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Technical Note

Salvage brachytherapy for locally-recurrent prostate cancer after radiation therapy: A comparison of efficacy and toxicity outcomes with high-dose rate and low-dose rate brachytherapy

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ABSTRACT

Background: Brachytherapy (BT) is widely used for salvage therapy in patients with biochemical failure (BF) after radiotherapy for prostate cancer (PCa). Although low-dose-rate (LDR) and high-dose-rate (HDR) BT are both used for salvage therapy, it is not clear whether there are any differences between these two approaches in terms of efficacy or toxicity in this setting. Therefore, we review the institutional experience of the members of the Urological Tumour Working Group (URONCOR) of the Spanish Society of Radiation Oncology (SEOR) to compare these two techniques.
Methods and materials: Between 2001 and 2016, 119 patients with biopsy-proven, locally-recurrent PCa underwent salvage BT (LDR, $n = 44$; HDR, $n = 75$) after primary radiotherapy. Relapse-free survival (RFS) and cause-specific survival (CSS) after salvage therapy were analyzed. Toxicity was assessed according to the RTOG scale.
Results: Median follow-up after salvage BT was 52 months. Overall, the 5-year prostate-specific antigen (PSA) RFS rate was 71% (95% CI, 65.9%–75.9%). No significant between-group differences in RFS were observed ($p = 0.063$). Five-year CSS for the LDR- and HDR-BT groups were 96.5% and 93%, respectively. Overall, 38 patients (32%) developed biochemical progression (Phoenix definition) after salvage BT: 14 patients (32%) in the LDR group and 24 (32.5%) in the HDR group. On the multivariate analysis, the following variables were significantly associated with progression, time to BF from primary radiotherapy <30 months ($p = 0.014$); and post-salvage nadir PSA ($p = 0.000$). There were no significant between-group differences in toxicity. Overall, there were 13 cases of urethral stricture, 22 cases of urinary incontinence, and 13 cases of haematuria. Toxicity ≥grade 3 was observed in 23.5% of patients.
Conclusions: These findings show that both HDR-BT and LDR-BT yield comparable efficacy and toxicity outcomes in patients undergoing salvage treatment for locally-recurrent prostate cancer after primary radiotherapy. Predictors of worse outcomes after salvage BT were post-salvage nadir PSA and time to BF from initial radiotherapy.

A substantial proportion—from 22% to 47%—of patients [1] who undergo high-dose external beam radiotherapy (EBRT) for localised prostate cancer (PCa) will develop biochemical failure (BF). Although up to 80% of recurrences are limited to the prostate gland, a subset of patients with unfavourable clinical and biological risk factors will develop distant metastasis, leading to death within 5 to 10 years after developing recurrent disease [1].

The management of locally-recurrent PCa after EBRT has primarily been limited to either observation or androgen deprivation

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therapy (ADT) because most of these patients are poor candidates for salvage treatment due to their age and/or comorbidities [2]. Data from the Spanish Registry of Prostate Cancer (RECAP) published in 2016 showed that more than 70% of patients who developed BF after radiotherapy received ADT whereas only 6% received salvage brachytherapy (BT) [3]. Nevertheless, several different potentially curative salvage therapies—including BT, cryotherapy, and radical prostatectomy—are available to treat prostate-confined recurrence in appropriately selected patients [4–10].

Salvage BT can be used to deliver an ablative dose of radiation to the prostate gland while minimizing normal tissue exposure [8]. Although either high-dose rate (HDR) or low-dose rate (LDR) BT can be used in the salvage setting, the optimal technique in patients with locally-recurrent disease after definitive EBRT remains unclear [7,12]. Moreover, it is difficult to predict the outcomes of salvage BT because the predictive factors identified to date (e.g., pre-salvage prostate-specific antigen [PSA] levels, nadir PSA after primary treatment, Gleason score at diagnosis, the time interval to relapse, and the salvage BT dose, etc.) [7,9,11] were obtained from studies with important limitations (e.g., small sample sizes, unselected patients, inappropriate imaging modalities, and/or short follow-up). For these reasons, the treatment of locally-recurrent PCa after radiotherapy presents a clinical challenge.

Given the limitations of the currently available evidence, the main aim of this study was to compare the clinical efficacy and toxicity of HDR-BT and LDR-BT in a large cohort of patients in Spain treated for locally-recurrent PCa after primary EBRT.

Methods and materials

Data source

Members of the Urological Tumour Working Group (URONCOR) of the Spanish Society of Radiation Oncology (SEOR) retrospectively collected (chart review) data for this multi-institutional study.

