Am J Clin Exp Urol 2022;10(1):52-62
www.ajceu.us /ISSN:2330-1910/AJCEU0139268

Original Article

PSA nadir predicts biochemical recurrence after external beam radiation therapy combined to high dose rate brachytherapy in the treatment of prostate cancer

Marcos OS Coelho, Luciana SB Dal Col, Diego M Capibaribe, Carla M Salgado, Thiago C Travassos, Vanderlei J Junior, Carlos R Monti, Leonardo O Reis

UroScience, University of Campinas (Unicamp) and Pontifical Catholic University of Campinas (PU-Campinas), Campinas, São Paulo 13034-685, Brazil

Received September 20, 2021; Accepted January 12, 2022; Epub February 15, 2022; Published February 28, 2022

Abstract: Introduction: Prostate cancer (PCa) is the second most prevalent neoplasm among men in the world. Its treatment has a wide spectrum of alternatives and variables, ranging from active surveillance through radio and/or brachytherapy, to surgery. Objective: The present work aimed to identify the predictive factors for biochemical recurrence and to evaluate the toxicity of the treatment using the association of external beam radiation therapy (EBRT) with high dose rate brachytherapy (HDR-BT) applied in the treatment of patients with prostate cancer. Methods: Longitudinal retrospective study, using a prospectively collected database between 2005 and 2014 of 186 consecutive patients records with a diagnosis of low, intermediate, or high-risk prostate cancer treated with EBRT combined with HDR-BT, in a single medical institution located in the city of Campinas, SP, Brazil (Radium Institute). PSA increase over 2 ng/ml above the nadir PSA was considered as biochemical recurrence, following the definition of the Phoenix Consensus. Continuous and clinically relevant categorical variables (age, initial PSA, delivered dose in EBRT, number of implants, number of positive cores in transrectal biopsy, use of hormone blockade, Gleason score, TNM staging, post treatment PSA and PSA Nadir) were evaluated with absolute (n) and percentage (%) values using multiple logistic regression and validated our previously described optimal PSA nadir as predictor of biochemical recurrence. Results: Post treatment PSA was the only independent predictor of biochemical recurrence, P<0.0001. The lower the PSA nadir the lower the biochemical recurrence risk (P=0.0009). PSA nadir >1 was the best cutoff (P=0.018) determinant of biochemical recurrence. The incidence of grade 3 late toxicity to the genitourinary tract was 0.6%, and there were no cases of severe complications to the gastrointestinal tract. Conclusion: External Beam Radiation Therapy conjugated to Brachytherapy in the treatment of Prostate Cancer has demonstrated low biochemical recurrence rates, mainly when PSA nadir <1, with low toxicity into both GU and GI tracts.

Keywords: External Radiotherapy, high dose rate brachytherapy, prostate cancer, biochemical relapse, toxicity, efficacy, PSA nadir

Introduction

Prostate cancer is the second most common malignant neoplasm among men in Brazil and worldwide [1, 2]. Several factors are associated with the risk of prostate cancer such as age [3], ethnic group [4], heredity [5], environmental and lifestyle factors [6, 7].

The choice of localized cancer treatment may include active surveillance [8, 9], radio and/or brachytherapy [10-14] and surgery [15, 16], considering not only tumor characteristics and staging but also individual patient features, expectations, and agreement with the treatment risks and benefits. D'Amico et al. proposed a risk stratification of biochemical relapse after the many treatment options, based on PSA, Gleason score and clinical staging (TNM) [17]. This classification system has simplified the way in which doctors predict the response to treatment modalities.

Brachytherapy as monotherapy for a low-risk prostate cancer is regarded as a good choice according to the D'Amico's classification [18]; however, in the intermediate and high-risk cases, isolated brachytherapy presents poor

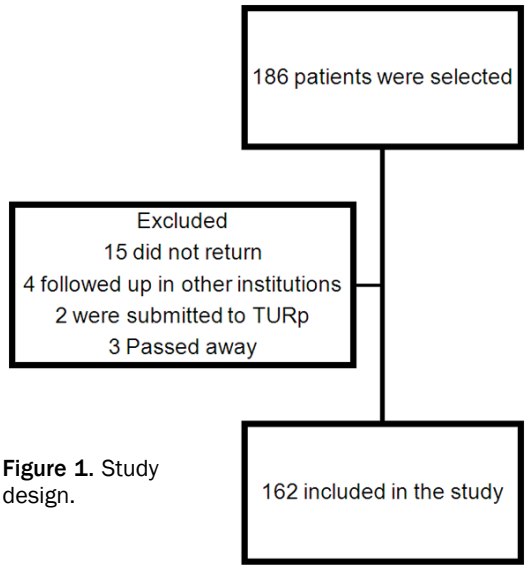

Figure 1. Study design.

results in terms of biochemical control [19], in which the association of brachytherapy and external beam radiation has been considered a viable alternative [20-23].

Objective

To identify predictive factors for biochemical recurrence and evaluate treatment toxicity using the association of external beam radiation therapy (EBRT) with high dose rate brachytherapy (HDR-BT) applied in the treatment of patients with PCa.

