate cancer with BCR after surgery are treated half the time with ADT.[20,21] This treatment shows a favourable clinical response in 80% of cases and, although it is always temporary and incomplete, it probably extends to the overall survival of patients. Its therapeutic benefit in the short term is unquestionable.

All patients treated with ADT become hormone-refractory[22] when they start to show a biochemical and clinical recurrence which leads to death. In metastatic patients with this treatment, 35% to 40% fail in the first year, 50% die before 3 years and only 5% to 10% live beyond 10 years. However, 66% of the metastatic patients who have not received ADT die within 9 months.[23]

In patients with localized prostate cancer with BCR, CR occurs much later in life. In our study, with a remarkable median follow-up of 9.2 years, the median time since surgery to CR was 14 years (from BCR 11.5 years, data not shown). There are several studies on BCR in patients treated with immediate or deferred ADT. The first extensive study was published by a Johns Hopkins group[1] and analyzed




| | Failure (%) | SS in CR to 5 years (%) | Patients at risk to 5 years |
|---|---|---|---|
| SS in CR | 61 | 30 ± 6 | 14 |

***Fig. 3.*** Specific survival (SS) in castration resistant (CR) patients (N=77). SS median of 3.2 years, 95% confidence interval (2.6-3.9).

304 patients (of the 1997 patients undergoing radical surgery) who were treated with ADT until death, who had a PSA >0.2 ng/mL and who were not treated until evidence of metastasis disease. The median time to metastatic disease was 8 years (in 5 years, 63% were free of metastasis disease) and it depended on the time from surgery to BCR (<2 years), on the PSA-DT <10 months and on the pathological Gleason 8-10. Since the development of metastatic disease, the median survival was less than 5 years. The only influential variable was the time from surgery to the development of metastatic disease (1-3 years vs. rest). In our study, the treatment started the moment in which BCR occurred, so we were only able to compare the SS, which is better in our case (17 years from surgery, 15 years from BCR) despite having a higher tracking.

We compared our data with those published in another extensive study.[10] This study analyzed 379 patients and showed a SS of 55% at 15 years (with a median follow-up of 10 years, SS median was not available). In our study, the SS at 15 years was 76% and we did not have either a SS median with the current tracking. The only difference in treatment was the time when it started (which was immediately in our study, and when the metastatic disease appeared in the other study.[10])

Another extensive study included 213 patients with BCR, with no variation in survival in 10 years from those who do not have recurrence (88% vs. 93%, respectively) and 74% in those who have not metastatic disease.[2] However, in our study there were significant differences between those who had BCR and those who did not. This difference was because the tracking was much higher in our study than in the other study (56 months from surgery, 34 from BCR). Rogers and colleagues studied patients with clinically localized cancer undergoing radical prostatectomy and whose PSA was never

negative, with 160 non-treated patients until there was evidence of metastatic disease.[24] At the end of the study, 21% of patients died as a result of prostate cancer and 47% had metastatic disease. The metastasis-free survival probability at 3, 5, 7 and 10 years was 68%, 49%, 38%, and 22%, respectively. The factors of influence were Gleason 8-10, median time to metastasis disease 2.5 years versus 6 years and above all the PSA rise curve inclination.

Some authors have found that a Gleason score 8-10 significantly influenced SS; this demonstrates that SS can be a prognostic factor in patients with CRPC.[25-30]

CR is the last step of an evolutionary scale whose point of departure is BCR. This resistance is determined by a series of intrinsic clinic-pathological tumour characteristics. The aim of the present study was to show the influential variables from surgery to CR and from CR to death. In addition to the conventional clinical-pathological variables, we emphasized that the PSA-DT prognostic value, a measurement that determines the biological activity of tumour, has capital prognostic value.[31] Typically, a PSA-DT of more than 80 days is associated with better treatment results.[32] In fact, in 2 large trials (i.e., the South West Oncology Group [SWOG 9916][33] or the Cancer and Leukemia Group B [CALGB][34]), the PSA-DT was the decisive criterion in the survival of patients. In our study, the CR independent predictive factors were seminal vesicle involvement, PSA-DT <6 months and PSA velocity >0.84 ng/mL/year.

From CR to death, although a Gleason score 8-10 was a factor of influence in the univariate study, contrary to other published papers, it was not influential in the multivariate study. Perhaps this was the case because of the evolution in the type of patient candidate to radical prostatectomy in 20 years,[35] or because of the changes in the pathological qualification criteria with a tendency to upgrade the Gleason score,[36] or because of the clinic-pathological stage migration of this disease.[37,38]

The only death survival independent predictor factor was the Ki-67 value. Ki-67 is a nuclear antigen in the G1, S, G2 and M phases of the cell cycle. It correlates with cell proliferation and it indirectly indicates an intense biological tumour activity and poor prognosis.[18,39-41] For every 1% of stained tissue that increases the expression of this marker, the risk of death in prostate cancer increases by 5% (HR:1.05; 95% CI 1.008-1.09, $p < 0.02$). The best cut-off point is 10% of stained cells (median survival from CR to death is 11 months if it is higher than 10% and 5.5 years if it is less than 10%). The originality of these data is obvious because they have not been published yet. It has a notable importance because if confirmed, these findings will lead us to a new prognosis assessment in these types of tumours. It also has the great advantage in that it is technically easy to analyze by immunohistochemistry with any prostate tissue (transurethral resection material,[40] prostate biopsy material,[41] radical prostatectomy specimen[18]) and it can easily be done at any histopathology department.

Finally, despite 75.3% (58 of 77) of patients with CR currently with metastatic disease, we have not studied the influence of time until metastatic disease in SS. We have not considered either the time from radical prostatectomy to BCR in association with SS. This is a major limitation of our study as long as there are published studies which show that this association with SS is an independent factor of influence.[10] In addition, it is a retrospective study, from a single centre and not centralized, in which the small number of patients does not allow us to make stronger assertions.

## Conclusion

With a median follow-up of 9.2 years in BCR patients treated with AD, the RFS median was 14 years (SS median time from surgery was not available). The RFS was 76 ± 3%, 62 ± 3% and 43 ± 9% at 5, 10 and 15 years, respectively. The PSA-DT <6 months, seminal vesicles involvement and PSA velocity >0.84 ng/mL/year were influential variables for RFS.

In the 77 patients with CR, the SS median time from surgery to death was 10.2 years. The median time from CR to death was 3.2 years. The only independent prognostic factor was Ki-67.

**Competing interests:** Dr. Algarra, Dr. Hevia, Dr. Tienza, Dr. Merino, Dr. Velis, Dr. Zudaire, Dr. Robles, and Dr. Pascual all declare no competing financial or personal interests.

This paper has been peer-reviewed.

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