Original paper

Salvage brachytherapy for locally recurrent prostate cancer after single-fraction 19 Gy high-dose-rate brachytherapy: toxicity, prostate-specific antigen kinetics, and cancer control

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Abstract

Purpose: To evaluate toxicity, prostate-specific antigen (PSA) kinetics, and cancer control of high-dose-rate brachytherapy (HDR-BT) as a salvage modality for men with locally recurrent prostate cancer, after primary HDR-BT failure.

Material and methods: Twelve patients with biochemical failure and a local relapse after 19 Gy single-fraction high-dose-rate brachytherapy (HDR-BT 19 Gy) were salvaged using two HDR-BT fractions. Salvage treatment consisted of two HDR-BT applications, one week apart, delivering 12 Gy to the prostate per application (HDR-BT 12 × 2).

Results: Median age and initial PSA prior to rescue treatment were 74 years (range, 65-80) and 5.29 ng/ml (range, 2.37-16.40), respectively. Forty-two percent had a low-risk and 58% presented with intermediate-risk prostate cancer. Median follow-up period was 26 months (range, 10-42). Median time to PSA nadir was 12 months, with a median value of 0.21 ng/ml. Most of the patients (11 of 12) achieved a PSA decline ≥ 90%. Acute grade 2 genitourinary (GU) toxicity occurred in 4 patients (33.3%) and none presented with acute gastrointestinal (GI) toxicity. Two patients (16.7%) suffered from late GU grade 2 toxicity. No grade 3 toxicity were recorded. To date, 2 patients (16.7%) have experienced biochemical failure after salvage treatment.

Conclusions: Salvage HDR-BT 12 × 2 is a feasible and well-tolerated treatment, with acceptable toxicity rates for men with locally recurrent prostate cancer, who failed after HDR-BT with 19 Gy. Moreover, PSA kinetics and cancer control after salvage treatment suggest that this strategy might be efficacious in this clinical setting.

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Key words: prostate cancer, salvage brachytherapy, high-dose-rate brachytherapy, recurrent prostate cancer.

Purpose

High-dose-rate brachytherapy (HDR-BT) has been increasingly used as monotherapy for treatment of patients with prostate cancer. Several studies have demonstrated favorable toxicity rates and excellent results in the impact on quality of life after 19 Gy single-fraction high-dose-rate brachytherapy (HDR-BT 19 Gy) [1,2,3,4,5]. However, in the last few years, some trials have reported higher biochemical and local failure rates than expected with this dose schedule [5,6,7,8,9].

On the other hand, salvage brachytherapy has shown promising outcomes in terms of toxicity and biochemical control in the local recurrence setting after primary radiation therapy in several prospective and retrospective series [10,11,12,13,14].

Patients with a local failure after HDR-BT 19 Gy, who were considered good candidates for salvage treatment were treated in our department with HDR-BT administered in two fractions of 12 Gy (HDR-BT 12 × 2).

The purpose of this retrospective study was to measure the safety and tolerance of HDR-BT 12 × 2 as a salvage treatment after HDR-BT 19 Gy, to evaluate prostate-specific antigen (PSA) kinetics with this schedule, and to describe biochemical and local control rates after a salvage treatment.

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Material and methods

In 2014, a phase II trial evaluating the safety and feasibility of HDR-BT 19 Gy for low- and intermediate-risk localized prostate cancer was initiated in our radiation oncology department. After a median follow-up of 48 months, 32% of patients developed a biochemical failure [7].

Patients with biochemical failure after HDR-BT 19 Gy, defined with a serum PSA 2 ng/ml above the PSA nadir, underwent re-staging multiparametric magnetic resonance imaging (mpMRI) and choline positron emission tomography-computed tomography (PET-CT). Patients with local relapse underwent MRI-transrectal ultrasound (TRUS) fusion biopsy to confirm local relapse. All subjects with a positive pre-treatment mpMRI were noted to have a recurrent nodule in the same location as the initial site of disease. Sixteen patients had a confirmation of a local relapse, and 4 did not receive a salvage treatment. One patient presented a negative transperineal biopsy, one died of non-oncological issue, one had advanced age and was not fit for a salvage treatment, and one refused to undergo staging studies after local failure.

