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ARTICLE

Relationship between D90 and D100 with Biochemical and Local Failure in Low-risk Prostate Cancer Treated with Low-rate Brachytherapy (LDR)

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ABSTRACT

Low dose rate brachytherapy (LDR) is an accepted, effective treatment with few local side effects, used as monotherapy in patients with low-risk prostate cancer (PC). The aim of this paper is to analyse 245 patients treated with LDR in the Radiation Oncology Department of the Hospital Gómez Ulla, from 2004 to 2016, evaluating the relationship of dosimetric parameters with biochemical and local recurrence as well as genitourinary and gastrointestinal toxicity derived from the technique. The results obtained show a clear relationship between the dose used and biochemical and local failure.

1. Introduction

There are strong data showing similar local control and survival rates when comparing LDR to other techniques such as external radiotherapy or radical surgery with lower risk of genitourinary and gastrointestinal side effects. Few studies in the literature analyse the relationship between the dose received by 90 and 100 percent of the prostate and the development of biochemical and local failure. This study offers some important insights in this regard, with the main objective of this paper being: *"To*

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demonstrate the relationship between D90 and D100 and biochemical and local failure."

2. Material and Methods

2.1 Design

This is a longitudinal observational survival study.

2.2 Study Population

Patients from the districts of Carabanchel and Latina, Military Health patients (ISFAS) from the Community of Madrid or from other Autonomous Communities or from another district in whose reference hospital the technique is not performed.

2.3 Sampling

Patients who met the criteria to be candidates for this treatment were selected by non-probabilistic consecutive sampling. Patients included adhere to the RTOG patient selection criteria [1].

2.4 Inclusion Criteria

- Males;
- No age limit. Life expectancy greater than 10 years;
- Diagnosed with low-risk prostate cancer, with which they must meet:
  - Gleason ≤ 6
  - PSA < 10
  - Clinical stage T1c-T2a

2.5 Exclusion Criteria

- Patients who have already received previous treatment with Brachytherapy or External Radiotherapy.
- Previous transurethral resection (TUR), in which a significant prostate volume has been resected (relative contraindication).
- Prominent median lobe.
- Pubic arch precluding seed insertion.
- Glandular size > 60 cc.

2.6 Sample Size

A total of 245 patients were recruited between 2004 and 2016. All of them signed the corresponding informed consent for the technique.

2.7 Material

- Computer with specific planning software.
- Stabiliser (stepper) fixed to the table with connectivity to the ultrasound machine.
- A template (template for needle placement) with a matrix of 13 Å~ 13, with 5 mm distance between the needle holes with a gauge of 17 and 18.
- Stabilising needles and specific brachytherapy needles with stylet with markings every 5 mm and radioactive seeds.
- Cutter or seed binding system with loading system when using needles preloaded with stranded, linked, or loose seeds and/or a Mick applicator or similar device to load seeds into the prostate and seed cartridges for this system.
- A source or needle holder with radiological protection where the loaded needles and/or carriers should be deposited until implantation.
- Ionisation chamber for calibration and control of the implant seeds.
- Radiation detector.
- Usual material for anaesthesia and surgical technique.

2.8 Method

2.8.1 Pre-implant

On the day of the first consultation, all the patient's clinical data is collected and a complete clinical examination and a transrectal ultrasound scan is performed to determine the prostate volume. The number of seeds required, and their activity, is requested on an individual basis, based on knowledge of the patient's prostate volume and anatomical characteristics.

2.8.2 Implant

On the day of the operation, the procedure is as follows:

Positioning

Once the anaesthesia (spinal anaesthesia or general anaesthesia) has been administered, the patient is placed in the lithotomy position.

Planning

The implant technique is carried out with intraoperative planning; ultrasound images are obtained every 0.5 cm from the base to the apex. The images are transferred to the planner. The images are processed, and the prostate, urethra and rectum are delimited in each of the slices and intraoperative dosimetric planning is performed. Seeds are inserted with pre-loaded needles. Evaluation of dose-volume histograms, limiting doses in organs at risk [2].

Dose prescription to target volume

If GTV is visible on imaging, it should be covered by

the 150% isodose [3]. For CTV, the dosimetric parameters should be:

- V100 ~ 100 %
- D90, CTV > 100% DP
- V150 < 50%

Organs at risk

Rectum (Dmax < 200 Gy, D100≤ 100% of dose prescription, D2 cc < 145 Gy) and urethra (D10 < 150% of dose prescription, D30 < 130% of dose prescription).

Despite previous recommendations, The Royal College of Radiologists in the UK, due to the historical experience of many centres, also considers V100prostate > 98% and V150prostate = 40%-65% acceptable. Post-implant dosimetry should be performed, and the following parameters should be analysed:

- Target volumes: D90%, V100%, and V150%.

Organs at risk: D10% and D30% for the urethra, and D2 cc and D0.1 cc for the rectum.