Methods

This is a retrospective longitudinal study, with a prospectively collected database of prostate cancer patients from January 2005 to January 2014, ethics committee approval number 374.513. Inclusion criteria consisted of patients diagnosed with prostate cancer, confirmed by transrectal ultrasound-guided biopsy, treated with an association of EBRT and HDBT at the Instituto do Radium, Campinas, SP, Brazil.

A total of 186 consecutive patients diagnosed with low, intermediate, and high-risk prostate cancer treated with EBRT, associated with HDR-BT in a single medical institution located in the city of Campinas, SP, Brazil (Instituto do Radium) was selected. Continuous and clinically relevant categorical variables were evaluated with absolute (n) and percentage (%) values using multiple logistic regression.

Twenty-four patients were later submitted to other treatment modalities or lost segment at the institution and were excluded. All patients were informed of all possible treatment methods, their risks and benefits, adverse side effects and complications. The study design is shown in **Figure 1**.

The patients were submitted to physical and digital rectal exams [24] and blood samples for laboratory testing. Distant metastases were excluded by total abdominal computed tomography, simple chest x-ray, and bone scintigraphy (if PSA >20 ng/ml). The Gleason score was used to determine tumor differentiation [25, 26]. The American Joint Committee on Cancer (AJCC) TNM system (2009) was used for clinical staging [27], and the patients were divided into risk groups according to D'Amico's classification [17].

Brachytherapy

Patients were treated in a lithotomy position (dorsal decubitus on leg holders), under spinal anesthesia or general anesthesia. A Foley catheter was used to fill the bladder with distilled water. The transrectal ultrasound probe was inserted, and the prostate, seminal vesicles, urethra, bladder, and rectum were visualized, thus preparing for the introduction of the radioactive implants. The entire prostate volume was targeted for HDR-BT. The maximum dose for the urethra and rectum was defined as being lower than 120% of the surrounding tissues and 7 Gy for the rectum, respectively. The implants (on average 20) were placed under ultrasound guidance. The first 45 patients received 2 fractions of 8 Gy, through HDR 192-Ir, Varian Gammamed brand and Vitesse Varian planning system. The other 117 patients received a single fraction of 10 Gy (**Figures 2** and **3**). High dose rate brachytherapy was performed after external beam radiation therapy, following a gap of 2 to 3 weeks.

External beam radiation therapy (EBRT)

Three-dimensional (3D) or conformational EBRT, with photon energy generated by a linear particle accelerator (Varian®, model 6EX, 120 slides) was used, and CT scan was performed in all patients using the software EclipseTM-Varian, version 11.0. The target area included the prostate, seminal vesicles and, in high-risk

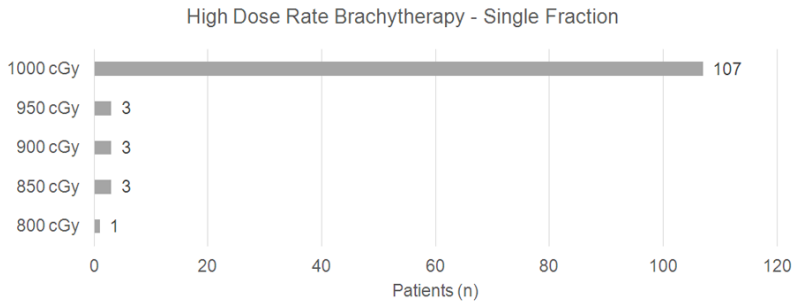

Figure 2. Patients who underwent HDRB (Gy) in a single fraction.

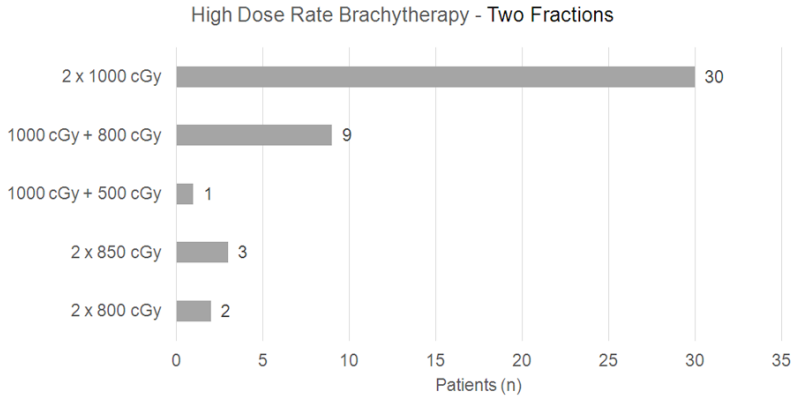

Figure 3. Patients who underwent HDRB (Gy) in two fractions.

cases, the pelvic lymph nodes. The patients were placed in dorsal decubitus position and with pelvic fixation system. The duration of EBRT treatment was 5 to 6 weeks, according to the brachytherapy planning. The applied dose was 50 Gy in fractions of 2 Gy (five times a week). When the brachytherapy planning was of only one insertion, the dose of external radiotherapy was 60 Gy in the prostate, 50 Gy in the seminal vesicles and in the cases of radiotherapy in pelvic lymph nodes, the dose was 50 Gy.

Androgen deprivation treatment (ADT)

Neoadjuvant treatment was performed in 46 (28.4%) subjects and was reserved for patients with prostate volumes greater than 40 g, confirmed by US. Adjuvant treatment was performed in 19 (11.7%) high risk cases. The mean duration of treatment was 6 to 18 months.