Finally, 12 patients were treated with salvage HDR-BT 12 × 2 between February 1, 2017 and October 2, 2019. This retrospective study was approved by the Cruces University Hospital research ethics board.

All patients were treated with a real-time MRI-guided HDR-BT technique, which has been previously reported elsewhere [15,16]. Moreover, in fifty percent of patients, a rectal spacer was used during the procedure [17,18]. Planning target volume (PTV) was defined as the entire prostate gland without margins. The prescription dose was 24 Gy in two fractions of 12 Gy each, one week apart. The dose was prescribed to the PTV as a minimum peripheral dose. Eight patients with visible dominant intra-prostatic lesion on mpMRI were treated with a simultaneous integrated boost prescribed to 13.5 Gy. Dwell time optimization was performed using inverse dose-volume histogram-based optimization (DVHO). Homogeneity of parameters used for dose optimization for the prostate included V_{100} > 95%, V_{150} of < 35%, and V_{200} < 8%, where V_n is the fractional volume of the organ that receives n% of the prescribed dose; maximum point dose inside the urethral volume (urethral D_{max}) < 110%, and the dose to 1 cc of rectal wall (R_{D1cc}) is limited to < 60% of the prescribed dose.

The patients were monitored prospectively for toxicity. Toxicity was assessed using common terminology criteria for adverse events (CTCAE), version 4.0, and was measured at 1, 3, and 6 months after treatment completion and 6 months thereafter. Biochemical recurrence was defined based on Phoenix criteria.

Statistical analysis

Descriptive analysis of the toxicity included absolute and relative frequencies for categorical variables. The dosimetric parameters were reported by median and range. These analyses were conducted using Statistical Package for the Social Sciences (SPSS v. 23.0) for Windows.

We evaluated data of PSA statistically and graphically with Microsoft Office Excel 2002.

Results

From February 2017 to October 2019, 12 consecutive patients with low- and intermediate-risk prostate cancer with local failure after HDR-BT 19 Gy, were treated with salvage HDR-BT 12 × 2 in our department. Median time from HDR-BT 19 Gy to local failure was 29 months (range, 19-41), and median PSA nadir after the initial treatment was 1.68 ng/ml (range, 0.33-3.76).

Table 1 summarizes the clinical and tumor characteristics at diagnosis and at relapse. Table 2 shows the dosimetric parameters of salvage HDR-BT 12 × 2.

After a median follow-up of 26 months (range, 10-42), none of the patients developed acute urinary retention. The maximal acute and late toxicity reported was of grade 2.

In general, acute grade 2 genitourinary (GU) toxicity occurred only during the first month after the treatment in 3 patients (25%). No patient presented with acute or late gastrointestinal (GI) toxicity. The acute grade 2 toxicities observed included dysuria (2 patients), urinary frequency (1 patient), and nocturia (1 patient). Four patients (33.3%) presented late GU grade 2 toxicities, such as dysuria (1 patient), augmentation of urinary frequency

Table 1. Patients and tumor characteristics at diagnosis and at relapse

	Category	Median	Range
Age at diagnosis (years)		71	61-78
Age at relapse (years)		74	65-80
PSA before HDR-BT 19 Gy (ng/ml)		8.96	5.60-17.87
PSA before HDR-BT 12 × 2 (ng/ml)		5.29	2.37-16.40
		n	%
ISUP grade at diagnosis	1	5	41.7
	2	7	58.3
Risk group at diagnosis	Low-risk	5	41.7
	Intermediate-risk	7	58.3

PSA – prostate specific antigen, ISUP – International Society of Urological Pathology

