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Long Term Results of High Dose Rate Brachytherapy and External Beam Radiotherapy for Local and Locally Advanced Prostate Cancer

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Abstract

Purpose: Several studies provided evidence for the efficacy of dose-escalation on biochemical control (BC) of prostate cancer and High-dose-rate brachytherapy (HDR) is one method for it.

Materials and Methods: Patients with histological diagnosis Gleason scored (GS), clinical stage T1 to T3a, no evidence of metastatic disease, prostate volume <60cc and initial PSA (PSAi) <60mg/ml were eligible.

Results: From 1997 to 2005 there were 273 patients treated with this treatment combination at AC Camargo Cancer Center, Sao Paulo, Brazil. The median age and FU time were 64.7 and 10.3 years, respectively. Two hundred thirteen (78.0%) patients had FU longer than 5 years. Actuarial 10-year overall survival (OS), Clinical Specific Survival (CSS) and BC were 89.8%, 63.6% and 71.8%, respectively. On univariate analysis GS<7, clinical stage<T2b, low risk group (LR), absence adjuvant androgen deprivation (ADT), age>65, PSAi<10, localized EBRT and 3D-HDR plan were associated with improved CSS and BC, excluding PSAi, age for the last one. Multivariate Cox regression analysis confirmed LR, GS<7, PSAi<10, absence of ADT, age<65 years as predictors of improved CSS and BC. For OS only LR was confirmed as predictive factor.

Conclusion: The present data represents a unique uni-institutional study at long FU for the given technique. A comparison with the current literature confirms the excellent results achieved with this treatment modality. HDR has also the advantage of treatment time reduction and increasing in the capability of work load of the linear accelerators, especially in developing countries, where waiting lists and lack of radiation oncology facilities are a reality.

Key words: *prostate cancer, radiotherapy, high-dose rate brachythrerapy, biochemical control, PSA*

Introduction

More than 62% of Prostate Cancers (PCa) are diagnosed in men over 65 years. It has become a public health and socioeconomic problem with increasing incidence, in special due to a rapidly aging population worldwide [1]. In Brazil it was expected the diagnosis of 61,200 new cases of PCa in 2016, and the crude mortality for 2013 was around 14,000 deaths [2].

Management options for localized and locally advanced PCa are controversial and include active surveillance, radical prostatectomy, external beam radiotherapy (EBRT) and brachytherapy with low or high dose rate sources. [3]

Several studies provided evidence for the efficacy of dose-escalation on biochemical control (BC) of PCa. Mature results from randomized trials show a direct relation between increasing the radiation dose given to the prostate and/or seminal vesicles and BC [4-7].

High-dose-rate after loading brachytherapy (HDR) is one method that can deliver a high localized radiation dose to the tumor with excellent BC when combined to EBRT [8]. One prospective randomized trial with up to 10 years follow up has proved that HDR plus EBRT is more efficient than EBRT alone in terms of BC with less acute rectal toxicity and improved quality of life [9].

The aim of this retrospective study is to evaluate the mature results of patients with local and locally advanced PCa treated with combination of HDR and EBRT.

Materials and Methods

Patients with confirmed histological diagnosis Gleason scored (GS) of PCa, AJCC clinical stage T1 to T3a, with no evidence of metastatic disease and initial PSA <60mg/ml, prostate volume <60 cc measured by transrectal ultrasound (TRUS) suitable for EBRT and HDR under spinal anesthesia were eligible. Prior to treatment, patients

had baseline investigations including pelvic computed tomography (CT) and/or magnetic resonance imaging, isotope bone scan, chest X-ray and serum PSA. Exclusion criteria were evidence of metastases, co-existing malignancy or medical condition that precluded spinal anesthesia.

This single-centre institutional protocol of treatment was performed in compliance with the Declaration of Helsinki and approved by the local research Ethics Committee. Written informed consent was mandatory.

External Beam Radiotherapy

The EBRT target volume was defined using diagnostics CT images on conventional two dimensional or 3D planning. The targets were the prostate gland and the proximal seminal vesicles with a 1 to 1.5 cm margin except to the posterior region, which margins were reduced to 0.5 to 1.0cm. The EBRT dose ranged from 45 to 54 Gy prescribed to the intersection point. Further details of the radiotherapy schedules have been published previously [10].

High Dose Rate Brachytherapy

HDR was done under spinal anesthesia. Using TRUS with a perineal template affixed to perineum the exact needles positions were determined intraoperatively. In a first moment treatments were planned based on semi-orthogonal X-rays - two dimensional planning (2D) - and after that we moved to three dimensional (3D) planning, based on CT images. The prostate gland, the rectum, and the urethral trajectory and length were countered and identified in both situations. Implant dosimetry geometric optimization was initially utilized, followed later by use of inverse planning. Treatment parameters and dose constraints changed minimally throughout the years. The patients considered low risk had 16 Gy given in 4 fractions BID, one single implant. Intermediate and high risk patients had 20 Gy given in the same treatment schedule. The dose-volume histogram constraints were as follows: the TRUS or CT-based prostate´s volume receiving 100% of the dose (V100) should be >95%, the uniformity index should be more than 50%, and the V150 less than 30%. The urethra maximum punctual and the maximal dose to 1cc of anterior rectal wall should not exceed 135% and 75% of prescribed doses, respectively.