Follow-up

Follow-up averaged 57 months (4.2-163). The patients were evaluated every three months in the first 2 years, every six months in the third year, and then annually. Post-treatment PSA levels were analyzed using the validated Immulite® PSA kit.

Statistical analysis

The sample was evaluated according to the frequency of categorical variables, with absolute (n) and percentage (%) values. Descriptive statistics of continuous variables were also analyzed, with mean values, standard deviation, minimum and maximum values, median and quartiles. Chi-Square or Fisher's Exact Test were used, when necessary, for the comparison of categorical variables: (i) age range, (ii) Gleason score (<7 vs. ≥7), (iii) pre-treatment PSA (<10 vs. ≥10 ng/ml), and (vi) TNM staging, among the groups.

For comparison of continuous variables: (i) age, (ii) PSA pre-treatment, (iii) PSA nadir at 12 months, (iv) number of needles used, (v) radiation dose, (vi) total number of fragments and positive fragments in the biopsy, (vii) percentage of positive fragments in the biopsy, and (viii) follow-up time. The Mann-Whitney test was applied due to the absence of normal distribution of the variables.

Biochemical recurrence after primary RT, with or without short-term hormonal manipulation is considered any PSA increase greater than 2 ng/ml above nadir, following the definition of the Phoenix Consensus [28]. The PSA as a parameter to define "biochemical recurrence" in the absence of clinical or histopathological evidence of recurrence which aims to define the best time for a new intervention to prevent disease progression. We validated our optimal PSA nadir as predictor of biochemical recurrence, previous calculated by receiver operating characteristic [ROC] curve [29].

Statistical Analysis in System (SAS) software, version 9.4 (SAS Institute Inc, 2002-2012, Cary, NC, USA) was used for statistical analysis

Table 1. Clinical features of patients

Variables	N (%)
Age (years)	
<65	63 (38.9)
≥65	99 (61.1)
Gleason Score	
6	58 (35.8)
7	69 (42.6)
8	19 (11.7)
9	13 (8.0)
10	3 (1.9)
Initial PSA (ng/ml)	
<10	111 (68.5)
10-20	30 (18.5)
>20	21 (13)
T Stage (AJCC)	
T1-T2a	62 (38.3)
T2b-T2c	77 (47.5)
T3a-T3b	23 (14.2)

and the significance level adopted for the statistical tests was 5% (P<0.05).

Results

Measured variables

The mean age found was 66 years (39-86), with an initial PSA of 11.6 ng/ml (1.06-28). Nadir PSA mean was 0.20 ng/ml (0.0-3.51). About 2/3 of patients had stage T2, followed by 23% of T3 cases. About half of the men had an intermediate degree of risk. Only twenty-six patients (16%) were low risk and 84% were intermediate/high risk. One hundred and four patients (64.2%) had a Gleason score ≥7 on prostate biopsy (**Table 1**). The mean follow-up time was 57 months (4-163). **Table 2** shows continuous and **Table 3** categorical measured variables.

Biochemical recurrence

We assess that biochemical recurrence occurred in 6 patients (3.7%), mean ± SD of PSA nadir 1.1±1.3, compared to 0.2±0.3 in those with oncological control (P=0.0009). Pre-treatment characteristics were comparable between those with oncological control and those presenting biochemical recurrence. The only independent predictor of oncological control was PSA nadir.

Toxicity

Grade 3 gastrointestinal toxicity was not found in any case, and only one patient (0.6%) had genitourinary Grade 3 toxicity (urethral stenosis). **Table 4** shows the comparison between the main clinical and pathological variables and biochemical recurrence. PSA nadir >1 was validated as the best cutoff (P=0.018) determinant of biochemical recurrence.

Discussion

This retrospective study demonstrated that the association of EBRT with HDR-BT is an effective and safe therapeutic option for localized prostate cancer, with a biochemical recurrence rate of 3.7%. PSA nadir <1.0 ng/dL was the only categorical variable predictive of biochemical recurrence. In relation to grade 3 late toxicities, only one case (0.6%) was observed in the GU (urethral stenosis) and no case in the GI. PSA nadir has been revealed as an important predictor of oncological control in the context of radiotherapy [29].

The association of EBRT with BT (high/HDR or low/LDR dose rate) was initially proposed to combine the many advantages of each technique. On the one hand, EBRT allows a large range radiation to treat possible tumor invasions in the seminal vesicles and prostatic capsule, while BT offers a dose of intraprostatic radiation, superior to that offered by EBRT and several studies have demonstrated the feasibility of this combination [30-32].

This study is one of the first carried out in Brazil referring specifically to the treatment of localized PCa, using the association of EBRT and HDR-BT as a therapeutic modality. The first one was published in 2006 by Esteves et al. [29], at the Hospital Beneficência Portuguesa-São Paulo (SP), with 46 patients, followed by two other articles published by Pellizzon et al. in 2008 [30] and 2011 [31] at the Hospital AC Camargo-São Paulo (SP).

Several other studies [32-37] have demonstrated the potential benefit of the synergism between EBRT and HDR-BT, in view of tumor control, biochemical recurrence and toxicity (**Table 5**).