2.9 Statistical Method

2.9.1 Descriptive Statistics

Indices of central tendency and dispersion for quantitative variables were the arithmetic mean and standard deviation $\bar{x}$(SD) or the median and interquartile range Md (IQR), depending on the assumption of normality as determined by the Kolmogorov-Smirnov (K-S) test, respectively.

For categorical variables, absolute and relative percentage frequencies were used.

As graphical representations, bar diagrams were used for categorical variables, and box plots for quantitative variables assuming or not, respectively, the assumption of normality (K-S or S-W).

2.9.2 Analytical Statistics

The measure of association between two categorical variables was performed using Pearson's χ^2, or Fisher's exact test if both were dichotomous, in which case the assessment of the effect was performed.

To determine the association between a dichotomous independent variable and a quantitative dependent variable with a parametric distribution, the Student's t-test for independent samples was used. The effect was assessed by the mean difference, and precision by the 95% confidence interval.

The measure of association between a polytomous independent variable and a quantitative dependent variable was estimated with Snedecor's F-test (one-way ANOVA) or the Kruskal Wallis test, depending on whether it was Gaussian or not, respectively.

The survival study was performed using the Kaplan Meier method. In all cases, a value of $p<0.05$ will be used as the degree of statistical significance and the statistical application will be the SPSS® package version 25.

3. Results

3.1 Sample Characteristics

In Table 1, the following sample characteristics are listed. The mean age was 68 years (49 years - 82 years). The mean Karnofsky index was 99.43 (4.1).

At diagnosis, 16.3% (40 patients of the total sample) had perianal pathology, such as external haemorrhoids: 13.5% (33 patients), anal fissures: 1.6% (4 patients), anal fistulas: 1.2% (3 patients).

Table 1. Characteristics of the patient sample

	Total N: 245 n (%)
Age	68 (6.2)
IK	99.43 (4.1)
Haemorrhoids n (%)	33 (13.5)
Anal Fissure n (%)	4 (1.6)
Anal Fistula n (%)	3 (1.2)
Oncological background n (%)	24 (9.8)
Previous pelvic surgery n (%)	89 (36.3)

Of the entire sample, 24 patients (9.8%) had been diagnosed with a previous oncological process.

In Table 2, patients with previous surgeries are classified by type, frequency and percentage:

Table 2. Type of previous surgery

	Frequency	Percentage (%)
Prostatic adenectomy	5	2.0
Inguinal Hernia	46	18.8
Appendectomy	15	6.1
Renal transplant	1	0.4
Lithotomy	1	0.4
Nephrectomy y lymphadenectomy	2	0.8
Right hemicolectomy	4	1.6
RTU	5	2.0
Total Surgery	79	32.2
Total Patients	245	100

The median time to PSA Nadir was 3.75 years (2.2) and the median PSA Nadir value was 0.2 ng/mL.

3.2 Biochemical Recurrence-free Survival

Biochemical Progression Free Survival is defined as the time from implantation to biochemical relapse according to the Phoenix criteria described above.

Of the total patients in the sample, 36 (14.69%) failed biochemically during follow-up and one third of the patients, 10 patients (4.08%) failed within the first two years after brachytherapy.

The biochemical progression-free survival at 5 years was found to be 88% and 78% at 10 years.

Half of the patients (46.8%) did not progress biochemically at 13.4 years of follow-up, as can be seen in Figure 1.

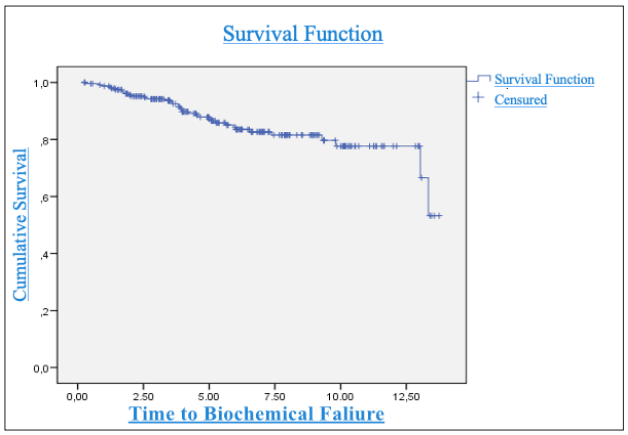

Figure 1. Graph of biochemical recurrence-free survival.

3.3 Relationship between Target Volume Dosimetry and Biochemical Recurrence

The possible relationship between D90 (dose received by 90% of the prostate) and D100 (dose received by 100% of the prostate) with biochemical recurrence has also been studied.

3.3.1 For D90

The mean dose at D90 of patients with biochemical recurrence was 149.5 (21.9).

The mean dose on D90 for patients who did NOT experience biochemical recurrence was 159.4 (12.5).

Thus, patients who did NOT have biochemical recurrence received 9.8 Gy more (95% CI 4.7 - 15) with a $p<0.001$.