Definition of end points and statistical analysis

BC was measured using PSA tests and assessed according to the Phoenix definitions [11]. Clinical Specific Survival (CSS) was calculated from the start of treatment to the lost of BC, diagnose of metastatic disease or death from PCa. The BC was evaluated from the date of start the treatment until date of first biochemical failure. The follow up (FU) program also included clinical investigation, digital rectal examination and image studies.

The statistical program SPSS (statistical package for the social sciences) Inc., released 2008, Statistics for Windows, version 20.0 (SPSS Inc., Chicago, IL) was used for all statistical analysis. The analysis of OS, CSS and BC was made using the Kaplan–Meier method. The log-rank test was used to test the significance when comparing different subgroups. Univariate and multivariate Cox regression analysis were also performed. The alpha level considered for statistically significant differences was 0.05.

Results

Between March, 1997 and March, 2005 there were 305 patients treated with combination of HDR and EBRT at the Department of Radiation Oncology, AC Camargo Cancer Center, Sao Paulo, Brazil. Thirty two patients were lost of FU and the data of 273 patients was available for analysis. Sixty four (27.1%) patients had pelvic EBRT and the remaining 209 (76.5%) localized EBRT. Clinical and treatments characteristics are depicted in **Tables 1 and 2.**

Table 1: Patients Characteristics

		Median	Range	Variable	n	%
	Age (years)	64.7	42-82			
	Prostate Vol (cc)	36.3	19-72	<35	121	44.3
				>35	152	55.7
	PSAi (ng/ml)	10.3	1-52	<10	173	16.8
				10-20	54	19.8
				>20	46	63.4
	Gleason Score			<7	190	69.6
				=7	58	21.2
				>7	25	21.2
				Yes	47	17.2
				No	226	82.8
	Clinical Stage			<T2b	192	70.3
				T2b-c	47	17.2
				>T2c	34	12.5
	Risk Group			Low	133	48.7
				Interm	76	27.8
				High	64	23.4
ADT	NAAD			Yes	93	34.1
				No	180	65.9
	ADJ				91	33.3
	Salvage				37	13.6
	WO				145	53.2
EBRT	Pelvic				64	23.4
	Localized				209	76.6
	Comorbidities			No	146	53.5
				SAH	42	15.4
				Diabetes	19	7.0
				Other	39	14.3
TOTAL					273	100.0

Legend: ADJ: (adjuvant hormonal therapy), ADT (Androgen deprivation therapy), BF (Bichemical failure, EBRT: (External beam radiotherapy), NAAD (neoadjuvant hormonal therapy), SAH (Systemic arterial hypertension), Salvage: (Salvage hormonal therapy)

Table 2: Treatment Characteristics

		Median	Range	Variable	n	%
Dose	EBRT	50	40-54	< 50	149	54.6
				>50	124	45.4
	HDR			16	133	48.7
		18.3	16-20	20	140	51.3
	HDR plan			2D	167	61.2
				3D	106	38.8
	Interval	18.5	9-61	<18	173	63.4
				>18	100	36.6

Legend: EBRT (External beam radiotherapy), HDR (High-dose-rate brachytherapy), HDR plan 2D/3D (two or three dimensional planning)

The median age and FU time were 64.7 (range, 42-82) and 10.3 (range, 1-15) years, respectively. Two hundred thirteen (78.0%) patients had FU longer than 5 years, and of these 153 (56.1%) longer than 10 years.

Androgen deprivation therapy

Androgen deprivation therapy (ADT) in a short course neo-adjuvant ADT, was prescribed for less than 6 months. Neoadjuvant hormonal therapy (NAAD) was administered to 34.1% of the patients. Adjuvant hormonal therapy (ADJ) was observed, mostly, for intermediate and high risk patients (33.4%), generally for no more than 6 months for intermediate risk and up to 3-years in high risk patients. Salvage ADT was observed in 37 (90.2%) of 41 patients dead due PCa. The profile of hormonal therapy is shown in **Tables 3 and 4.**

Table 3: Neoadjuvant Hormonal therapy according to Risk Group - Risk NAAD Cross tabulation

	NAAD					
Risk Group	**WO %**		**YES %**		**Total %**	
Low	74	27.1	8	2.9	82	30.0
Interm	65	23.8	35	12.8	100	36.6
High	41	15.0	50	18.3	91	33.3
Total	180	65.9	93	34.1	273	100

Legend: ADJ (adjuvant hormonal therapy), Interm (intermediate), NAAD (neoadjuvant hormonal therapy), WO (without hormonal therapy).

