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Original article

Salvage high-dose-rate brachytherapy for locally recurrent prostate cancer after primary radiotherapy failure

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ABSTRACT

Background and purpose: To evaluate high-dose-rate brachytherapy (HDR BT) as a salvage modality for locally recurrent prostate cancer after primary radiotherapy failure.
Materials and methods: Eighty-three prostate cancer patients, who locally relapsed after radiotherapy, were treated with salvage HDR BT. The schedule was three implantations, every two weeks, with 10 Gy per implant, to a total dose of 30 Gy. Acute and late toxicity rates were evaluated. Overall survival (OS) and biochemical control were calculated using Kaplan–Meier method.
Results: Median follow-up after salvage HDR was 41 months. The 3-year and 5-year OS were 93% and 86%, respectively. The 3-year and 5-year biochemical disease-free survival (bDFS) were 76% and 67%, respectively. The single factor associated with biochemical control was time to achieve salvage PSA nadir (p-.006). OS was linked significantly with primary nadir level (p-.001) while primary biochemical relapse interval was of borderline significance (p-.07).
Conclusions: Salvage HDR BT is a promising treatment option for patients with localized relapse of previously irradiated prostate cancer. Lower PSA nadir after primary radiotherapy and longer primary disease-free interval influence the outcome.
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Due to the increasing use of external beam radiotherapy (EBRT) the number of cured prostate cancer patients has grown significantly over the past two decades. However, even one third of them undergo biochemical failure after the primary radiotherapy [1–4], which may be linked to distant metastases, local failure or both [5,6]. Moreover prostate apex is more exposed for radiotherapy failure than other sections [7]. Therefore, an effective radical treatment is needed for patients suffering from localized prostate cancer relapse [8,9].

High-dose-rate brachytherapy (HDR BT), has gained much interest due to its ability to deliver localized radiation dose to the prostate gland while minimizing normal tissue exposure. The method provides ablative doses per fraction (i.e. >7.5 Gy) for the whole prostate gland with even higher doses reached inside the target (i.e. >100%). Another advantage is overall shorter treatment time, compared to conventional EBRT, which probably enhances the radiation effect inside the target volume.

A number of studies present the efficacy and safety of the salvage HDR BT. The first published research conducted on a group of 7 men brought results of 58-month median follow-up and 5-year disease-free survival of 71% [10]. Chen et al. presented results for 52 patients with a median follow-up of 59.6 months, and 5-year overall survival (OS) and biochemical relapse-free survival (bDFS) of 92% and 51%, respectively [11]. Yamada et al. enrolled 42 patients into phase II prospective trial, and achieved 36-month median follow-up, 5-year OS of 79%, and 5-year bDFS of 68.5% [12]. Although Tharp et al. reported that only 1 of 7 patients suffered from grade 2 rectal injury, while 5 patients developed urethral strictures (grade 2) (including 2 patients with grade 3 urethral necrosis, and 2 with grade 3 perineal pain), the salvage HDR BT toxicity rates have improved significantly over the last few years. Recent studies report just mild to moderate (i.e. ⩽grade 2) acute GU toxicity in 78–98% of patients, and mild to moderate late GU toxicity in 86–98% of patients [11,12]. Similar trends are observed for acute and late GI toxicity, with no patients suffering from grade 4, and no more than 3% suffering from grade 3 toxicity. Given these benefits, HDR BT is becoming an attractive option for salvaging locally recurrent prostate cancer.

The goal of this retrospective study is to evaluate salvage HDR BT of the recurrent prostate cancer on a large group (83) of previously irradiated patients. HDR BT boost was applied in prostate

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cancer treatment for the first time in our center in 2003. Due to an increasing number of patients with locally recurring prostate cancer, particularly after primary radiotherapy failure, a new approach for these men was needed immediately. We adapted our prostate cancer HDR monotherapy schedule with decreased dose per fraction (i.e. from 11 Gy to 10 Gy). The first salvage HDR BT implantation was performed in our center in 2008.

Materials and methods

One hundred and three men were treated with salvage HDR BT between 08/04/2008 and 30/06/2014. To achieve the longest follow-up we analyzed only those, who finished brachytherapy before 31/12/2012. Eighty-three men were enrolled into the retrospective analysis. All data were collected from the retrospective chart review.

Primary treatment

Fifty-one men (61%) were treated with external-beam radiotherapy (EBRT). Thirty-two patients (39%) were treated with EBRT combined with one fraction of HDR boost. Median primary PSA peak was 13.7 ng/ml. Median Gleason score was 6. Fifty-eight patients (70%) underwent adjuvant androgen deprivation therapy (ADT) after first prostate cancer diagnosis. Primary ADT duration ranged from one month (52 days) to over 6.5 years (Table 2). Two patients were treated with oral steroidal anti-androgens alone.