Table 2. Prostate, urethra, and rectum dosimetric characteristics

	First fraction		Second fraction	
	Median	Range	Median	Range
Prostate volume (cc)	29.17	7.63-59.54	28.91	7.8-59.38
V_{100} (%)[1]	97.99	95.65-99.41	98.07	95.5-99.41
V_{125} (%)[1]	57.44	45.29-74.62	61.34	44.24-89.66
V_{150} (%)[1]	22.97	18.82-42.36	24.05	16.65-51.93
V_{200} (%)[1]	5.67	3.79-8.45	5.98	3.61-11.43
D_{90} (%)[2]	108.73	103.87-113.87	108.53	104.65-124.51
Urethra D_{max} (%)[3]	110.72	94.43-115.0	110.87	88.29-115.0
Rectum D_{max} (%)[4]	64.07	46.15-80.09	63.77	45.47-83.32
Rectum D_{1cc} (Gy)[5]	5.86	4.06-7.62	5.71	4.09-7.54

[1]fractional volume of the organ that receives n% of the prescribed dose, [2]percentage of the dose prescribed receiving 90% of volume of the organ, [3]maximum point dose inside the urethral volume, [4]maximum point dose inside the rectal volume, [5]dose to 2 cc of rectal wall

Table 3. Toxicity results at each follow-up visit (CTCAE v. 4.0)

		Grade 1 *n* (%)	Grade 2 *n* (%)	Grade 3 *n* (%)
Genitourinary	1 month	2 (16.7)	3 (25)	No toxicity reported
	3 months	1 (8.3)	0 (0)	
	6 months	6 (50)	2 (16.7)	
	12 months	4 (33.3)	2 (16.7)	
	18 months	2 (16.7)	2 (16.7)	
	24 months	0 (0)	2 (16.7)	
	30 months	1 (8.3)	1 (8.3)	
	36 months	0 (0)	1 (8.3)	
	42 months	1 (8.3)	0 (0)	
Gastrointestinal	No toxicity reported			

CTCAE – common terminology criteria for adverse events version 4.0

(2 patients), nocturia (1 patient), incontinence (1 patient), and urgency (2 patients). None presented with urethral stenosis. No grade 3 toxicity was reported. The proportion of patients who reported toxicity at each follow-up visit is presented in Table 3. The median PSA nadir was 0.21 ng/ml (range, 0.05-1.12) reached 12 months after the treatment.

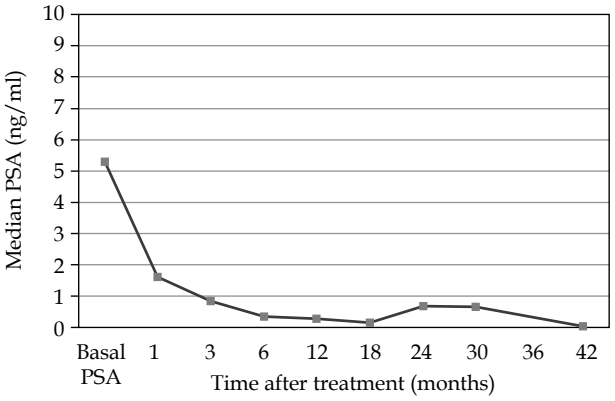

Fig. 1. Median prostate specific antigen (PSA) over time of all 12 patients after salvage brachytherapy

When compared to the initial schedule, the PSA nadir after HDR-BT 12 × 2 was lower, and higher number of patients achieved appropriate nadir values. Nine patients (75%) achieved a PSA nadir lower than 0.5 ng/ml, and 6 patients (50%) reached lower than 0.2 ng/ml, whereas only two patients (16.7%) achieved a PSA nadir lower than 0.5 ng/ml after HDR-BT 19 Gy. PSA kinetics of all 12 patients after the salvage brachytherapy are shown in Figure 1. Maximum percentage of decline of PSA achieved after salvage brachytherapy is presented in Figure 2. Most of the patients (11 of 12 patients) treated with HDR-BT 12 × 2 had a PSA decline ≥ 90%.

After the salvage treatment, 2 patients with intermediate-risk prostate cancer (16.67%) experienced biochemical failure. The mean time from the treatment to biochem-

ical failure was 8.5 months. Re-staging choline PET-CT was performed in both patients showing a regional relapse limited to pelvic lymph nodes. No local relapse was demonstrated. One patient was treated with both androgen deprivation therapy (ADT) and stereotactic ablative body radiotherapy (SABR), and the second patient with ADT only.