Table 4: Adjuvant and Salvage Hormonal therapy according to Risk Group

	WO %		ADJ %		Salv %		Total %	
Low	72	26.4	7	2.6	3	1.1	82	30.0
Interm	57	20.9	34	12.5	9	3.3	100	36.6
High	16	5.9	50	18.3	25	9.2	91	33.3
Total	145	53.2	91	33.4	37	13.6	273	100

Legend: ADJ (adjuvant hormonal therapy), Interm (intermediate), NAAD (neoadjuvant hormonal therapy), Salv (Salvage hormonal therapy), WO (without hormonal therapy).

The crude 10-year overall survival (OS) rate at was 52.7%. Actuarial 5- and 10-year OS, CSS and BC were 80.1%, 89.8%, 83.7%, 63.6%, 85.5% and 71.8%, respectively. (**Figures 1-3)**

Univariate and multivariate analysis

On univariate analysis GS <7, clinical stage <T2b, low risk group, absence adjuvant ADT, older age (>65-years), PSAi <10 ng/ml, localized EBRT and 3D HDR plan were favorable predictors of CSS. For BC all above have also confirmed as favorable predictors of BC, excluding PSAi, age and localized EBRT (p=ns). **Table 5**.

Univariate analysis failed to identify neoadjuvant androgen deprivation therapy (NAAD) as a predictor for BC in all group risks (p=ns). When we pooled the intermediate and high risk group into a unique denominated unfavorable risk group, NAAD also failed to predict improved CSS and BC.

Multivariate Cox regression analysis confirmed low risk group (HR 0.03, 95% CI 0.006-0.116, p<0.001) and intermediate risk (HR 0.09, 95% CI 0.042-0.216, p<0.001) compared to high risk, presence of ADT (HR 0.39, 95% CI 0.179-0.868, p=0.021) as favorable predictors for CSS. GS >7 (HR 3.24, 95% CI 1.279-8.220, p<0.001), PSA >10 (HR 6.19, 95% CI 2.015-19.041, p=0.001), age >65 years (HR 2.87, 95% CI 1.264-6.504, p=0.012) and EBRT dose >50 Gy (HR 14.50, 95% CI 1.874-112.164, p = 0.010) were confirmed as adverse predictors for CSS. **Tables 6-8, Figures 4-9.**

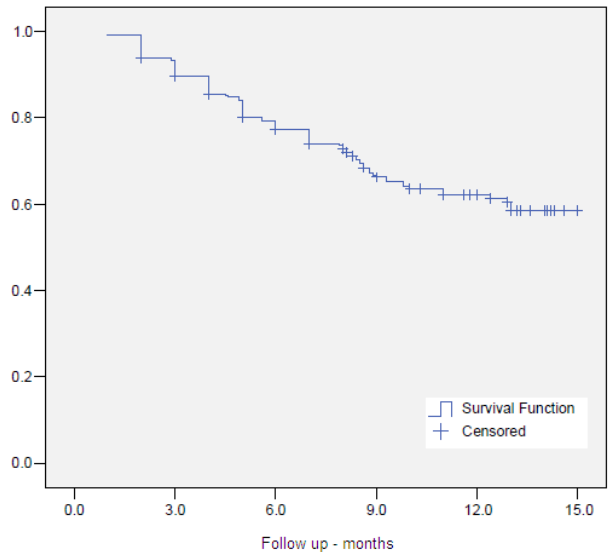

Figure 1: Overall Survival

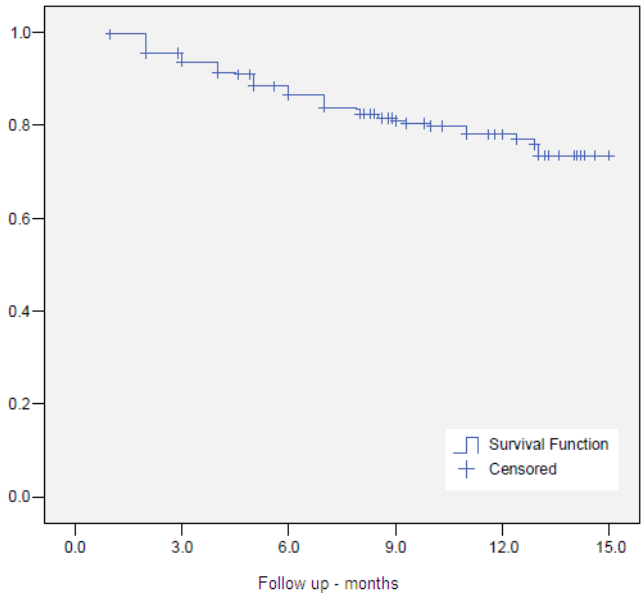

Figure 2: Clinical Specific Survival

Low risk group compared to intermediate, (HR 0.70, 95% CI 0.023-0.213, p<0.001) and high risk (HR 0.99, 95% CI 0.052-0.190, p<0.001) groups, was a favorable predictive factor for BC. GS >7 (HR 3.09, 95% CI 1.473-6.473, p=0.003) and PSAi >10 (HR 6.18, 95% CI 2.331-16.393, p<0.001) were negative predictive factor for BC.