Forty-seven EBRT patients (56%) were treated with conventional schedules. Median total dose was 74 Gy (52–76 Gy). Three patients received hypofractionated EBRT (i.e. dose per fraction 2.6 Gy). Five or four-field planning technique was used most often, in 11 and 9 plans, respectively (4–9 fields; median 5). HDR boost patients were treated with EBRT (54 Gy/27 fx) followed by HDR boost (10 Gy). Three-field planning technique was used in 17 patients. Prostate implant needles number ranged from 10 to 18 with a median of 15.

Primary follow-up

Eighty-three patients (53–76 y.o.; median 63 y.o.) failed after primary irradiation. Three patients (4%) relapsed during adjuvant ADT. Twenty-two patients (26%) were diagnosed with local relapse with no prior biochemical relapse. Eighteen (22%) of them were diagnosed using MRI. Forty-four patients (53%) had ADT reassigned. Median time to relapse after primary radiotherapy was 67 months (22–124 months). Median relapse peak PSA was 3.1 ng/ml (0.065–19.9 ng/ml).

Local relapse confirmation

Patients with biochemical recurrence or suspicious lesion in MRI underwent clinical evaluation. Local recurrence was verified in the 12 core biopsy, no earlier than 18 months after radiotherapy. MRI imaged relapses were additionally targeted and sampled (without TRUS/MRI fusion). For biopsies performed outside our center, a pathologist review was required. Gleason score was reported if available. Moreover immunohistochemistry was done (Alpha-methylacyl CoA racemase (AMACR) combined with p63) to confirm prostate cancer relapse. Patients diagnosed with radiation atypia only were excluded from the salvage HDR BT treatment. Gleason sum was available for 44 patients (53%) with a majority of 7 or below. Biochemical relapse patients with negative biopsy remained under active surveillance (i.e. MRI after 3–6 months, biopsy repeated after 6 months) until positive biopsy.

Table 2
Patient characteristics.

Characteristics	Median (range)	$n = 83$ (100%)	
		n	%
Primary treatment age	63 (53–76)		
Age at salvage HDR	70 (57–81)		
Primary peak PSA	13.7 (3.11–366)		
Primary T stage			
T1c		33	40
T2		44	53
T3		5	6
n/d		1	1
Primary PSA (ng/ml)			
<10		24	29
10–20		32	39
>20		21	25
n/d		6	7
Primary Gleason sum			
⩽6		50	60
7		17	20
⩾8		3	4
n/d		13	16
Primary D'Amico risk groups			
Low		16	19
Intermediate		25	30
High		29	35
n/d		13	16
Primary ADT		71	86
Primary ADT duration (months)	13 (1–82)		
Primary prostate volume (cm3)	51.5 (17.8–119.9)		
EBRT		51	61
52 Gy/20 fx (EQD_{2Gy} = 58.2 Gy)*		3	4
70 Gy/35 fx		8	10
72 Gy/36 fx		6	7
74 Gy/37 fx		22	26
76 Gy/38 fx		11	13
n/d		1	1
EBRT + HDR		32	39
54 Gy/27 fx + 10 Gy (EQD_{2Gy} = 80 Gy)*			
Time to relapse (months)	67 (22–124)		
Primary biochemical relapse		61	73
Relapse peak PSA (ng/ml)	3.1 (0.065–19.9)		
Relapse ADT		44	53
Relapse Gleason sum			
⩽6		16	19
7		22	27
⩾8		6	7
n/d		39	47

* EQD_{2Gy} for $\alpha/\beta = 3$; EQD_{2Gy} – equivalent dose in 2 Gy fractions; EBRT – external beam radiotherapy; HDR – high-dose-rate brachytherapy; ADT – androgen deprivation therapy; PSA – prostate-specific antigen.

Every patient was carefully examined after histological confirmation of the recurrence. X-ray chest, bone scan, TRUS, abdominal and pelvic ultrasound were obligatory at the beginning of salvage HDR BT. Later, as we gained more insight into salvage HDR BT we required abdominal and pelvic computed tomography. Additionally, for patients with suspicion of extraprostatic extension an MRI scan was performed.

Patients who suffered from urge incontinence (pharmacoresistant), frequent urination (⩾6 times per night or hourly or more frequent) or gross hematuria were excluded from the study. Urodynamics testing was not routinely performed. Radical prostatectomy patients were excluded. Due to the salvage goal of HDR BT our decision was to treat patients with every prostate volume (i.e. including <15 ccm and >60 ccm) with no pubic interference. Written informed consent was required from every patient.

Salvage HDR procedure

Each qualified patient was planned for three fractions of HDR, 10 Gy each to a total dose of 30 Gy. Biologically equivalent doses

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