The precision of the 95% confidence interval for the extra Gy for those with biochemical recurrence is quite wide, possibly more precise if the number of patients with biochemical recurrence were increased in a subsequent study.

We can therefore conclude that there is a statistically significant relationship between D90 and biochemical recurrence, in the sense that patients with a D90 of 149.52 Gy on average (21.91) relapsed more, $p<0.001$, as seen in Table 3:

3.3.2 As for D100

The mean dose on D100 for patients with biochemical recurrence was 94.8 (19.6).

The mean dose on D100 of patients who did NOT have biochemical recurrence was 106.2 (13).

Thus, patients who did NOT have biochemical recurrence received 11.4 Gy more (95% CI 6.2 - 16.6) with a $p<0.001$, as seen in Table 4.

The precision of the 95% confidence interval for the extra Gy for those with biochemical recurrence is quite wide, possibly made more precise by increasing the number of patients with biochemical recurrence in a subsequent study.

3.4 Local Recurrence-free Survival

The number of local recurrences observed during the study period was 18 cases (7.4%). All these patients had previous biochemical recurrence.

Table 3. Relationship between D90 and biochemical relapse

	Biochemical recurrence	N	Mean	Standard Deviation	Deviation Mean Error
Dose in 90% of the prostate	yes	36	149.5290	21.90853	1.56092
	no	197	159.3511	12.47962	2.07994

Table 4. Relationship between D100 and biochemical recurrence

	Biochemical recurrence	N	Mean	Standard Deviation	Deviation Mean Error
Dose in 100% of the prostate	yes	191	94.7461	19.63371	1.42065
	no	36	106.1517	13.01777	2.16963

The first one appeared at 1.5 years and the last one at 13.7 years.

At 5 years 95.3% were free of local recurrence and at 10 years 89.2% were free of local recurrence.

Slightly more than half of the patients (51.8%) had local recurrence at 12.1 years with a 95% CI (11.4 years and 12.6 years) as can be seen in Figure 2.

3.5 Relationship between Target Volume Dosimetry and Local Recurrence

We have also studied the possible relationship between D90 (Dose receiving 90% of the prostate) and D100 (Dose receiving 100% of the prostate) with local recurrence.

3.5.1 As for D90

The mean dose at D90 of patients with local recurrence was 150.47 (21.24).

The mean dose at D90 for patients who did NOT experience local recurrence was 157.9 (17.11).

Thus, patients who did NOT have local recurrence received 7.43 Gy more (95% CI 1.47 -16.32) with a p: 0.097, as seen in Table 5.

The precision of the 95% confidence interval for the extra Gy for those with local recurrence is quite wide (1.47 - 16.32), possibly more precise if the number of patients with local recurrence was increased in a subsequent study.

We can therefore conclude that there is NO statistically significant relationship between D90 and local recurrence, although there is a clear tendency for patients with higher D90 doses to have less local recurrence.

3.5.2 As for D100

The mean dose on D100 for patients with local recurrence was 95.72 (19.29).

The mean dose on D100 of patients who did NOT have local biochemical recurrence was 106.16 (15.03).

Thus, patients who did NOT have local recurrence received 10.44 Gy more (95% CI 1.23 -19.63) with a p: 0.026, as seen in Table 6.

The precision of the 95% confidence interval for the extra Gy for those with local biochemical recurrence is, as in the previous results, quite wide and would possibly be more precise if the number of patients with local recurrence were increased in a subsequent study.

Therefore, we can conclude that there is a statistically significant relationship between D100 and local recurrence, in the sense that patients with a higher mean dose of 106.16 Gy (15.03) relapsed less. 95% CI (95% CI 1.23 - 19.63) with a p: 0.026.