Low risk group was confirmed as the only predictive factor for OS when compared to intermediate (HR 0.28, 95% CI 0.133-0.608, p=0.001) and high (HR 0.38, 95% CI 0.223-0.665, p=0.001) risk groups.

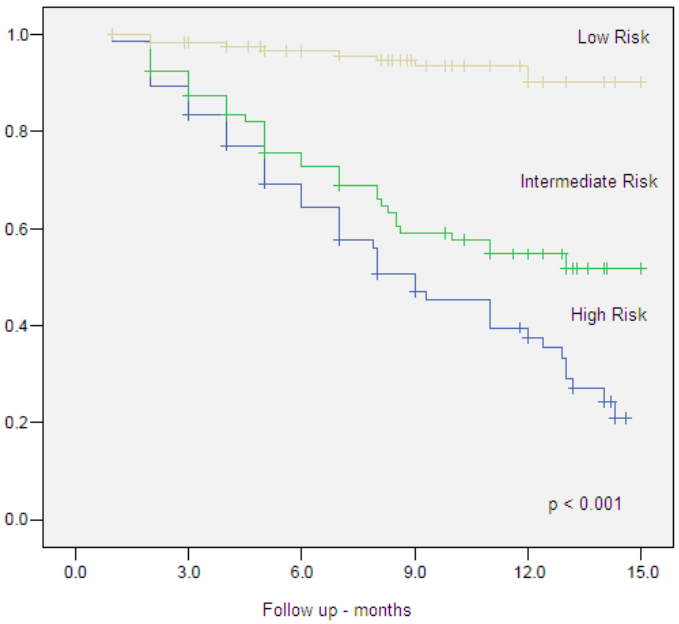

Figure 3: Clinical Specific Survival by Risk Group

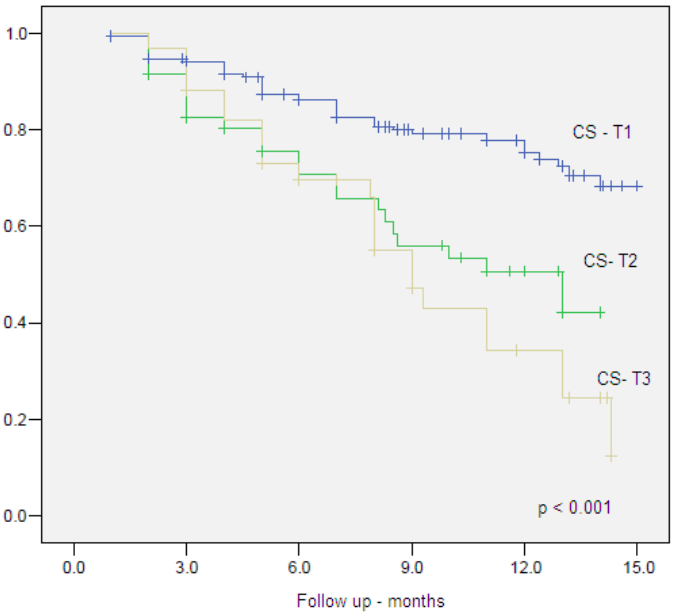

Figure 4: Clinical Specific Survival by Clinical Stage

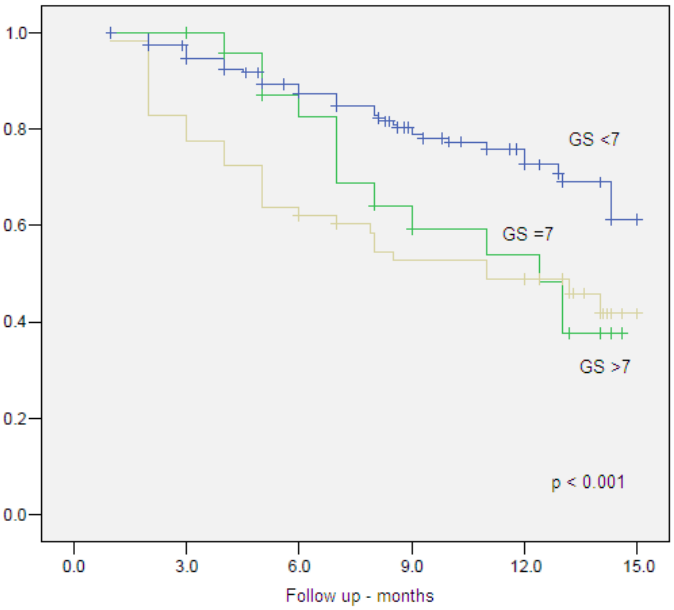

Figure 5: Clinical Specific Survival by Gleason Score

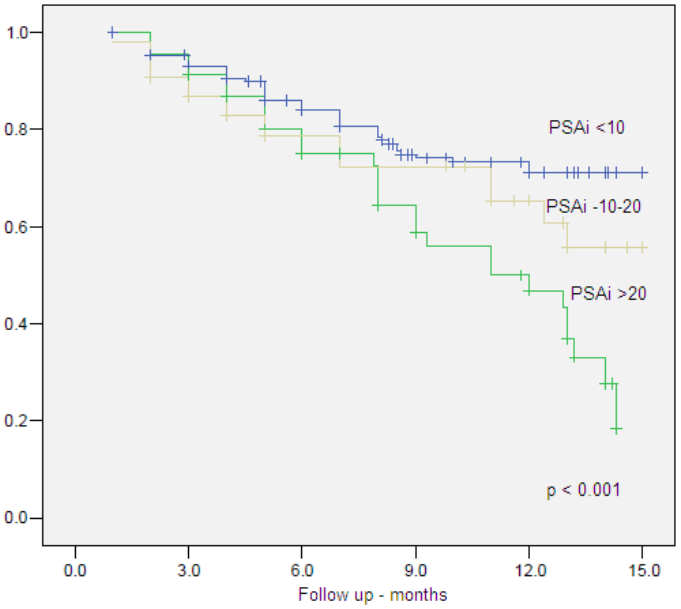

Figure 6: Clinical Specific Survival by Initial PSA

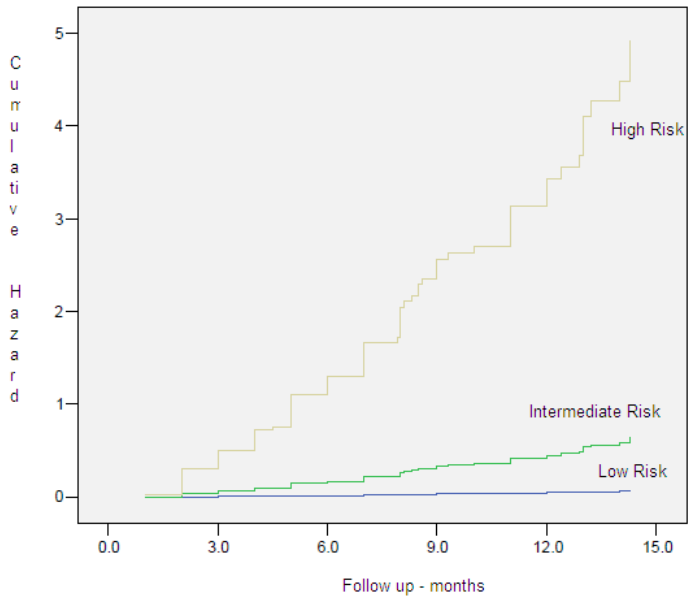

Figure 7: Hazard Plots – Clinical Specific Survival by Risk Group

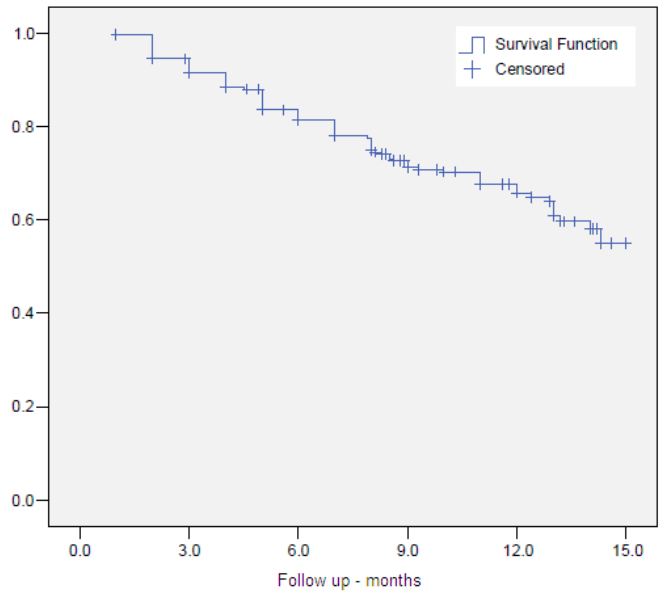

Figure 8: Biochemical Control

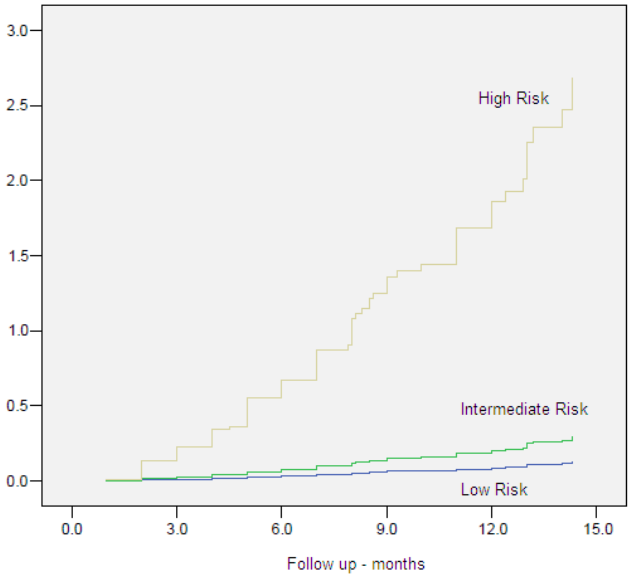

Figure 9: Hazard Plots – Biochemical Control by Risk Group

Table 5: Univariate Analysis

			CSS			BC			OS		
		N	C	%	P	C	%	P	C	%	
Risk	Low	82	9	11.0	<0.001	5	6.1	<0.001	17	6.2	<0.001
	Interm	100	19	19.0		5	5.0		33	12.1	
	High	91	61	67.0		24	26.4		49	17.9	
HDR Plan	2D	167	74	44.3	<0.001	30	18.0	<0.001	56	20.5	0.549
	3D	106	15	14.2		4	3.8		43	15.8	
ADJ	No	152	27	17.8	<0.001	13	8.6	0.017	45	16.5	0.004
	Yes	121	62	51.2		21	17.4		54	19.8	
NAAD	No	226	72	31.9	0.315	29	12.8	0.924	80	29.3	0.269
	Yes	47	17	36.2		5	10.6		19	7.0	
PSAi (ng/mL)	<10	173	43	24.9	0.001	15	8.7	<0.001	63	23.1	0.514