A total of 10 centres in Spain participated in this study. All of the brachytherapy units at the participating centres have been fully accredited by the Spanish Ministry of Health and by the Spanish Society of Radiation Oncology (SEOR). By centre, the patient distribution was as follows: Hospital Universitario Ramon y Cajal (Madrid), 25 patients (21%); Institut Català de Oncologia (Barcelona), 29 patients (24%); Hospital Universitario Sant Joan (Reus), 13 patients (11%); Hospital Universitario Sanchinarro (Madrid), 9 patients (7.5%); Hospital General Universitario Gregorio Marañón (Madrid), 10 patients (8.5%); Hospital Doce de Octubre (Madrid) 10 patients (8.4%); Hospital Universitario Fundacion Jimenez Diaz (Madrid) 7 patients (6%); Clinica Benidorm (Benidorm), 7 patients (6%); Hospital de la Santa Creu i Sant Pau (Barcelona), 7 patients (6%); and Hospital Universitario de la Princesa (Madrid) 2 patients (1.5%).

Patient characteristics

Patients treated for recurrent PCa after primary EBRT or LDR-BT from January 2002 to December 2016 were considered for inclusion. Inclusion criteria were: (1) biochemical failure (ASTRO or Phoenix definition) after definitive EBRT or LDR-BT for the primary tumour, and (2) recurrence confirmed by transrectal ultrasound-guided biopsy. All patients were required to have a good urinary and bowel function prior to salvage treatment determined clinically. Exclusion criteria were: (1) radiographic evidence of extraprostatic or metastatic disease; (2) frequent urination (>5 times per night), urge incontinence, or gross haematuria; (3) history of inflammatory bowel disease or rectal surgery.

The Gleason score was recorded if available. All patients underwent metastatic workup before salvage BT, including computed tomography (CT) and/or magnetic resonance imaging (MRI), and a bone scan. The International Prostate Symptom Score (IPSS) questionnaire was not routinely administered.

The following tests were performed at relapse: abdominal-pelvic CT (77% of patients), pelvic MRI (57%), bone scan (82%), choline-PET-CT (34%), and colonoscopy (12%). In most cases (91%), BF was defined according to the Phoenix criteria.

Based on the initial PCa diagnosis (primary tumour), 86% (LDR group) and 65% (HDR group) had intermediate or high-risk disease ($p = 0.044$), with a median PSA of 14.2 and 8.9 ng/ml, respectively. Treatment of the primary tumour consisted of LDR-BT in 23 patients (19%) and EBRT in the remaining 81%. Patients who received primary treatment with LDR-BT underwent salvage HDR-BT for the recurrence.

Time to BF from the initial treatment was >30 months in 85% (HDR-BT) and 93% (LDR-BT) of cases. The median PSA nadir post-EBRT was 0.5 and 0.4 ng/ml, respectively. At relapse, 33 patients (44%) in the HDR group and 4 patients (9%) in the LDR group had a Gleason score of 8–10 ($p = 0.002$). The median PSA in the HDR and LDR groups prior to salvage treatment was 4.1 ng/ml and 3.6 ng/ml, respectively.

Patient characteristics at the initial diagnosis and at recurrence are described in Table 1.

Salvage treatment

The BT dose rate (HDR or LDR) was chosen according to the institutional policies in place at each participating centre. A detailed explanation of the process for administering BT was described in our previous publication [7].

All implants were planned and performed with transrectal ultrasound using a transperineal guide-template with ^{125}I or ^{192}Ir. The following preplan dosimetric parameters for ^{125}I were established to prevent high dose inhomogeneities: V100 >95% (percentage of the prostate receiving at least 100% of the prescribed dose), V150 <45%, V200 <10%, and D90 >100% of the prescribed dose. For the rectum, the parameters were as follows: $D2cc_{rectum}$ (minimum dose to the maximally irradiated 2 cm^3 rectal volume) <100% prescribed dose. $D0.1cc_{rectum}$ (minimum dose to the maximally irradiated 0.1 cm^3 rectal volume) <200 Gy. For the urethra, the $D10\%_{urethra}$ (minimum dose to the maximally irradiated 10% of the urethral volume) was <150% of the prescribed dose. $D30\%_{urethra}$ (minimum dose to the maximally irradiated 30% of the urethral volume) was <130% of the prescribed dose.

The mean prescription dose for LDR-BT was 145 Gy (range, 140–160). The clinical target volume (CTV) included the prostate. According to the criteria of the American Association of Physicists in Medicine (AAPM), post-implantation CT dosimetry was recommended 4–6 weeks after BT [13].

The total dose administered to patients treated with HDR-BT ranged from 30 to 36 Gy (mean prescribed dose, 32 Gy). The HDR doses were administered in 2–4 fractions of 7 Gy (11 patients), 9 Gy (38 patients), or 10 Gy (26 patients). The number of implants ranged from 1-3, as follows: one implant ($n = 3$), 2 implants ($n = 40$), and 3 implants ($n = 32$), with one week between implants. Prior to administering the second fraction a CT scan was performed to verify and reposition the needles if necessary (in these cases, a new dosimetric plan was created). A mean of 14 (range, 12–16) plastic tubes were used to guide the implant.