In 2012, Hoskin Póse et al. proposed that the combined treatment (EBRT + HDR-BT) resulted

Table 2. Descriptive analysis of the categorical measured variables

	Frequency	Percentage (%)	Cumulative frequency
Preliminary PSA			
<10 ng/mL	110	68.75	110
10-20 ng/mL	29	18.13	139
>20 ng/mL	21	13.13	160
Gleason			
6	58	35.80	58
7	69	42.59	127
8	19	11.73	146
9	13	8.02	159
10	3	1.85	162
Stage			
Low risk	26	16.05	26
Medium risk	79	48.77	105
High risk	57	35.19	162
T stage			
T1	41	25.31	41
T2	99	61.11	140
T3	22	13.58	162
Neoadjuvant hormone blockade			
No	116	71.60	116
Yes	46	28.40	162
Post treatment hormone blockade			
No	143	88.27	143
Yes	19	111.73	162
Perineural invasion (PNI)			
No	142	87.65	142
Yes	20	12.35	162
PSA nadir			
<1	121	96.03	121
≥1	5	3.97	126
Biochemical Recurrence			
No	156	96.30	156
Yes	6	3.70	162

in significant improvement of biochemical recurrence rates, when compared to isolated EBRT. In their study, a 31% reduction in the risk of recurrence (P=0.01) was obtained, alongside a reduction of acute morbidity and similar incidence of late severe toxicity in the genitourinary and gastrointestinal tracts [38]. In 2013, Kotecha et al. published results on recurrance-free survival and morbidity in 229 patients with localized PCa treated with EBRT + HDR-BT. They concluded that this combination provided a high rate of radiation to the prostate and was associated with better tumor control and grade 3 toxicity in the genitourinary tract (GU) remained inferior to 4% [39].

Regarding the prognostic value of nadir PSA, Tsumura *et al.* (2016) analyzed data from 216 high-risk or locally advanced PCa patients who underwent EBRT associated HDR-BT with long-term androgen deprivation therapy (ADT) for a period of 6 years. A post-radiotherapy nadir PSA value of ≤0.02 ng/mL was associated with better long-term biochemical control [40].

Data from 3,424 patients treated with EBRT + HDR-BT between 1997 and 2014 were collected from 16 Asian hospitals (Japan and Singapore), using a standardized database. The risk category was defined as low, intermediate, high and very high risk, according to NCCN criteria (www.nccn.org). The mean dose of HDR-BT was 18 Gy and the EBRT was 39 Gy. Neoadjuvance was given to 27.7% and 49.5% received both. The mean follow-up was 66 months (1-250). Biochemical control at 5 and 10 years was 90.6% and 81.4%, respectively. High risk was detected as a predictor of biochemical recurrence. They concluded that, in cases of very high risk, the time of ADT should be prolonged, even with HDR-BT; while also being useful to suppress late toxicity [41].

An Australian study published in July 2017 retrospectively evaluated the results (biochemical relapse and incidence of urethral stenosis) in 507 patients with intermediate and high-risk PCa treated with EBRT + HDR-BT in the period of August 2000 to December 2009. All patients received neoadjuvant hormonal blockade (6 months), and only 11 (2.1%) required adjuvant treatment (all high risk). Three doses of HDR-BT were prescribed (the first dose on the day of

Table 3. Descriptive analysis of continuous variables

	n	Mean	SD	Min	Q_1	Median	Q_3	Max
Age	162	66.21	8.51	39.00	60.00	67.50	72.00	86.00
Preliminary PSA	160	11.63	17.19	1.06	4.98	7.40	11.40	28.00
Post treatment PSA	135	0.60	1.15	0.00	0.03	0.10	0.35	8.60
EBRT dose (Gy)	162	56.20	71.47	30.00	48.00	60.00	61.20	67.00
Number of implants	147	20.62	6.41	10.00	15.00	19.00	24.00	48.00
IPSS	121	14.04	8.61	0.00	7.00	13.00	22.00	35.00
Number of cores in biopsy	125	15.67	7.19	6.00	12.00	14.00	16.00	29.00
PSA nadir	126	0.20	0.44	0.00	0.01	0.04	0.21	3.50
Follow-up (months)	147	56.92	31.58	4.17	32.43	53.49	79.70	163.65

SD: Standard Deviation; EBRT: External Beam Radiation Therapy.

implant and the other two on the following day, with a minimum interval of 6 hours with a dose of 6.6 Gy each). The EBRT dose was 46 Gy (divided in 23 sessions). With a mean follow-up of 124 months (10.3 years), the authors concluded that, with the association of EBRT + HDR-BT, the results were better in terms of biochemical recurrence when compared to previous results from EBRT only treatments in the same institution. The biochemical recurrence free rates for intermediate and high-risk cases were 93.3% and 74.2% at 5 years and 86.9% and 56.1% at 10 years, respectively. The rate of urethral stenosis was 28.9% before 2005 and 4.2% after 2005 [42].

In our study, from 2005 to mid-2007, almost all patients received 2 HDR-BT fractions, the majority being two 10 Gy doses. From 2007 until the end of the first half of 2008 there was a diversification of the treatment, sometimes 1 dose of 10 Gy, or 2 doses, ranging from 16 to 20 Gy. From August 2008, all patients underwent a single dose of HDR-BT of 10 Gy. This trend was demonstrated by Falk *et al.* [43] and Hoskin *et al.* [44] and concluded that the single fraction for PCa produces similar results in terms of biochemical control and late toxicity compared to two or three fractions' schemes and is acceptable to "boost" the final EBRT with similar rates.