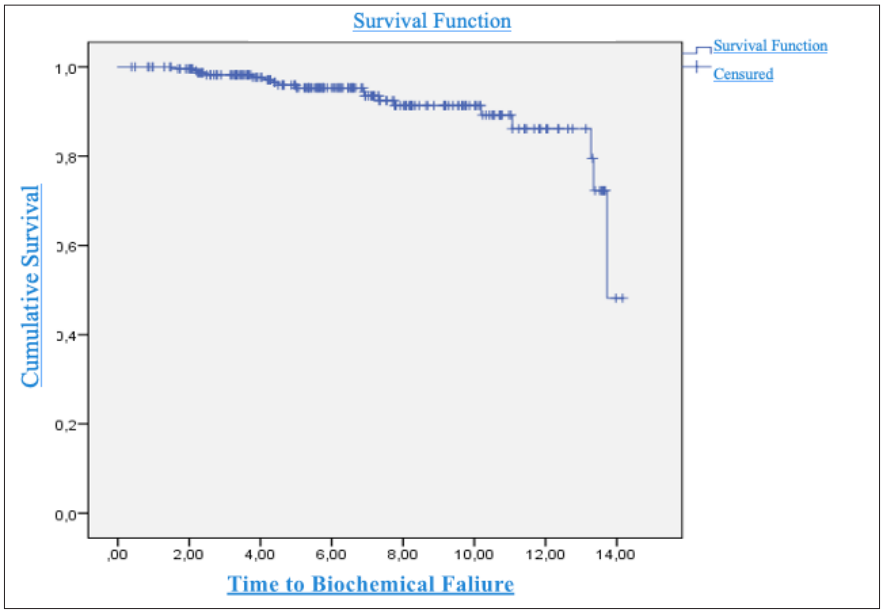

Figure 2. Time to local recurrence

Table 5. Relationship between D90 and local recurrence

	Local Recurrence	N	Mean	Standard Deviation	Deviation Mean Error
Dose in 90% of the prostate	yes	215	150.4727	21.24236	1.44872
	no	18	157.9017	17.11992	4.03520

Table 6. Relationship between D100 and Local Recurrence

	Local Recurrence	N	Mean	Standard Deviation	Deviation Mean Error
Dose in 100% of the prostate	yes	209	95.7276	19.29846	1.33490
	no	18	106.1611	15.03660	3.54416

4. Discussion

Prostate cancer is the second most diagnosed cancer in men with an estimated 34,394 cases in 2019, it has a high prevalence and although in terms of mortality it is not at the forefront, it is essential for a cure to choose the best therapeutic strategy, individualising each case according to risk groups and patient characteristics.

Despite the advances made in recent years in the treatment of localised prostate cancer with robotic surgery and new external radiotherapy techniques, this work focuses on demonstrating that low-dose rate (LDR) prostate brachytherapy is an excellent technique for the treatment of low-risk prostate cancer, with excellent results in terms of disease control and survival, while offering a good quality of life for the patient with acceptable genitourinary and gastrointestinal toxicity results.

Brachytherapy has rapidly gained popularity as an accepted, effective, and safe therapy for localised prostate cancer. There is strong follow-up data beyond 10 years showing similar biochemical control rates to radical prostatectomy and external beam radiotherapy [4,5] with lower risk of incontinence and impotence compared to surgery and better preservation of healthy tissues compared to EBRT [6,7].

The aim of this work is to analyse the 245 patients diagnosed both in our hospital centre and in others, in the community of Madrid or outside the EU, who were treated with low dose rate brachytherapy in monotherapy in our service from 2004 to 2016.

The data obtained in the analysis of results have been compared with data obtained from publications from specialised centres worldwide and it has been found that both the primary and secondary objectives are consistent with what has been published in the last ten years.

However, we have focused on analysing in more depth the most recent publications, specifically since 2014.

In recent years numerous groups have reported medium- and long-term results, however, many of these studies were multicentre and had variable patient selection criteria (such as including not only low-risk patients, but also unfavourable intermediate-risk patients in combination with ETN).

Furthermore, few of these studies were European, the first results published by Prada et al. in 2010 [8] were very encouraging, although the patient sample was very heterogeneous.

Given this context, we present in this paper our experience over 14 years in the treatment with low-rate brachytherapy for patients with low-risk prostate cancer in monotherapy with a homogeneous sample of patients treated in a single institution, the Defense Central Hospital.

The characteristics of our series are very similar in terms of median age (67 to 69 years) to most publications [9,10], as well as the maximum prostate volume which in all cases has been less than 50cc or the number of seeds and needles used with a median very similar to that of our series [11,12].

However, there is a very important aspect that differentiates us from other publications and that is that in our study we only included patients with low-risk prostate cancer and did not use other treatments such as androgen derivation therapy (ADT), which is a factor that in some studies may be related to the results of local control; nor was combined treatment with external radiotherapy carried out in any of the cases. All the published studies include a lower percentage of patients with intermediate risk prostate cancer with a good prognosis to whom ADT treatment [13] was added and some studies even publish results for high-risk prostate cancer [14], which is why the results must be evaluated taking these aspects into account.

4.1 Survival Free of Biochemical Recurrence.

To calculate this, we have considered the date of implantation and the date of biochemical recurrence, defined by the PHOENIX criteria [15] (3 consecutive elevations that are two points above the PSA Nadir figure).

Of the 245 patients in our study, 38 patients relapsed biochemically, giving a 5-year biochemical recurrence-free survival rate of 88% and a 10-year survival rate of 78%.

We have seen that these data are slightly below the survival rates of other studies (we will look at the most relevant ones, because of their similarity to our study, because they have a large sample size, because they are published in high impact journals and finally because they are very recent publications).

The study by Chao et al. [16] (Australian Study) published in 2018, analyses overall survival and biochemical recurrence-free survival in 371 patients all treated with LDR brachytherapy in monotherapy, reports 5-year data of 95%. This study included 33% of patients with intermediate-risk prostate cancer; subgroup analysis found a higher rate of biochemical recurrence in the intermediate-risk group. The dose administered was the same as ours, 145 Gy, and the median D90 was 144 Gy with an SD (64-215).