The CTV for HDR-BT included the prostate gland and, if necessary, the seminal vesicles. The following dose constraints were recommended: V100 $\geq$95% of the CTV; D90 >100% of the prescribed dose.

Table 1
Patient characteristics at initial diagnosis and at salvage treatment (n = 119).

	HDR-BT (n = 75)	LDR-BT (n = 44)	p-Value
Initial diagnosis			
Mean age (range)	62.1 (47–75)	60.4 (47–71)	0.129
Risk group			
Low	26 (35%)	6 (14%)	
Intermediate	26 (35%)	20 (45%)	0.044
High	23 (30%)	18 (41%)	
Gleason score			
6	35 (47%)	20 (46%)	
7	21 (28%)	18 (41%)	0.100
8–10	15 (20%)	5 (11%)	
Indeterminate	4 (5%)	1 (2%)	
Median PSA in ng/ml, (range)	8.9 (3.5–42.1)	14.2. (3.2–167)	0.002
Primary treatment (technique)			
3D-EBRT	41 (55%)	42 (96%)	0.000
IMRT	8 (11%)	1 (2%)	
LDR-BT	23 (30%)	0	
Others	3 (4%)	1 (2%)	
ADT			
Yes	34 (45%)	23 (52%)	0.464
No	41 (55%)	21 (48%)	
PSA nadir post-EBRT ng/mL (range)	0.5 (0.01–3.03)	0.4 (0.01–4.34)	0.631
Salvage treatment			
Median PSA ng/ml (range)	4.1 (1.5–16.7)	3.6 (1.02–11)	0.150
Gleason score			
6	11 (15%)	10 (23%)	
7	25 (33%)	16 (36%)	0.002
8–10	33 (44%)	4 (9%)	
Indeterminate	6 (8%)	14 (32%)	
Nadir PSA post-salvage BT ng/mL	0.18 (0.01–14)	0.31 (0.01–6.08)	0.559
ADT			
Yes	22 (29%)	8 (18%)	0.176
No	53 (71%)	36 (82%)	
Time to BF from initial treatment to salvage BT			
<30 m	11 (15%)	3 (7%)	0.200
>30 m	64 (85%)	41 (93%)	
Treatment technique			
Mean BED Gy^2 α/β 1.5 Gy	220 Gy (90–230)	170 Gy (120–250)	0.213

HDR-BT: high dose rate brachytherapy; LDR-BT: low dose rate brachytherapy; BT: brachytherapy; EBRT: external beam radiation therapy; IMRT: intensity-modulated radiation therapy; BED: biologically equivalent dose; Gy: gray; ADT, androgen-deprivation therapy.

The mean D90 (dose to 90% of the prostate volume) was 123.8% (range, 98–184). The mean D90 values for the HDR and LDR groups were, respectively, 108% (range, 98–120) and 139.6% (101–184).

Contouring of the urethra, rectal wall, and balloon catheter (urinary bladder) was performed according to the following dose volume constraints: 120% of prescription dose (PD) for the maximum urethra dose, and maximum rectal dose ≤100% of the PD.

HDR-BT was performed with an encapsulated ^{192}Ir source (Microselectron®, Nucletron). The needles were removed immediately after irradiation, and patients were discharged in most cases one day after the procedure.

Biologically equivalent doses (BED) were calculated for both LDR and HDR implants using a α/β ratio of 1.5 [13]. The median BED was 170 Gy^2 (range, 120–250) for the LDR group and 220 Gy^2 (range, 90–230) for HDR group.

Follow up after salvage BT consisted of clinical examination and PSA testing every 3–6 months for the first 2 years and annually thereafter. Urinary and bowel function were assessed at each visit.

Endpoints

The primary endpoint was PSA relapse-free survival (RFS) after salvage BT. The Phoenix definition of biochemical relapse (PSA nadir + 2 ng/ml) was used in most cases. Cause-specific survival (CSS) and disease-free survival (DFS) were assessed. The CSS was defined as the time from salvage BT to death from prostate cancer or unknown causes, and DFS defined as the time from salvage BT to clinical progression or censoring at the date of the last contact. Toxicity was graded according to the Radiation Therapy Oncology Group (RTOG) scale.

Potential predictors of salvage BT outcomes

A wide range of variables were evaluated as potential predictors of BF. Variables related to the primary treatment included the following: treatment modality (^{125}I BT vs. EBRT); EBRT dose (>72 Gy or ≤72 Gy); initial PSA (iPSA); T stage; initial Gleason score (<6, 7, or 8–10); and D'Amico risk group. Variables assessed prior to or after salvage BT included: biochemical-free survival interval (bFSI) after primary treatment; age; PSA value; ADT (yes vs. no); Gleason score prior to salvage BT; and PSA nadir after salvage BT.