	10-20	54	19	35.2		3	5.6		23	8.4	
	>20	46	27	58.7		16	34.8		13	4.8	
GS	<7	190	45	23.7	<0.001	19	10.0	0.107	67	24.5	0.728
	=7	58	31	53.4		12	20.7		21	7.7	
	>7	25	13	52.0		3	12.0		11	4.0	
CS	<T2b	192	45	23.4	<0.001	13	6.8	<0.001	69	25.3	0.588
	T2b-c	47	22	46.8		9	19.1		19	7.0	
	>T2c	34	22	64.7		12	35.3		11	4.0	
Age (years)	<65y	151	62	41.1	0.001	21	13.9	0.264	61	22.3	0.062
	>65y	122	27	22.1		13	10.7		38	13.9	
P vol.	<35cc	121	40	33.1	0.775	18	14.9	0.236	44	16.1	0.910
	>35cc	152	49	32.2		16	10.5		55	20.1	
EBRT	<50Gy	149	70	47.0	<0.001	27	18.1	0.002	55	20.1	0.397
	>50Gy	124	19	15.3		7	5.6		44	16.1	
	Local	209	54	25.8	<0.001	22	10.5	0.055	66	24.2	0.004
	Pelvic	64	35	54.7		12	18.8		33	12.1	
HDR (Gy)	<16Gy	133	17	12.8	<0.001	5	3.8	<0.001	46	16.8	0.306
	>16Gy	140	72	51.4		29	20.7		53	19.4	
Interval	<18m	173	57	12.1	0.882	21	32.9	0.812	60	22.0	0.636
	>18m	100	32	13.0		13	32.0		39	14.3	
Comorb	No	146	45	30.8	0.117	18	12.3	0.467	47	17.2	0.040
	Yes	127	44	34.6		16	12.6		52	19.0	
Total		273	89	36.2		34	12.5		99	36.3	

Legend: ADJ (adjuvant hormonal therapy), BC (biochemical control), C (Censored), Comorb (Comorbidites), CSS (Clinical Specific Survival), EBRT (External beam radiotherapy), Interval m (Interval in months), NAAD (neoadjuvant hormonal therapy), OS (overall survival), P vol. (Prostate volume cc), Plan 2D/3D (two or three dimensional planning)

Table 6: Cox regression for CSS