In the present study the only categorical variable that presented a statistically significant difference was the nadir PSA value <1 ng/ml (P=0.018) and patients who presented nadir PSA 0.2±0.3 (n=120) did not present biochemical recurrence (P=0.009). Post treatment PSA (P<0.0001) showed statistical value in terms of biochemical recurrence: 1) PSA nadir as continuous variable (P=0.0009) and PSA nadir <1 (P=0.018). No other variable (age, initial PSA, dose employed in EBRT, number of implants, number of positive cores in the biopsy, use of hormone blockade, Gleason score or TNM staging) was determinant for biochemical recurrence.

The incidence of grade 3 late toxicity in the GU was 0.6%, and there were no cases of severe complications in the gastrointestinal tract (GI).

We acknowledge the limitations of a retrospective study, carried out in a single reference center with a restricted number of patients and heterogeneous characteristics. In addition, different HDR-BT schemes (1 or 2 fractions) have been used over the years. However, this is also found in the literature, as seen in a systematic review published by Zaorsky *et al.* [45] in which the authors concluded that the limitations of current EBRT + HDR-BT studies include reports from single institution experiments and unrefined results in terms of patient toxicity or quality of life. Regarding disease control, biochemical relapse, and side effects (toxicity), our study presents results compatible with other series published before.

High-dose brachytherapy associated with image-guided EBRT is an effective and safe method for dose delivery with a similar and safe tumoricidal effect added to the advantage of treatment optimization with fewer sessions and a greater number of patients treated with same resources. In addition, recent radiobiological data on the treatment of prostate cancer suggest that HDBT should produce tumor control

Table 4. Comparison between the main clinical and pathological variables and biochemical recurrence

Variables	Without biochemical recurrence (n=156)	With biochemical recurrence (n=6)	*P*-value
Age			
(mean ± SD) (n)	66.4±8.5 (N=156)	61.5±9.3 (N=6)	0.20
(median) (min-max)	68.0 (39.0-86.0)	63.0 (49.0-72.0)	
Initial PSA			
(mean ± SD) (n)	11.5±17.3 (N=154)	14.5±13.6 (N=6)	0.41
(median) (min-max)	7.4 (1.1-189.0)	9.1 (4.9-40.5)	
RT dose (Gy)			
(mean ± SD) (n)	5606.7±722.9 (N=156)	5970±309.3 (N=6)	0.43
(median) (min-max)	6000.0 (3000.0-6700.0)	6040 (5580.0-6400.0)	
Number of implants			
(mean ± SD) (n)	20.8±6.4 (N=141)	16.2±4.3 (N=6)	0.62
(median) (min-max)	20.0 (10.0-48.0)	14.5 (13.0-24.0)	
IPSS			
(mean ± SD) (n)	14.0±8.6 (N=117)	14.0±9.9 (N=4)	0.98
(median) (min-max)	13.0 (0.0-35.0)	13 (3.0-27.0)	
Number of cores			
(mean ± SD) (n)	15.8±7.3 (N=120)	13.6±1.7 (N=5)	0.67
(median) (min-max)	14.0 (6.0-69.0)	14.0 (12.0-16.0)	
PSA nadir			
(mean ± SD) (n)	0.2±0.3 (N=120)	1.1±1.3 (N=6)	0.0009
(median) (min-max)	0.0 (0.0-2.2)	0.6 (0.1-3.5)	
Post PSA			
(mean ± SD) (n)	0.4±0.6 (N=129)	4.4±2.3 (N=6)	<0.0001
(median) (min-max)	0.1 (0.0-2.2)	4.3 (2.3-8.6)	
Follow-up (months)			
(mean ± SD) (n)	56.6±31.9 (N=141)	63.4±22.3 (N=6)	0.49
(median) (min-max)	53.6 (4.2-163.6)	52.4 (44.8-96.8)	
Gleason			
7	67 (42.9%)	2 (33.3%)	0.76
<7	56 (35.9%)	2 (33.3%)	
>7	33 (21.2%)	2 (33.3%)	
Perineural invasion			
No	137 (87.8%)	5 (83.3%)	0.55
Yes	19 (12.2%)	1 (16.7%)	
Neoadjuvant hormone blockade			
No	111 (71.2%)	5 (83.3%)	0.68
Yes	45 (28.8%)	1 (16.7%)	
Post treatment hormone blockade			
No	137 (87.8%)	6 (100%)	1.00
Yes	19 (12.2%)	0 (0.0%)	

SD: Standard deviation; RT: Radiation Therapy; IPSS: International Prostate Symptom Score; PSA: Prostatic Specific Antigen.

and late side effects that are at least as good as those achieved with conventional fractionation, with the additional possibility that acute side effects may be reduced [46].