Statistical analysis

The SAS software, v.12 (SAS Institute, Cary, NC) was used to perform the statistical analyses. Descriptive statistics were performed. The 5-year actuarial PSA-RFS, DFS, OS, and CSS were calculated using the Kaplan–Meier method. Survival rates were compared using log-rank statistics. A multivariate analysis was performed with Cox regression modelling. Statistical significance was set at $p < 0.05$.

Results

A total of 119 patients who underwent salvage BT were included in the study. Of these, 75 (63%) underwent HDR-BT and

44 (37%) LDR-BT. Overall, 38 patients (32%) developed biochemical progression after salvage therapy, with a median time to relapse of 24 months.

At a median follow-up of 52 months (range, 4–186), the 5-year actuarial PSA-RFS was 71% (95% confidence interval [CI], 65.9–75.9%) (Fig. 1). Of the 38 patients who developed BF after salvage BT, 14 (32%) had been treated with the LDR technique and 24 (32.5%) with HDR.

The 5-year PSA-RFS was: LDR, 79% (95% CI, 71–83) vs HDR, 65% (95% CI, 60–72) ($p = 0.063$, log-rank test; Fig. 2) and 5-year CSS: LDR, 97% (95% CI, 94–100) vs HDR, 93% (95% CI, 90–96) ($p = 0.44$, log-rank test; Fig. 3).

A total of 10 patients died during follow-up; of these, 4 deaths were due to causes other than PCa.

The median PSA nadir at the last follow-up after salvage BT was 0.18 ng/ml (range, 0.01–14) for the HDR group and 0.30 ng/ml (0.01–6.08) for the LDR group.

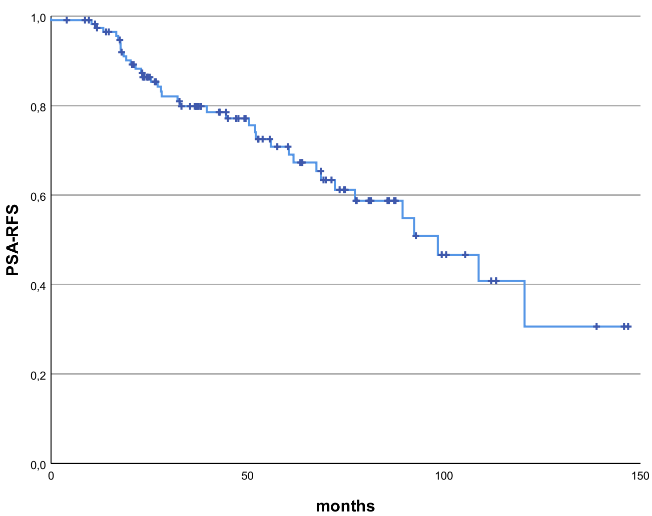

Fig. 1. Prostate-specific antigen (PSA) relapse-free survival (RFS) for all patients ($n = 119$).

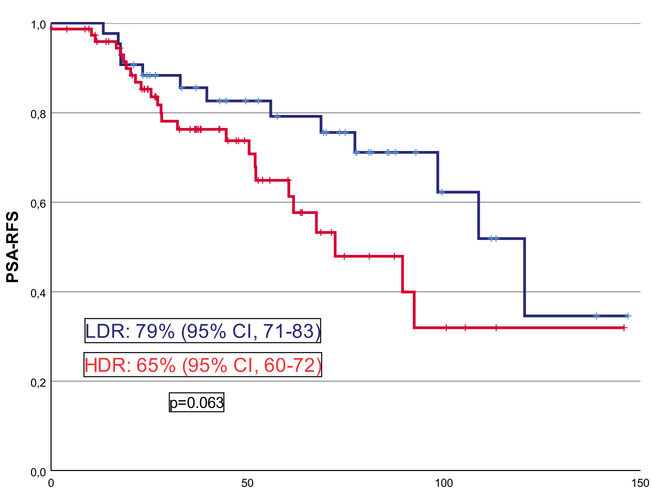

Fig. 2. Prostate-specific antigen relapse-free survival (PSA-RFS) for high-dose rate (HDR) and low-dose rate (LDR) salvage brachytherapy.