	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
LR			44.294	2	.000			
IR	-3.641	.761	22.910	1	.000	.026	.006	.116
HR	-2.351	.418	31.579	1	.000	.095	.042	.216
EBRT Pelvic x Local	-.110	.312	.124	1	.724	.896	.486	1.651
2D x 3D	-1.861	1.134	2.693	1	.101	.156	.017	1.436
ADT	-.931	.403	5.336	1	.021	.394	.179	.868
PSAi <10			10.858	2	.004			
PSAi (>10<20)	1.925	.661	8.481	1	.004	6.856	1.877	25.048
PSAi (>20)	1.824	.573	10.133	1	.001	6.195	2.015	19.041
GS <7			7.328	2	.026			
GS = 7	.335	.709	.223	1	.636	1.398	.349	5.608
GS >7	1.176	.475	6.145	1	.013	3.243	1.279	8.220
CS <T2b			3.350	2	.187			
CS T2b/T2c	-.662	.551	1.443	1	.230	.516	.175	1.519
CS >T2c	.464	.818	.321	1	.571	1.590	.320	7.895
Age <65y	1.053	.418	6.352	1	.012	2.867	1.264	6.504
EBRT <50Gy	2.674	1.044	6.562	1	.010	14.498	1.874	112.164
HDR dose <20Gy	1.763	1.023	2.973	1	.085	5.830	.786	43.261
Interval EBRT to HDR	-.187	.303	.381	1	.537	.829	.458	1.502

Legend: 2D (two dimensional plan), 3D (tridimensional plan), ADT (Androgen deprivation therapy), BC (biochemical control), Comorb (Comorbidites), CS (Clinical stage), CSS (Clinical Specific Survival), EBRT (External beam radiotherapy), GS (Gleason score), IR (Intermediate risk group), HDR (High-dose-rate brachytherapy), HR (High risk group), LR (Low risk group), NAAD (neoadjuvant hormonal therapy), OS (overall survival), P vol. (Prostate volume cc).