While we have identified the PSA nadir >1 as the best marker of biochemical recurrence both for monotherapy (29) and for combined radiotherapy in the current study, future stud-

Table 5. Comparison between literature studies: External beam radiatilon therapy associated to high dose rate brachytherapy in the treatment of localized Prostate Cancer-low (L), intermediate (I) and high (H) risk

Authors	Study Design	Patients (n)	Total HDR BT dose (Gy)	Gy/fractionation	Total EBRT dose (Gy)	Follow-up (years)	Recurrence free (%)			3rd or 4th degree late toxicity (%)		Erectile preservation (%)
							Low	Intermediate	High	GU	GI	
Borghede (1997)	Prospective	50	10	5	50	1.5	97	97	92	2	0	74
Demanes (2005)	Prospective	209	23	6	36	7.3	90	87	69	7.7	0	67
Kalkner (2007)	Phase I	154	20	10	50	6.1	97	83	83	5	1	NA
Pellizzon (2008)	Phase II	209	20	10	45	5.3	92	90	89	NA	NA	NA
Demanes (2009)	Prospective	211	23	6	36	6.4	92	87	63	0	0	NA
Liu (2016)	Prospective	156	18	9	39	3.1	100	100	96.9	2.6	0	NA
This study	Retrospective	162	8-20	8-10	45-66	4.75	96.5	96.2	96.2	0.6	0	NA
Mean		170	19.6	7.4	41.7	5.1	94.3	90.2	79.4	2.9	0.2	69.5

EBRT: External beam radiation therapy; high dose rate brachytherapy (HDR-BT); BT: Brachytherapy; Gy: Radiation dose Unit (Gray); GU: genitourinary system; GI: gastrointestinal system; NA: not available.

ies should look for new and more specific markers with potential for higher precision.

Conclusion

External Beam Radiation Therapy conjugated to Brachytherapy in the treatment of Prostate Cancer has demonstrated low biochemical recurrence rates (3.7%), mainly when PSA nadir <1, with low toxicity (0.6%) into both GU and GI tracts.

Acknowledgements

To the involved institution(s), the patients, and those that provided and cared for study patients.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Leonardo O Reis, UroScience, University of Campinas and Pontifical Catholic University of Campinas, Av. John Boyd Dunlop-Jardim Ipaussurama, Campinas, SP 13034-685, Brazil. Tel: +55-19-3343-8600; E-mail: reisleo.l@gmail.com

References

[1] Estimativa 2016: Incidência de câncer no Brasil. Instituto Nacional de Câncer José Alencar Gomes da Silva. Rio de Janeiro: INCA, 2015.
[2] World Health Organization Classification of Tumours. In: Eble JN, Sauter G, Epstein JI, Sesterhenn IA, editors. Pathology and genetics of tumours of the urinary system and male genital organs. Lyon: IARC Press; 2004.
[3] Yancik R and Ries LA. Cancer in older persons: an international issue in an aging world. Semin Oncol 2004; 31: 128-36.
[4] Romero FR, Romero AW, Almeida RM and Tambara Filho R. The prevalence of prostate cancer in Brazil is higher in black men than in white men: systematic review and meta-analysis. Int Braz J Urol 2012; 38: 440-7.
[5] Alberti C. Hereditary/familial versus sporadic prostate cancer: few indisputable genetic differences and many similar clinicopathological features. Eur Rev Med Pharmacol Sci 2010; 14: 31-41.
[6] Cohen JH, Kristal AR and Stanford JL. Fruit and vegetable intakes and prostate cancer risk. J Natl Cancer Inst 2000; 92: 61-8.
[7] Richman EL, Kenfield SA, Chavarro JE, Stampfer MJ, Giovannucci EL, Willett WC and Chan JM. Fat intake after diagnosis and risk of lethal prostate cancer and all-cause mortality. JAMA Intern Med 2013; 173: 1318-26.
[8] Gomez P, Manoharan M, Sved P, Kim SS and Soloway MS. Radical retropubic prostatectomy in Hispanic patients. Cancer 2004; 100: 1628-32.
[9] Klotz L. Active surveillance for prostate cancer: a review. Curr Urol Rep 2010; 11: 165-71.
[10] Eade TN, Hanlon AL, Horwitz EM, Buyyounouski MK, Hanks GE and Pollack A. What dose of external-beam radiation is high enough for prostate cancer? Int J Radiat Oncol Biol Phys 2007; 68: 682-9.
[11] Trojan L, Harrer K, Schäfer J, Voss M, Welzel G, Bolenz C, Wenz F, Alken P and Michel MS. Complications and side effects of low dose rate brachytherapy for the treatment of prostate cancer: data on a 13 year follow-up study from Mannheim. Urologe A 2007; 46: 1542-7.
[12] Pellizzon AC, Salvajoli J, Novaes P, Maia M and Fogaroli R. Updated results of high-dose rate brachytherapy and external beam radiotherapy for locally and locally advanced prostate cancer using the RTOG-ASTRO phoenix definition. Int Braz J Urol 2008; 34: 293-301.
[13] Zamboglou N, Tselis N, Baltas D, Buhleier T, Martin T, Milickovic N, Papaioannou S, Ackermann H and Tunn UW. High-dose-rate interstitial brachytherapy as monotherapy for clinically localized prostate cancer: treatment evolution and mature results. Int J Radiat Oncol Biol Phys 2013; 85: 672-8.
[14] Morton GC. High-dose-rate brachytherapy boost for prostate cancer: rationale and technique. J Contemp Brachytherapy 2014; 6: 323-30.
[15] Bill-Axelson A, Holmberg L, Filén F, Ruutu M, Garmo H, Busch C, Nordling S, Häggman M, Andersson SO, Bratell S, Spångberg A, Palmgren J, Adami HO and Johansson JE; Scandinavian Prostate Cancer Group Study Number 4. Radical prostatectomy versus watchful waiting in localized prostate cancer: the Scandinavian prostate cancer group-4 randomized trial. J Natl Cancer Inst 2008; 100: 1144-54.
[16] Briganti A, Chun FK, Salonia A, Gallina A, Farina E, Da Pozzo LF, Rigatti P, Montorsi F and Karakiewicz PI. Validation of a nomogram predicting the probability of lymph node invasion based on the extent of pelvic lymphadenectomy in patients with clinically localized prostate cancer. BJU Int 2006; 98: 788-93.
[17] D'Amico AV, Whittington R, Malkowicz SB, Schultz D, Blank K, Broderick GA, Tomaszewski JE, Renshaw AA, Kaplan I, Beard CJ and Wein A. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically

localized prostate cancer. JAMA 1998; 280: 969-74.
[18] Mohler JL, Armstrong AJ, Bahnson RR, D'Amico AV, Davis BJ, Eastham JA, Enke CA, Farrington TA, Higano CS, Horwitz EM, Hurwitz M, Kane CJ, Kawachi MH, Kuettel M, Lee RJ, Meeks JJ, Penson DF, Plimack ER, Pow-Sang JM, Raben D, Richey S, Roach M 3rd, Rosenfeld S, Schaeffer E, Skolarus TA, Small EJ, Sonpavde G, Srinivas S, Strope SA, Tward J, Shead DA and Freedman-Cass DA. Prostate cancer, version 1.2016. J Natl Compr Canc Netw 2016; 14: 19-30.
[19] Cosset JM, Flam T, Belin L, Thiounn N, Pierrat N, Pontvert D, Wakil G, Savignoni A and Chauveinc L. Long-term results of permanent implant prostate cancer brachytherapy: a single-institution study of 675 patients treated between 1999 and 2003. Cancer Radiother 2016; 20: 261-7.
[20] Dattoli M, Wallner K, True L, Bostwick D, Cash J and Sorace R. Long-term outcomes for patients with prostate cancer having intermediate and high-risk disease, treated with combination external beam irradiation and brachytherapy. J Oncol 2010; 2010: 471375.
[21] Hurwitz MD, Halabi S, Archer L, McGinnis LS, Kuettel MR, DiBiase SJ and Small EJ. Combination external beam radiation and brachytherapy boost with androgen deprivation for treatment of intermediate-risk prostate cancer: long-term results of CALGB 99809. Cancer 2011; 117: 5579-88.
[22] Martinez AA, Gonzalez J, Ye H, Ghilezan M, Shetty S, Kernen K, Gustafson G, Krauss D, Vicini F and Kestin L. Dose escalation improves cancer-related events at 10 years for intermediate- and high-risk prostate cancer patients treated with hypofractionated high-dose-rate boost and external beam radiotherapy. Int J Radiat Oncol Biol Phys 2011; 79: 363-70.
[23] Chapet O, Bossi A, Horn S and Créhange G. Combination external beam radiation and brachytherapy boost for prostate cancer. Cancer Radiother 2017; 21: 473-477.
[24] Reis LO, Simão AF, Baracat J, Denardi F and Gugliotta A. Digital rectal examination standardization for inexperienced hands: teaching medical students. Adv Urol 2013; 2013: 797096.
[25] Gleason DF and Mellinger GT. Prediction of prognosis for prostatic adenocarcinoma by combined histological grading and clinical staging. J Urol 1974; 111: 58-64.
[26] Tan PH, Cheng L, Srigley JR, Griffiths D, Humphrey PA, van der Kwast TH, Montironi R, Wheeler TM, Delahunt B, Egevad L and Epstein JI; ISUP Prostate Cancer Group. International Society of Urological Pathology (ISUP) Consensus Conference on handling and staging of radical prostatectomy specimens. Working group 5: surgical margins. Mod Pathol 2011; 24: 48-57.
[27] Edge SB and Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 2010; 17: 1471-4.
[28] Roach M 3rd, Hanks G, Thames H Jr, Schellhammer P, Shipley WU, Sokol GH and Sandler H. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. Int J Radiat Oncol Biol Phys 2006; 65: 965-74.
[29] Reis LO, Sanches BC, Zani EL, Castilho LN and Monti CR. PSA-nadir at 1 year as a sound contemporary prognostic factor for low-dose-rate iodine-125 seeds brachytherapy. World J Urol 2014; 32: 753-9.
[30] Pellizzon AC, Salvajoli J, Novaes P, Maia M and Fogaroli R. Updated results of high-dose rate brachytherapy and external beam radiotherapy for locally and locally advanced prostate cancer using the RTOG-ASTRO Phoenix definition. Int Braz J Urol 2008; 34: 293-301.
[31] Pellizzon AC, Fogaroli RC, Silva ML, Castro DG, Maia MC and Lopes A. High-dose-rate brachytherapy combined with hypofractionated external beam radiotherapy for men with intermediate or high risk prostate cancer: analysis of short- and medium-term urinary toxicity and biochemical control. Int J Clin Exp Med 2011; 4: 43-52.
[32] Borghede G, Hedelin H, Holmäng S, Johansson KA, Aldenborg F, Pettersson S, Sernbo G, Wallgren A and Mercke C. Combined treatment with temporary short-term high dose rate iridium-192 brachytherapy and external beam radiotherapy for irradiation of localized prostatic carcinoma. Radiother Oncol 1997; 44: 237-44.
[33] Demanes DJ, Rodriguez RR, Schour L, Brandt D and Altieri G. High-dose-rate intensity-modulated brachytherapy with external beam radiotherapy for prostate cancer: California endocurietherapy's 10-year results. Int J Radiat Oncol Biol Phys 2005; 61: 1306-16.
[34] Kälkner KM, Wahlgren T, Ryberg M, Cohn-Cedermark G, Castellanos E, Zimmerman R, Nilsson J, Lundell M, Fowler J, Levitt S, Hellström M and Nilsson S. Clinical outcome in patients with prostate cancer treated with external beam radiotherapy and high dose-rate iridium 192 brachytherapy boost: a 6-year follow-up. Acta Oncol 2007; 46: 909-17.
[35] Pellizzon AC, Salvajoli J, Novaes P, Maia M, Fogaroli R, Gides D and Horriot R. The relation-