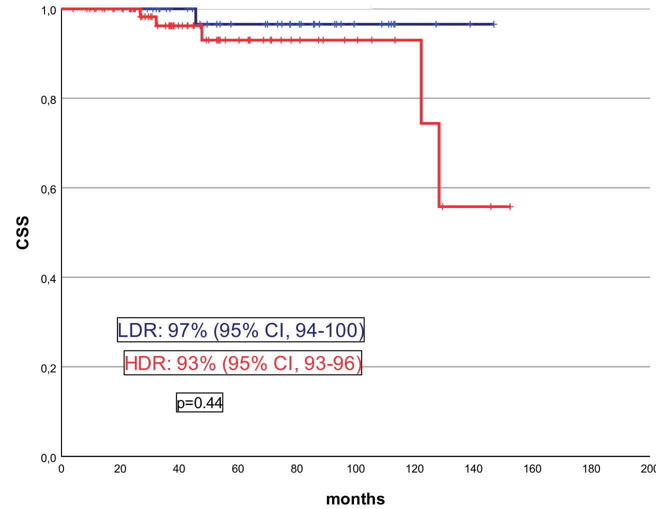

Fig. 3. Cause-specific-survival (CSS) for high-dose rate (HDR) and low-dose rate (LDR) salvage brachytherapy.

At the time of salvage BT, 8/44 patients (18%) in the LDR group and 22/75 (29%) in the HDR group were prescribed hormone therapy (HT). However, most patients (82% and 71%, respectively, in the LDR and HDR groups) did not receive HT; the mean PSA nadir values in this subset of patients were 0.9 ng/mL (LDR) and 1.59 ng/mL (HDR) ($p = 0.47$). Similarly, no significant differences in PSA nadir values were observed between the patients treated with or without HT, nor between the LDR and HDR groups overall.

On the Cox multivariate analysis (Table 2), two variables were significantly associated with PSA-RFS: (1) PSA nadir after salvage BT ($p < 0.001$, relative risk [RR] = 1.288, 95% CI [1.18–1.40) and (2) time to BF (<=30 vs. >30 months) from primary radiotherapy ($p = 0.014$, RR = 3.162; 95% CI, 1.26–7.91).

A total of 39 patients (33%) developed acute urinary toxicity ≤grade (G) 2, most commonly increased frequency, urgency, and dysuria. No cases of G4 or G5 acute genitourinary (GU) toxicities were observed. Twenty-two patients (18.5%) developed incontinence requiring the use of pads. Late G3 GU toxicities occurred in 28 patients (23.5%: HDR group = 21.3% vs. LDR group = 27.3%, $p = 0.75$. These G3 toxicities included one fistula, 13 cases of haematuria (all of which were resolved with conservative management), and 13 cases of urethral stricture (all corrected with urethral dilation). No cases of severe (≥G3) gastrointestinal (GI) toxicity were observed.

We compared the two groups to assess differences in G3 GU toxicity rates. In the LDR group, 12 patients (27.3%) developed G3 GU toxicity versus 16 patients (21.3%) in the HDR group ($p = 0.756$). The type of GU toxicity differed according to the technique used. A total of 13 patients (11%) developed urethral strictures (9 in the LDR group [20.5%] and 4 in the HDR group [5.3%]). Twenty-two patients developed urinary incontinence: 2 patients (4.5%) in the LDR group and 20 (26.7%) in the HDR group ($p = 0.001$).

The mean D90 value was higher ($p = 0.000$) in the LDR group. However, the D90 value did not influence the type of GU toxicity in either group ($p = 0.098$).

Overall, 33 (27.7%) patients (HDR, $n = 25$ vs. LDR, $n = 8$; $p = 0.09$) developed loco-regional failure (prostate and/or pelvic lymph nodes).

A total of 20 patients (HDR-BT: 14/75 [19%] and LDR-BT: 6/44 [14%]) presented distant metastases (extra-pelvic nodes, or bone and/or visceral metastases), without significant between-group differences ($p = 0.61$).

Table 2
Multivariate analysis for PSA relapse-free survival using Cox model.

Variable	B	*p*-Value	RR	RRinf	RRsup
PSA nadir after salvage BT	0.253	<0.001	1.288	1.18	1.406
Time to BF from initial RT (≤30 m vs >30 m)	1.151	0.014	3.162	1.26	7.91

Abbreviations: RR, relative risk; RRinf, relative risk inferior; RRsup, relative risk superior; BT, brachytherapy; BF, biochemical failure; RT, radiotherapy; PSA, prostate-specific antigen; M, months.

Discussion

The findings of this multi-institutional study show that both HDR-BT and LDR-BT provide comparable efficacy and toxicity outcomes in patients undergoing salvage treatment for locally-recurrent PCa after primary radiotherapy. To our knowledge, the present study includes the largest number of patients treated with salvage BT reported to date.

The clinical outcomes reported here are consistent with our previous study [7] as well as with other published reports [5,6,8–12,14,15], providing further support for the efficacy of salvage BT in appropriately selected patients (Table 3). Kollmeier et al. [12] recently published results from the first study comparing HDR-BT to LDR-BT as salvage treatment in patients with locally-recurrent PCa after primary EBRT. In that study, 98 patients underwent salvage BT (LDR = 37; HDR = 61), with a 3-year PSA RFS of 60.1% at a median follow-up of 31 months. There were no significant between-group differences in efficacy or toxicity between the two BT modalities, findings that are in line with our results, leading those authors to conclude that these two techniques are equally effective with encouraging biochemical control rates in appropriate selected patients. Several studies [7,10,16] have examined LDR and HDR separately, finding that both techniques are effective salvage therapies. These findings, together with those of previous reports [7,12], suggest that salvage BT should be offered to patients with suitable clinical and biological characteristics.