Another very interesting study looking at possible factors associated with biochemical recurrence and survival in 974 patients treated with LDR brachytherapy is Routman et al. [9] (Mayo Clinic) published in 2018.

In this study the baseline characteristics of the patients are very similar to ours but as in the previous study, 20% of the patients were intermediate risk of which 30% received ADT.

The 5-year biochemical recurrence-free survival results were 96% at 5 years and 88% at 10 years; however, analysing only those in the intermediate-risk group, the 10-year survival rate dropped to 74%.

The most significant conclusions of this study were the following:

- The use of ADT reduced the risk of biochemical recurrence with statistical significance. In our study, no patients were treated with ADT, so our poorer results may be partly related to this fact.

- Gleason (4 +3) was the variable most frequently associated with biochemical recurrence and reached statistical significance.

The third most relevant study is that of Rasmusson et al. [10] (Swedish study) published in 2016, whose primary objective is to study the relationship between D90 and biochemical recurrence.

In this study only 10% of the 195 patients were intermediate risk and a percentage of the low-risk patients received ADT to reduce prostate volume. The 5-year biochemical recurrence-free survival was 95.7%.

Older series with similar patient characteristics also show biochemical recurrence-free survival rates of around 90% at 5 years.

The fact that we were below these values led us to wonder about the possible causes. Upon close observation of the sample, we saw an abnormal PSA evolution in some patients who relapsed biochemically in the first months after treatment, even presenting extreme PSA values at the third- and sixth-month post-implantation, in all cases it was ruled out that it was a PSA rebound and biochemical recurrence was confirmed according to the Phoenix criteria. This can be seen in Figure 1. PSA evolution over time up to 40 ng/mL.

Therefore, we wondered whether there might have been a diagnostic failure, among other causes, and these patients really had a more aggressive cancer and hence the poor outcome.

Of the 36 patients who relapsed biochemically during the entire follow-up period, 18 patients were diagnosed in our centre and the other 18 outside, both in the community of Madrid and in other autonomous communities, making it impossible for us to access samples from other centres for reanalysis.

Given the accessibility we had with the Anatomical Pathology Service, we asked them to review the samples from our hospital. Thus, all the crystals were removed again to re-evaluate the cases with an observer who would either ratify the diagnosis or perform new sections stained with haematoxylin-eosin or with immunohistochemistry techniques as required.

The results of this reassessment showed that of the 18 patients referred, 15 were understaged and corresponded to a Gleason 7 (4+3).

There were several explanations for the variation in the results. Firstly, the lack of homogeneity in the samples received by the Urology Department. Some containers contained only fragments of cylinders separated into left and right, with minimal thickness which, when processed, was reduced to a quantity of tissue that might not be representative of the entire lesion. At the time when these diagnoses were made, there was a shortage of technicians and pathologists in the Anatomical Pathology Department. The technicians cut the cylinders, stained them with haematoxylin-eosin, and the pathologists, lacking sub-specialisation in uropathology, reported the case.

In the cases in which cylinders with little tissue were observed, they were deepened to obtain a larger study surface. In the new observation, tumour areas of the same diagnosed grade appeared but the percentage changed in some of the patients. In others, a higher grade that had not initially been diagnosed appeared. In doubtful cases, immunohistochemical techniques (Racemase, p. 63) were used to establish the diagnosis.

Therefore, the fundamental cause of the variation in grading was insufficient devascularisation of the cylinders.

Given these findings, we wondered whether the rest of the patients diagnosed in our centre, even if they had not had a poor clinical course, were correctly staged, so we re-evaluated the biopsies of 110 patients (the rest had been diagnosed in other centres); all of them were correctly staged (Gleason 6 or less).

Therefore, the statistical analysis was redone excluding those 15 patients who, because they were Gleason 7

(4+3) and this factor was considered intermediate risk, brachytherapy alone would not have been the treatment of choice.

As for the 18 patients who relapsed biochemically and were diagnosed outside the centre, we left them in the initial sample as we were unable to access the biopsies and re-evaluate them.

Thus, 5-year survival free of biochemical recurrence, excluding the 15 intermediate-risk patients, would be 91.8% at 5 years and 87.2% at 10 years. This represents an improvement of 4% and 9% respectively with respect to the initial sample. These results are more in line with those reported in the literature.

We can conclude that in our procedure, several factors may have contributed to biochemical recurrence-free survival rates slightly below the mean of other studies.

Perhaps the most significant, as it is the one, we have been able to verify, was the Gleason understaging of the 15 patients at our centre and perhaps of a high percentage of patients diagnosed at other centres.

It is also a factor to consider that our patients did not receive ADT and as concluded in the study by Routman et al., the use of hormonal treatment reduced the risk of biochemical failure reaching statistical significance.