Discussion

Up to 70% of biochemical recurrences after definitive radiation therapy are due to local recurrence [19]. Local salvage therapies can provide a curative option in such cases. Our study indicated that salvage HDR-BT in patients with local recurrence of prostate cancer after primary treatment with HDR-BT 19 Gy, was feasible and safe.

PSA kinetics has proven to be an important factor to predict biochemical control and cure after brachytherapy [11,19,20,21,22,23,24]. Helou *et al*. found that value of PSA nadir was strongly correlated with biochemical outcomes in patients treated with HDR-BT and external beam radiotherapy (EBRT). In fact, they reported that PSA nadir < 0.4 ng/ml at any time point was associated with 5-year biochemical disease-free-survival (bDFS) of 100% vs. 72% for patients with PSA nadir ≥ 0.4 ng/ml [23].

Recently, Crook *et al*. performed an analysis of prospectively collected data from 7 institutions from over 14,000 patients with localized prostate cancer treated with LDR brachytherapy (LDR-BT) monotherapy, LDR-BT plus EBRT, LDR-BT plus ADT, or LDR-BT plus EBRT and ADT, to identify a PSA threshold value associated with cure. They found that patients who achieved a PSA ≤ 0.2 ng/ml at 3.5-4.5 years had a probability of being free of clinical failure at 10 years with 98.7% and at 15 years with 96.1%. Moreover, for patients with PSA > 0.2 but ≤ 0.5 ng/ml, the probability of being disease-free decreased but remained high at 93.5% at 10 years [24].

Finally, Wojcieszek *et al*. reported that the outcome after salvage brachytherapy depends on the PSA nadir level and disease-free interval after primary treatment. Particularly, in this study, they showed a 3-year and 5-year bDFS of 76% and 67%, respectively, and a PSA nadir of 0.35 ng/ml after a median follow-up of 41 months [21].

In our previous phase II trial, the median PSA nadir was 1.68 ng/ml and only 2 of 12 (16.7%) patients achieved a PSA nadir lower than 0.5 ng/ml after HDR-BT 19 Gy. However, after HDR-BT 12 × 2, the median PSA nadir was 0.21 ng/ml. Nine patients (75%) achieved a PSA nadir lower than 0.5 ng/ml, and six patients (50%) presented with lower than 0.2 ng/ml. The median time to a relapse after primary treatment was 29 (range, 19-41) months, and the median time to a PSA nadir after salvage treatment was 12 months. Although these results suggest a greater ablative capacity of the multifractional schedule compared to single-fraction treatment, and these data should be considered cautiously. The clinical setting of salvage and primary treatments are different in terms of PTV volumes definition and PSA kinetics, and therefore, it was not possible to compare these two treatments.

In the present study, the patients had an excellent PSA response after HDR-BT 12 × 2 treatment schedule, and

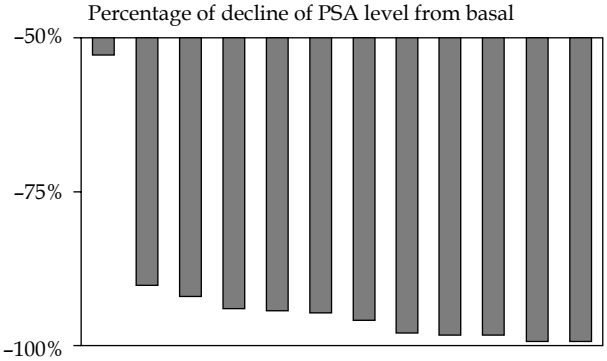

Fig. 2. Waterfall plot of maximum percentage of decline of prostate specific antigen (PSA) level from basal PSA after HDR-BT 12 × 2

HDR-BT 12 × 2 – high-dose-rate brachytherapy with two-fractions of 12 Gy

their PSAs' dropped to very low levels after the treatment (Figure 1). This can suggest that HDR-BT 12 × 2 caused enough lethal damage to achieve biochemical control in a patients' population with a previous local failure after HDR-BT 19 Gy. Our data suggest that re-irradiation with HDR-BT may be an appropriate salvage approach to eradicate tumor cells that have survived a previous treatment with 19 Gy single-fraction.