Although we did not find any significant differences on any of the outcome measures between these two BT modalities, it is

Table 3
Salvage brachytherapy series after radiation failure.

Study, year	Salvage brachytherapy Doses	N	Pre-salvage PSA (ng/ml)	Median f/u (years)	Outcome	Grade 3/4 GU late toxicity
Wong et al. [24]	LDR 126 Gy	17	4.7	3.7	75% 4-y FFbF¶	41%
Nguyen et al. [17]	LDR 137 Gy◇	25	9.46	3.8	70% 4-y FFbF†	13%
Lee et al. [25]	LDR 90 Gy◇◇	21	3.8	3	38% 5-y FFbF¶	0%
Aaronson et al. [26]	LDR 144 Gy	24	3.4	2.5	89% 3-y FFbF†	0%
Vargas et al. [27]	LDR	69	<10 (90%)	5	74% 5-y FFbF	9%
Burri et al. [16]	LDR 135 Gy ^{125}I 110 Gy ^{103}Pd	37	12.6	7.2	65% 5-y FFbF 54% 10-y FFbF†	11%
Peters et al. [9]	LDR 144 Gy	20	4.7	3	70% 5-y FFbF	5%
Crook et al. [21]	LDR 144 Gy	92	<10 (100%)	4.5	NR	14%
Chen et al. [6]	HDR 36 Gy	52	9.3	5	51% 5-y FFbF†	2%
Wojcieszek et al. [8]	HDR 30 Gy	83	3.1	3.4	67% 5-y FFbF	13%
Yamada et al. [10]	HDR 32 Gy	42	<10 (88%)	3	69% 5-y FFbF	10%
Kollmeier et al. [12]	HDR 32 Gy* LDR 125 Gy ^{103}Pd	98	3.8	2.6	60% 3-y FFbF	9%
Henríquez et al. [7]	HDR 32 Gy* LDR 145 Gy	56	5	4	77% 5-y FFbF†	HDR GU/GI G3 21%/2%; LDR GU/GI G3 24%/0% G4 0%/ 2.7%
Present series (2018)	HDR 32 Gy* LDR 145 Gy	119	3.8	4.3	Global 71% 5-y FFbF (95% CI, 65.9–75.91%); LDR 79% 5-y FFbF (95% CI, 71–83%); HDR 65% 5-y FFbF (95% CI, 60–72%)	HDR GU G3 22%; LDR GU G3 27%

Abbreviations: LDR indicates low-dose rate; HDR, high-dose rate; bDF, biochemical disease-free survival; FFSR, freedom from second relapse; NR, not reported; GU, genitourinary; GI, gastrointestinal; G3, grade 3; G4, grade 4.
* Most patients treated with that dose.
¶ Failure defined as ASTRO definition.
† Failure defined as Phoenix definition.
◇ Median minimum peripheral dose.
◇◇ Minimum peripheral dose.

important to note that the HDR group presented several favourable pre-treatment and patient characteristics compared to the LDR group, including a higher BED (220 Gy vs. 170 Gy), a lower proportion of intermediate and high-risk patients at diagnosis (65% vs 86%), and a higher proportion of patients receiving ADT (29% vs. 17%). Despite these advantages, biochemical control rates were higher (non-significantly) in the LDR group. This difference is probably attributable to several factors, primarily the higher percentage (20% vs. 11%) of patients in the HDR-BT group with high Gleason scores (GS: 8–10) at diagnosis, the greater proportion of patients in the HDR group with a positive biopsy at relapse who had Gleason scores >7 (44% vs. 9%), and the shorter time from primary treatment to BF in the HDR group.

Numerous authors have reported that PSA kinetics—including PSA velocity [17], PSA nadir after salvage BT [18], pre-salvage PSA [7,16,18,19,21], and PSA doubling time (PSADT) [20]—are predictive of treatment outcomes in patients undergoing salvage BT. Nonetheless, these predictors are based on data from small series and thus must be interpreted cautiously. Due to the retrospective nature of our study, we were not able to analyse the predictive value of all these variables. In our series, in line with the findings by Grado et al.[18], the PSA nadir after salvage BT was the best predictor (multivariate analysis) of RFS.