From the study by Prada et al. [17] published in 2016, we can also draw results that are like those of our series, even though it is a smaller sample of patients, 57 patients were studied, all with previous TUR, from which results were obtained for Survival free of biochemical recurrence, Overall Survival and Survival free of local recurrence. The sample included patients with low and intermediate risk and 40% received hormone therapy for 3 months.

Biochemical recurrence-free survival was 94% at 5 years and 91% at 10 years.

The most important finding of this study that differentiates it from others previously described is that Cox proportional hazards regression revealed NO statistically significant association for clinical T stage, Gleason value, pre-treatment PSA, age, brachytherapy dose (D90) and ablative hormonal treatment with biochemical recurrence. Although this is a very comprehensive study, the sample size is small.

In 2016 the results of a multicentre study in Italy were also published by Fellin et al. [13]. This is a very relevant study as it includes 2,237 patients from 11 hospitals in Italy in whom low dose rate brachytherapy was performed with a median D90 of 149 Gy, very similar to that obtained in our study.

The largest percentage of patients was low risk (66.4%) but patients with intermediate risk prostate cancer (26%) and even 1.8% of high-risk patients were also included. Hormone therapy was given to 39.4%.

In this study the 5-year and 7-year biochemical recurrence-free survival results were 91.8% and 88.7% for the total sample, and the results improved in the subgroup analysis, being worse as expected in the intermediate risk group.

The results of this study are very similar to ours, perhaps because we also included a percentage of patients with intermediate risk of worse prognosis (Gleason 4+3) which, although not considered at the time of implantation, has been confirmed a posteriori.

A very complete and relevant study in our setting was published in 2015 by Martínez et al. [14] from the Catalan Institute of Oncology (ICO) in which the results of brachytherapy in monotherapy were presented for 700 patients, 91% of whom were low risk, which represents a very high percentage of the total; the characteristics of the patients in terms of median age, prostate volume, recurrence criteria, follow-up, implant dosimetry and evaluation of toxicity is practically the same as that carried out in our centre.

The results obtained for biochemical progression-free survival at 5 years and 10 years were 95% and 85%, respectively.

In 2014, the Department of Radiation Oncology at Cleveland University, Ohio, published a very interesting study led by Kittel et al. [18], with a large sample size (1,989 patients from a single institution) that mainly evaluated the efficacy and toxicity of low-dose rate brachytherapy in all prostate cancer risk groups.

Importantly, in multivariate analysis, biochemical progression-free survival decreases significantly as we increase in risk groups, as seen on Figure 3.

Thus:

- For Low risk at 5 and 10 years the bRFS is 95.3% and 86.7%.

- For Intermediate Risk of good prognosis at 5 years and 10 years the bRFS is 90% and 79.3%.

- For Intermediate Poor Prognostic Risk at 5 years the bRFS is 80.9%.

- For High 5-year risk the bRFS is 67.5%.

Intermediate-risk prostate cancer with a good prognosis is defined as having only one intermediate risk factor excluding Gleason 7 (4 +3) and a PSA greater than 15 ng/mL.

Although in our work we did not perform a multivariate study as such since it was only a posteriori that we were able to verify that 15 of our patients were understaged and would currently be classified as intermediate risk prostate cancer with worse prognosis, Gleason 7 (4 +3), we can conclude that in the second outcome analysis

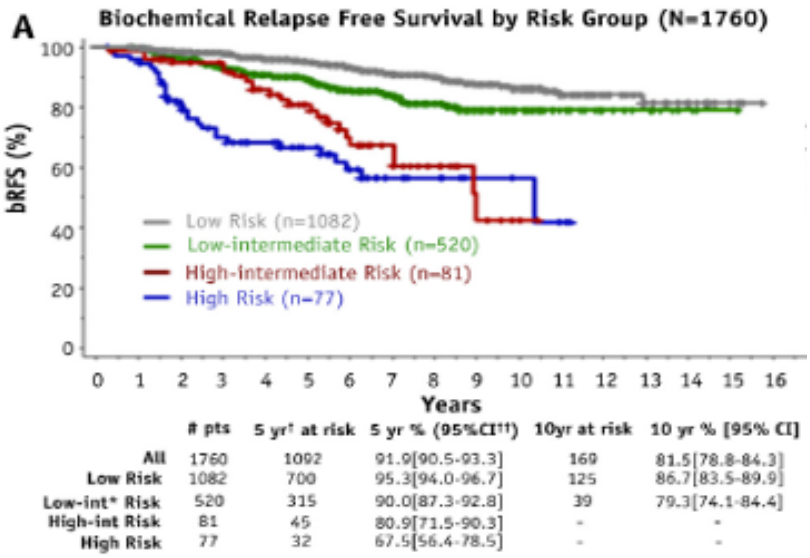

Figure 3. Biochemical recurrence-free survival by risk groups

we performed, our 5-year bRFS rate was similar to the one presented in this study, 91.8% vs 95.3% for low risk.

However, at 10 years we were slightly above 87.2% vs. 86.7%.