ship between the biochemical control outcomes and the quality of planning of high-dose rate brachytherapy as a boost to external beam radiotherapy for locally and locally advanced prostate cancer using the RTOG-ASTRO phoenix definition. Int J Med Sci 2008; 5: 113-20.

[36] Demanes DJ, Brandt D, Schour L and Hill DR. Excellent results from high dose rate brachytherapy and external beam for prostate cancer are not improved by androgen deprivation. Am J Clin Oncol 2009; 32: 342-7.

[37] Liu J, Kaidu M, Sasamoto R, Ayukawa F, Yamana N, Sato H, Tanaka K, Kawaguchi G, Ohta A, Maruyama K, Abe E, Kasahara T, Nishiyama T, Tomita Y and Aoyama H. Two-fraction high-dose-rate brachytherapy within a single day combined with external beam radiotherapy for prostate cancer: single institution experience and outcomes. J Radiat Res 2016; 57: 280-7.

[38] Hoskin PJ, Rojas AM, Ostler PJ, Bryant L and Lowe GJ. Randomised trial of external beam radiotherapy alone or combined with high-dose-rate brachytherapy boost for localised prostate cancer. Radiother Oncol 2021; 154: 214-219.

[39] Kotecha R, Yamada Y, Pei X, Kollmeier MA, Cox B, Cohen GN, Zaider M and Zelefsky MJ. Clinical outcomes of high-dose-rate brachytherapy and external beam radiotherapy in the management of clinically localized prostate cancer. Brachytherapy 2013; 12: 44-9.

[40] Tsumura H, Satoh T, Ishiyama H, Tabata K, Komori S, Sekiguchi A, Ikeda M, Kurosaka S, Fujita T, Kitano M, Hayakawa K and Iwamura M. Prostate-specific antigen nadir after high-dose-rate brachytherapy predicts long-term survival outcomes in high-risk prostate cancer. J Contemp Brachytherapy 2016; 8: 95-103.

[41] Ishiyama H, Kamitani N, Kawamura H, Kato S, Aoki M, Kariya S, Matsumura T, Kaidu M, Yoshida K, Hashimoto Y, Noda Y, Lim KHC, Kawase T, Takahashi T, Inaba K, Kumano M, Yoshikawa N, Yoshioka Y, Nakamura K, Hiratsuka J, Itami J and Hayakawa K. Nationwide multi-institutional retrospective analysis of high-dose-rate brachytherapy combined with external beam radiotherapy for localized prostate cancer: an Asian Prostate HDR-BT Consortium. Brachytherapy 2017; 16: 503-510.

[42] Yaxley JW, Lah K, Yaxley JP, Gardiner RA, Samaratunga H and MacKean J. Long-term outcomes of high-dose-rate brachytherapy for intermediate- and high-risk prostate cancer with a median follow-up of 10 years. BJU Int 2017; 120: 56-60.

[43] Falk AT, Demontoy S, Chamorey E, Chand ME, Gautier M, Azria D, Zaki S, Chevallier D, Cham Kee DL and Hannoun-Lévi JM. High-dose-rate brachytherapy boost for prostate cancer: comparison of three different fractionation schemes. Brachytherapy 2017; 16: 993-999.

[44] Hoskin P, Rojas A, Ostler P, Hughes R, Alonzi R and Lowe G. Single-dose high-dose-rate brachytherapy compared to two and three fractions for locally advanced prostate cancer. Radiother Oncol 2017; 124: 56-60.

[45] Zaorsky NG, Ohri N, Showalter TN, Dicker AP and Den RB. Systematic review of hypofractionated radiation therapy for prostate cancer. Cancer Treat Rev 2013; 39: 728-736.

[46] de Cerqueira MA, Laranja WW, Sanches BC, Monti CR and Reis LO. Burden of focal cryoablation versus brachytherapy versus active surveillance in the treatment of very low-risk prostate cancer: a preliminary head-to-head comprehensive assessment. Eur J Cancer Care (Engl) 2015; 24: 929-37.