Several retrospective studies [7,16,19] and one recent prospective trial [21] have shown that a PSA level <10 ng/ml prior to salvage BT is a valuable indicator of treatment efficacy. Based on the available data, it is clear that patient selection has a substantial influence on treatment outcomes. Burri et al. [16], Zelefsky et al. [19], and Henríquez et al. [7] all found a correlation between pre-salvage PSA levels <10 ng/ml and better outcomes. In the RTOG 0526 trial [21], all of the patients who underwent salvage LDR-BT had PSA levels <10 ng/ml. Although Kollmeier et al. [12] did not find a statistically significant correlation between pre-salvage PSA and BF, the pre-salvage PSA in most cases was <10 ng/mL. By contrast, the Netherlands trial [22] reported a 5-year biochemical RFS rate of only 28% at a median follow-up of 74 months. The poor outcomes in that study are likely attributable, at least partially, to the relatively high median pre-salvage PSA levels (8.6 ng/ml), suggesting the presence of a greater disease burden in those patients, which is a predictor of worse results in the salvage BT setting. The good results in our series appear to be, at least partially, attributable to the relatively low pre-salvage PSA levels in the two groups (4.1 and 3.6 ng/ml in the HDR and LDR groups, respectively). This finding supports the overall body of published evidence [11] suggesting that salvage BT should ideally be performed before the PSA exceeds 10 ng/ml.

Some studies have reported that the PSA nadir after salvage BT may be a prognostic factor for tumour control. Grado et al. [18] found that a PSA nadir <0.5 ng/ml after salvage BT was associated with better biochemical DFS. Shimbo et al. [23] reported similar results in a small series of patients, finding that those with a PSA nadir <0.2 ng/ml after salvage treatment had a better prognosis in terms of RFS. In our previous study [7], PSA nadir >1 ng/ml after salvage BT was associated with worse RFS, although this association was not statistically significant ($p = 0.087$). In the present study, the PSA nadir was strongly associated with better RFS ($p < 0.001$).

The Gleason score at diagnosis is another prognostic indicator of poor biochemical control in patients undergoing salvage BT. Several primary tumour characteristics (e.g., clinical stage >T2c, PSA >20 ng/mL, and Gleason score 8–10) have been associated with an increased risk of BF [1]. Indeed, this is logical given that these factors suggest the presence of co-existing metastases [1]. However, in the salvage setting, only limited data are available regarding the prognostic value of the Gleason score at diagnosis of the primary tumour. In this regard, the recent RTOG (NRG) 0526 trial excluded patients with unfavourable risk disease at diagnosis. In our series, the univariate analysis showed that patients with an initial Gleason score $\geq$8 had worse biochemical control outcomes after salvage BT, although this was not statistically significant on the multivariate analysis. Currently, there is a lack of consensus about whether or not the Gleason score should be considered an exclusion criterion for salvage BT.

Patients with a long PSADT (>30 months) have a more favourable prognosis than those with a shorter PSADT, suggesting that the biological behaviour of the tumours in these patients is more indolent and thus this patient subset is more likely to benefit from salvage therapy. In this regard, Kollmeier and colleagues [12] found that PSADT was the most significant predictor of PSA RFS and distant metastasis-free survival. In that study, patients with PSADT >12 months had significantly better biochemical outcomes. Similarly, Moman et al. [20] found that patients with a PSADT >10 months had a longer biochemical recurrence-free survival (BRFS) interval than those with PSADT <10 months. Nonetheless, the PSADT cut-off point at which patients are likely to present a high risk of BF—thus making salvage BT risky—remains undefined and should be addressed in future trials [11].

The BRFS interval after primary treatment appears to be associated with better outcomes in patients undergoing salvage BT. Chen et al. [6] found that the BRFS was close to significance as a predictor of BF in patients with a long disease-free interval after initial radiotherapy. In our study, patients with a BRFS from initial treatment >30 months had a better BRFS after salvage BT ($p = 0.014$). This result is consistent with the findings from our previous study [7], suggesting that patients with a longer BRFS interval after primary treatment may be more likely to present locally-recurrent disease versus regional or distant recurrence.

Treatment-related toxicity

The potential for increased radiation-induced toxicity in the salvage setting represents an important clinical challenge. In the published literature, toxicity associated with salvage BT varies widely due to the many variables that contribute to toxicity, which may include the following factors: patient selection; the total salvage BT dose; presence of persistent grade $\geq$2 late GU/GI after primary EBRT; prostate volume; constraints applied to the organs at risk; dose distribution heterogeneity; early administration of salvage BT after post-EBRT BF; and ADT, among other factors [11].