In our study we would most probably have obtained higher rates if we had been able to analyse the biopsies of patients with a poor outcome diagnosed outside our centre.

Finally, other renowned authors in the treatment of prostate cancer, such as Zelefsky et al. [19], who published in previous years (2007) very satisfactory results in terms of biochemical recurrence in the treatment of low-risk prostate cancer as monotherapy.

The most relevant data in this aspect can be seen summarised in Table 7, which shows that the 5-year biochemical progression-free survival percentages vary from 86.9% to 98% depending on the study.

Table 7. List of studies with prostate cancer treated with brachytherapy as monotherapy

Author (yr)	Low-risk patiens/total no.	PSA relapse definition	Median folloup month	% BRFS (yr)
Ellis et al. (2007)	110 (239)	Phoenix	47.2	86.5 (yr)
Zelefsky et al. (2012)	840 (1466)	ASTRO	49	98 (5 yr)
Zelefsky et al. (2007)	319 (367)	ASTRO	63	96 (5 yr)
Henry (2010)	575 (1298)	ASTRO, Phoenix	4.9 yr	86.4, 72.3 (10 yr)
Zeleksy et al. (2007)	1444 (2693)	ASTRO, Phoenix	63	82 (8 yr), 74
Prada et al. (2010)	487 (734)	Phoenix	55	92 (10 yr)
Potters et al. (2005)	481 (1449)	ASTRO	82	89 (12 yr)
Sharkey et al. (2005)	723 (1177)	ASTRO	36	89 (3 yr)
Sylvester et al. (2011)	128 (215)	Phoenix	11.7 yr	89.5 (15 yr)
D'Amico et al. (2003)	196 (322)	ASTRO	3.95 yr	95 (5 yr)
Dickinson et al. (2013)	1038 (1038)	ASTRO, Phoenix	60	94.1 (ASTRO) (5 yr), 94.2 (Phoenix) (5 yr)
Martin et al. (2007)	273 (396)	ASTRO, Phoenix	60	91.5 (5 yr), 94.6
Merrick et al. (2005)	Not available (202)	ASTRO	5.2 yr	93.2 iodine-125 (8 yr)
Lubbe et al. (2012)	341 (341)	Phoenix	41.6	91.1 (6 yr)
Hinnen et al. (2012)	262 (975)	Phoenix	69	90 or 70 (bounce vs. no bounce) (6 yr)
Martinez et al. (2015)	664 (700)	Phoenix	63	94 (5 yr), 84 (10 yr)

4.2 Relationship between D90 - D100 and Biochemical Recurrence

As already mentioned, there are several studies whose primary objective is the logical study of the possible relationship between the dose received by 90% or 100% of the prostate and possible biochemical recurrence or, in other words, whether increasing the dose to D90 can have a benefit in terms of biochemical control of the disease.

In our work this objective has also been studied both in the whole cohort of initial patients (245 patients) and in the second analysis carried out excluding anatomopathological understaged patients, and we have found that for the total (245 patients), there was a statistically significant relationship between D90 and biochemical recurrence in the sense that patients with D90 of 149.52 Gy (21.91) relapsed more than those who received an average of 159.35 Gy (12.48).

The same is true when comparing the mean D100 of the entire cohort. Patients without biochemical recurrence received 11.4 Gy more on average (95% CI: 6.2 - 16.6) with a $p < 0.001$.

In the second analysis with the 230 patients:

- The mean for D90 was 149.43 Gy with a SD (21.92) in those who DID have biochemical recurrence.
- The mean for D90 was 160.4 Gy with a SD (12.39) in those who did NOT have biochemical recurrence.
- The mean for D100 was 94.61 Gy with a SD (19.54) in those who DID have biochemical recurrence.
- The mean for D100 was 106.24 Gy with a SD (11.10) in those who did NOT have biochemical recurrence.

We can conclude that a higher mean dose for D90 or D100 in either group is related to better biochemical control.

Regarding the results of other studies:

- Routman et al.:

A 10 Gy increase in D90 (Dose receiving 90% of the prostate) correlated with a decrease in local recurrence due to increased target volume coverage but did not reach statistical significance in this respect.

- Rasmusson et al.:

This study begins by introducing the existence of many studies relating biochemical control to the dose received by 90% of the prostate. The first was a study from Mount Sinai in 1998 [11] that suggested a D90 in the range of 140 Gy-160 Gy using the AAPMTG guidelines 43 [3].

In a large study conducted by Morris et al. (Canadian group) in 2014; D90 was not a predictor of disease-free survival in the entire cohort; however, for the subgroup of low-risk patients without ADT, increased dose was associated with improved disease-free survival.

They conclude by stating that although there should logically be a dose threshold for which response is optimal, these remain unknown and, in their study, they could not confirm a correlation between prostate D90 and biochemical failure.

Returning to the study by Rasmusson et al., in their analysis of study results they conclude that: Median D90: 174 Gy with a SD (155 Gy-190 Gy).