Table 7: Cox regression for BC

	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
LR			62.053	2	.000			
IR	-2.660	.568	21.948	1	.000	.070	.023	.213
HR	-2.309	.330	48.920	1	.000	.099	.052	.190
2D x 3D	-.789	.656	1.448	1	.229	.454	.126	1.642
ADT	-.455	.307	2.192	1	.139	.634	.347	1.159
PSAi <10			13.634	2	.001			
PSAi (>10<20)	1.822	.498	13.403	1	.000	6.182	2.331	16.393
PSAi >20	1.346	.462	8.494	1	.004	3.843	1.554	9.502
GS <7			8.944	2	.011			
GS =7	.957	.465	4.240	1	.039	2.603	1.047	6.469
GS >7	1.127	.378	8.915	1	.003	3.088	1.473	6.473
CS <T2b			2.825	2	.244			
CS T2b/T2c	-.647	.410	2.493	1	.114	.523	.234	1.169
CS >T2c	-.306	.580	.278	1	.598	.737	.236	2.294
EBRT 50Gy	1.411	.550	6.590	1	.010	4.101	1.396	12.044
HDR dose <20Gy	-.470	.680	.477	1	.490	.625	.165	2.370
Interval EBRT to HDR	-.064	.230	.078	1	.780	.938	.597	1.473

Legend: 2D (two dimensional plan), 3D (tridimensional plan), ADT (Androgen deprivation therapy), BC (biochemical control, Comorb (Comorbidites), CS (Clinical stage), CSS (Clinical Specific Survival), EBRT (External beam radiotherapy), GS (Gleason score), IR (Intermediate risk group), HDR (High-dose-rate brachytherapy), HR (High risk group), LR (Low risk group), NAAD (neoadjuvant hormonal therapy), OS (overall survival), P vol. (Prostate volume).

Table 8: Cox regression for OS

	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
ADJ	.149	0.3	0.3	1	.580	1.161	.684	1.970
Age <65y	.223	0.2	1.0	1	.322	1.250	.804	1.942
Comorbidity	-.310	0.2	2.1	1	.149	.734	.482	1.117
EBRT Pelvic x Local	-.089	0.2	0.1	1	.722	.915	.560	1.494
LR			14.3	2	.001			
IR	-1.259	0.4	10.5	1	.001	.284	.133	.608
HR	-.954	0.3	11.7	1	.001	.385	.223	.665

Legend: ADJ (adjuvant hormonal therapy, EBRT (External beam radiotherapy), IR (Intermediate risk group), HDR, HR (High risk group), LR (Low risk group), OS (overall survival).

Table 9: Results of biochemical control by risk groups in series of HDR plus EBRT with more than 5-year follow up

Reference	n	Median FU (months)	Biochemical control by risk groups (%) Low	Intermediate	High	Dose in Gy (HDR(n.fx)/ EBRT)
13	344	61		84	74	19.5(3) / 46
14	121	63		91		10(1)/50
15	313	68	100	88	79	23(2)/46
16	229	61	95	90	57	21(3)/50.4
17	64	105		84	80	18(3)/45
18	90	95			80	16.5(3)/45
19	264	75	97			18(3)/45
20	100	62		84	82	10(1)/60
21	64	61		100	91	21(3)/50
22	196	66		86		18(3)/46
23	131	63		87	71	30(4)/45

Discussion

Conventional EBRT to treat PCa is securely limited to doses of 64–70 Gy in 1.8–2.0 Gy fractions. These levels of doses are determined by the risk of long-term toxic effects to the bladder and rectum. The clinical and biochemical relapse rates associated with these dose levels are around 33% within 5 years. Peeters *et al*[12] published the results of a randomized trial comparing total doses of 68 Gy and 78 Gy using EBRT alone. The 5-year OS in the higher dose arm of that study was 83% using ASTRO definition and the BC was significantly better in the 78-Gy arm compared to the 68-Gy arm, with an adjusted hazard ratio of 0.74 (p=0.02). Other published reports using dose-escalated photon beam EBRT alone also point in the same direction with respect to their long-term BC results [13-14].

HDR can escalate the dose given to the prostate by the combination with EBRT, and further more, in locally advanced disease has also the possibility of including the seminal vesicles when they needed to be encompassed. HDR has also a potential biological advantage through the delivery of high doses per fraction [10]. It is important to note that the comparisons between series published are difficult due differences in the techniques and planning for both, EBRT and HDR.

The combination of values of PSAi, GS and CS to identify a more or less aggressive disease has being extensively discussed in the literature, and was confirmed by this study. The most frequent challenge is to identify, for example the indication of prostate versus pelvic EBRT, varying risk categories, absence or use of NAAD, ADT and their length. Despite this, the combination of HDR and EBRT provides an optimal modulation of dose delivery. Results of this combination, in terms of BC and with more than 5 years of FU, range from 57% to 100% according to the risk group for biochemical failure (**Table 9**).