In recent years, efforts to limit doses to the rectum and urethra have led to a lower incidence of toxicity in patients undergoing salvage BT. The primary endpoint of the phase II RTOG 0526 trial [21] was late treatment-related grade 3 or higher GU/GI toxicity 9–24 months after salvage ^{125}I LDR-BT in selected patients with low- or intermediate-risk PCa with BF post-EBRT. The incidence of adverse events (AE) was estimated to be $\leq$10%, with $\geq$20% of these events considered unacceptable. Of the 92 patients evaluated for toxicity, at a median follow-up of 54 months only 14% of patients had late grade 3 GI/GU AEs, with no treatment-related grade 4 or 5 AEs. Only the implant dosimetry (V100) was predictive of late AE, leading the authors to suggest that the V100 may be a surrogate for bladder neck dose, and therefore it could be beneficial to avoid prescribing the full radiotherapy dose to this region. Kollmeier et al. [12] reported a late grade 3/4 GU toxicity rate of 9%, but no significant differences in toxicity between patients treated with LDR-BT or HDR-BT. Those authors did, however, observe a higher rate of acute urinary retention and late urethral strictures (8:1) in the HDR group. By contrast, the LDR group presented a higher peak in urinary symptoms (IPSS scores), although most urinary scores returned to baseline levels 24–36 months after treatment.

Moman et al. [20] reported late grade 3 GU toxicity rates of 20% in 31 patients treated with salvage LDR-BT (prescribed dose: 145 Gy). The higher toxicity was probably due to the higher D90 (median, 196 Gy), V150 (median, 74%), and V200 (median, 33%) in the LDR group. At a median follow-up of 5.6 years, Wojcleszek et al. [8] reported an incidence of late grade 3 GU toxicity of 13% in 83 patients treated with salvage HDR-BT. Yamada et al. [10] reported a 10% late grade 3 toxicity rate in patients treated with salvage HDR-BT.

In our series, the reported D90 (median, 123.8 Gy) was higher in patients treated with LDR-BT. However, when we compared the two groups, we found no association between the D90 values and the type of urinary toxicity. It should be noted, however, that the two techniques have different toxicity patterns: urethral stricture is more common in patients who undergo LDR-BT whereas incontinence is more common in patients treated with HDR-BT.

Although the percentage of patients with late G2 GU toxicity in our series was relatively high (28%), this was lower than the rates reported in other studies (Moman 39%, Wojcieszek 39%, Yamada 48%). The late G3 GU toxicity rates in our study were slightly higher (23.5%) than other published series, but similar to those reported by Moman et al. (20%). This higher G3 GU toxicity in our series is probably multifactorial, and may be due to (1) inadequate patient selection, (2) absence of a validated instrument (e.g., IPSS) to assess urinary toxicity risk prior to BT, (3) the BT technique used, (4) the fractionation schedule and dose administered to the primary tumour, and by the time of failure, among other factors. In this regard, it is essential to carefully evaluate the risk of pelvic interventions manoeuvres' to minimize the likelihood of inducing severe (grade 3–4) toxicity. One patient in our series developed a prostate-urethrorectal fistula after biopsy of an anterior rectal lesion. Another patient required a cystectomy due to infection after implantation of an artificial urinary sphincter to treat incontinence caused by post-BT transurethral resection.

It is difficult to compare reported toxicity outcomes among the published case series for salvage BT due to the inherent bias of retrospective studies, including ours (except for phase II studies by Yamada et al. and Crook et al). However, the long inclusion period in our series (2002–2016) could partly explain our toxicity outcomes, which were similar to those reported by Moman et al., who also included patients over an extended time period (1994–2009).

Strengths and limitations

The main limitations of this study are the retrospective design and differences among the participating centres with regard to (1) metastatic workup at relapse, (2) the limited use of validated instruments to assess urinary-related quality of life prior to salvage BT, (3) inter-center variability in ADT prescriptions and the consequent potential impact of ADT on biochemical control, and (4) differences in other patient and treatment-related parameters that might have impeded our ability to identify toxicity-related factors. By contrast, the main study strengths are the large sample size, long follow-up, and the identification of several significant prognostic factors for PSA RFS, and the confirmation that these two BT techniques present similar efficacy.

Due to the risk of urinary toxicity in patients previously treated with EBRT, careful selection of patients for salvage BT is crucial. Our recommended selection criteria, based on our data and a review of the literature, include: (1) low or intermediate risk disease at diagnosis; (2) biopsy-proven local recurrence >24 months after primary treatment; (3) life expectancy >5 years; (4) no distant metastasis using novel imaging; (5) PSADT >6 months; (6) minimal toxicity from prior EBRT (GU/GI grade ≤ 2); (7) good urinary function (IPSS <15, American Urological Association score <10) before salvage BT; (8) well-defined dose constraints. In the future, partial prostate focal salvage implant should be considered to reduce toxicity and dose painting.

The results of this study show that HDR and LDR BT appear to be equally effective salvage treatments in patients with biochemical failure after primary radiotherapy. Both treatment modalities offer encouraging rates of biochemical control with acceptable toxicity. Several variables—including nadir PSA after salvage BT and the biochemical failure-free interval after primary treatment—are prognostic factors for better outcome after salvage BT. Appropriate selection of patients for salvage BT is crucial.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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