The study concludes that D90 was an important predictor for biochemical recurrence reaching statistical significance (HR 0.90 95% CI 0.83 to 0.96 p less than 0.002) suggesting an optimal cut-off level of 167 Gy.

These results agree with those obtained in our study, where we obtained a mean D90 of 159.35 Gy (12.45) in the first analysis and 160.46 Gy (12.4) for the second analysis, reaching statistical significance.

The Kaplan-Meier survival table for D90 = 167 Gy is shown in the figure below in Figure 4.

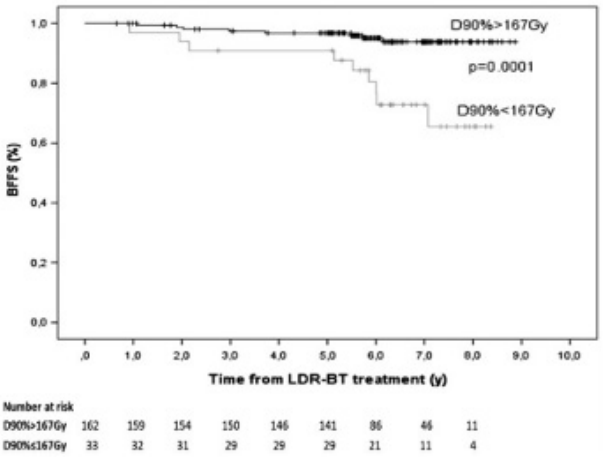

Figure 4. Kaplan-Meier survival for D90 = 167 Gy

- Prada et al.:

Increasing the dose received by 90% of the prostate volume (D90) of > 160 Gy was not associated with better biochemical control (P = 0.37).

- Kittel et al.:

Although it was not their aim to study the relationship between D90 and possible biochemical or local recurrence. The median was like that of our study, 146 Gy with an SD (24.48 Gy).

- Martinez et al.:

No statistically significant relationship was found between dose at D90 and a decrease in biochemical recurrence-free time.

4.3 Local Recurrence-free Survival

Local recurrence-free survival is not an objective that has been analysed in most of the studies reviewed. In our

work we have obtained the following results for the whole sample (245 patients):

- 5-year local recurrence-free survival rate: 95.3%.
- 10-year local recurrence-free survival rate: 91.3%.

For the sample excluding intermediate risk patients (230 patients), the same results were obtained as for the entire initial cohort. Surprisingly, local recurrence-free survival is an objective that has not been studied in most of the studies reviewed, but not in the Spanish studies.

- Prada et al.:

Local recurrence-free survival at 5 and 10 years was 96% and 96(+/-2) respectively.

- Martinez et al.:

5- and 10-year local recurrence-free survival was 95% and 85%, respectively.

We can conclude that our results are practically the same at 5 years and even better at 10 years than in the most relevant Spanish studies in recent years.

4.4 Relationship between D90 -D100 and Local Recurrence

As is logical, the probable relationship between the dose received by 90% and 100% of the prostate and local recurrence has been studied both for the initial sample of 245 patients and for the second sample in which we excluded the 15 patients who were found to be under-staged.

In all cases except for the relationship of prostate D90 and local recurrence for the first sample, we obtained statistical significance.

Thus, for the sample of 245 patients:

- Patients with NO local recurrence received 7.43 Gy more (95% CI 1.47 -16.32) with a p: 0.097 at D90.
- Patients with NO local recurrence received 10.44 Gy more (95% CI 1.23 -19.63) with a p: 0.026 at D100.

For the sample of 230 patients:

- Those with NO local recurrence received 10.35 Gy more (95% CI 1.9 - 18.79) with a p: 0.019 at D90.
- Those who did NOT have local recurrence received 13.8 Gy more (95% CI 6.7-20.8) with a p: 0.001 at D100.

It is important to note that if we were to balance the sample, we could possibly verify that the patients who received higher mean doses at D90 in the sample of 245 patients relapsed less locally.

Also striking is the width of the Confidence Interval, which could possibly be reduced by increasing the sample size of the patients who did not relapse locally.

We have not found any publication in which the relationship between local recurrence and dosimetry to target volume has been studied, so we can conclude that the data obtained are encouraging and are related to those described above.

When we administer higher dose averages to the D90 and D100 of the prostate we obtain a significant reduction in biochemical recurrence and consequently also in local recurrence.

5. Conclusions

The results obtained in our series in terms of local and biochemical failure-free survival are comparable to those published in the literature with patients with similar characteristics. We found better results when intermediate-risk patients were excluded from the sample. In subsequent studies, it would be interesting to see if with average doses at D90 of 160cGy (12.4) we improve the results of biochemical and local control.

Authors Contribution

All participants have contributed by updating and including data for the study in our database. María Concepción López Carrizosa (editor of the journal) has directed this work.

Conflict of Interest

There is no conflict of interest.

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