Pre-salvage PSA has proven to be another important variable in previous studies. Burri *et al*. reported a series of 37 patients with radiorecurrent prostate cancer treated with LDR. The authors noted that a pre-salvage PSA < 6 ng/ml was a significant predictor of improved biochemical outcome in multivariate analysis [11]. Also, Henriquez *et al*. reported pre-salvage PSA > 10 ng/ml as a predictor of biochemical failure [20]. In our series, median pre-salvage PSA was 5.29 ng/ml (range, 2.37-16.40).

Moreover, we found that HDR-BT 12 × 2 delivered as a salvage treatment after primary treatment with HDR-BT 19 Gy was well-tolerated with low toxicity rates. In our study, none of the patients developed acute urinary retention. Twenty-five percent and a 33.3% of patients suffered from acute and late grade 2 GU toxicity, respectively. No GI toxicity was recorded.

Our toxicity rates are comparable to those reported by Wojcieszek *et al*. They reported retrospective results of 83 patients treated with three fractions of 10 Gy of HDR-BT after primary treatment with EBRT and HDR-BT boost or EBRT alone. Grade 1 and 2 acute GU toxicities were observed in 43 (52%) and 29 (35%) men, respectively. Thirty-two (39%) and eleven (13%) patients were reported as grade 2 and 3 late GU toxicity, respectively. Acute GI toxicity grade 1 was reported in 5 (6%) patients. Grade 1 late GU toxicity was observed in 27 (33%) men [21].

A group from the Memorial Sloan Kettering Cancer Center described their experience with salvage low-dose-rate (^{125}I, n = 37) or high-dose-rate brachytherapy (^{192}Ir, n = 61). Acute grade 1 or 2 gastrointestinal toxicity occurred in 14 of 98 patients. Two patients developed acute grade 3 GI toxicity (HDR, 1, LDR, 1). Grade 3 late genitourinary toxicity appeared in 9% of patients (HDR, 8, LDR, 1) [22]. These numbers are comparable with those described in a previously reported phase II

study of the same group on 42 patients undergoing salvage HDR-BT [10]. Both studies are potential indicators of the validity of HDR-BT in the salvage setting to provide patients with an additional chance of cure with potentially more acceptable toxicity rates compared to postponed ADT.

Recently, an interesting study about health-related quality of life (QoL) in patients treated with HDR-BT with two fractions has been published. Harris *et al*. reported retrospective results of 122 patients with low- or intermediate-risk prostate cancer treated with HDR-BT as monotherapy with 27 Gy in 2 fractions. They compared patient-reported health-related QoL and physician-graded toxicity as a function of time interval between implants (patients were dichotomized into one-week and two-week cohorts). The overall rate of grade 2 GU and GI physician-graded toxicity were 67% and 3%, respectively. They found no differences in patient-reported health-related QoL scores or in physician-graded toxicity rates between the one-week and two-week cohorts. They concluded that HDR-BT consisting of two implants is a well-tolerated treatment for men with localized prostate cancer, and that there are no significant differences in the rates of patient-reported health-related QoL or physician-graded toxicity in patients as a function of time between each treatment [25].

The published evidence on salvage HDR-BT has shown 5-year bDFS rates ranging from 51% to 69% [10,13,21]. In our study, the biochemical control was 83.3%; however, longer follow-up is needed as well as further studies to validate and accurately demonstrate the true benefit and value of salvage HDR-BT 12 × 2 in terms of cancer control.

We acknowledge several limitations of our study. The number of patients was small (n = 12), and follow-up was limited to the median of 26 months; therefore, longer follow-up is required to assess late toxicity or biochemical control. Also, the retrospective nature of this study allowed to generate hypothesis only.

Conclusions

Salvage HDR-BT 12 × 2 is a feasible and well-tolerated treatment, with acceptable toxicity rates when administered in patients with local failure after HDR-BT 19 Gy. Additionally, PSA kinetics and cancer control after salvage treatment suggest that this strategy might be efficacious in this clinical setting.

Disclosure

The authors report no conflict of interest.

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