The search for factors predicting BC and CSS is important on defining what patients should be treated more aggressively. We, as other authors [26-28] observed that PSAi <10 ng/ml was confirmed as a favorable predictive factor related to BC and CSS.

Age<65 years was found to be an adverse prognostic factor in our analysis for CSS, with a marginally statically significance impact on OS, not confirmed on multivariate analysis. Smolska-Ciszewska et al, conversely to our results, noted that younger age at time of treatment impacted only on OS, not explaining if there was any association between treatment and side effects or worsening of associated comorbidities. As in our analysis, they found that low risk group and association of HDR to EBRT correlated with improved BC [29].

As in our results, Kamrava *et al* found that T stage, GS, and use of ADT were significantly associated with CSS on univariate analysis, but on multivariate analysis only GS and use of ADT were significantly associated CSS [30]

It is expected that the grouping of the patients in risk groups for biochemical failure based on PSAi, GS and CS, to aggregate patients with adverse features in the intermediate and high risk, leading to worse CSS and BC for the two last one, what was confirmed in our analysis. This was also observed by Morris *et al [31].*

In our series, as in others, patients who received adjuvant ADT had significantly higher risk features suggesting patient selection bias for CSS in this group of patients, instead of a negative interaction between HDR and EBRT [31-32].

Mature data in the literature evaluated the 10-year outcomes of intermediate- and high-risk patients noting a clear dose response by increasing the dose escalation through HDR doses [27]. More recently the use of Intensity modulated radiation therapy combined to HDR has being investigated. Chen *et al*. published the results of 148 patients treated with HDR – 22 Gy in 4 fractions followed IMRT up to 50.4Gy. All patients with Gleason score of 8 or higher had ADT for 1 year. They noted a 4-year actuarial CSS of 96.8% and of 100%, 100% and 94% for low, intermediate and high risk, respectively [32].

The results of the first randomized prospective trial, which has addressed dose escalation using an HDR and EBRT is a trial with a relatively slow accrual rate. There are some critics that must be addressed as the changes in EBRT technique during the time of the study, and, by current standards, the control arm is a relatively low-dose treatment. Despite that, the study reported the results of 218 patients treated between 1997 and 2005. There were 108 patients assigned to EBRT alone and 110 patients treated by EBRT followed by HDR. They noted that CSS was significantly higher in patients treated with combined modality (p = 0.04). In multivariate analysis

the category treatment modality and ADT were significant covariates for BC, but with no differences in OS, as observed in our study. After a median follow-up time of 10.5 year follow-up, an 18% increase in CSS was obtained relative to EBRT alone, reflecting a 31% reduction in the risk of recurrence ($p = 0.01$) and no evidence of an increase in long-term severe morbidity [9].

Surgically induced gland deformation is inevitable during brachytherapy procedures. We observed that the use more of advanced methods of images (3D plan based on CT, MR or TRUS) images to identify the target, organs at risk and needles is important and have already been reported to impact on BC and CSS [33]. In our analysis Multivariate Cox regression analysis confirmed EBRT dose >50 Gy as predictor for CSS and BC, but with no impact on OS. This may be explained by the relative low dose per fraction schedule used in both groups. Of importance is to note that the dose given by HDR was relative constant thorough the risk groups, leading to higher biological effective dose to intermediate and high risk patients, and even though, these patients had a worse outcome, showing that there is space for further studies of dose escalation or treatment combination. After 2005 with the introduction of real time TRUS image acquisition and planning we have changed our protocol and moved forward for a more intense dose escalation, increasing dose and reducing the number of fractions.

Other information of this study is that presence of NAAD had no impact on DSS, BC or OS in any risk group, showing that this treatment strategy should be reserved for downsizing the prostate prior to treatment, in special for low risk patients.

In conclusion, this report demonstrates that HDR combined with EBRT is an important and effective method in achieving dose escalation in the radical radiotherapy of PCa. This combination has also the advantage of treatment time reduction and in increasing in the capability of work load of the linear accelerators, especially in developing countries, where waiting lists and lack of radiation oncology facilities are a reality. The present data represents a unique uni-institutional study at long FU for the given technique, and a comparison with the current literature confirms the excellent results achieved with this treatment modality. The satisfactory BC, CSS and OS are probably result of improved LC achieved with dose escalation, showing that HDR is an optimal alternative method of local dose escalation when combined to EBRT.

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Abbreviations and Acronyms

ADT: Adjuvant Androgen Deprivation

AJCC: American Joint Committee on Cancer

BC: Biochemical Control

CSS: Clinical Specific Survival

EBRT: External Beam Radiotherapy

FU: Fallow Up

GS: Gleason Score

HDR: High-Dose-Rate Brachytherapy

LR: Low Risk Group

NAAD: Neoadjuvant Hormonal Therapy

OS: Overall Survival

PSAi: Initial Prostate-Specific Antigen

TRUS: Trans Rectal Ultrasound

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