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Original article

Health-related-quality-of-life and toxicity after single fraction 19 Gy high-dose-rate prostate brachytherapy: Phase II trial

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ABSTRACT

Purpose: To evaluate the safety, tolerance and impact on health-related-quality-of-life (HRQoL) of the high-dose-rate brachytherapy of 19 Gy (BRT-HDR-19 Gy) single fraction in prostate cancer.
Methods: From January 2014 to July 2016, 43 patients with low/intermediate risk were treated with BRT-HDR-19 Gy. The patients were monitored prospectively for toxicity and HRQoL.
Results: The median age, initial PSA and the International Prostate Symptom Score (IPSS) were 71 years (55–78), 7.0 ng/mL (4.2–17.8) and 5 (0–14) respectively. 44% were low-risk and 56% intermediate-risk. Median CTV-V100 (where Vn is the fractional volume of the organ that receives *n*% of the prescribed dose) was 96.5%, Urethral-Dmax 106% and rectum-2 cc (the dose to 2 cc of rectal wall) 53%. After a median follow-up of 20 months (4–26), acute grade-2 genitourinary (GU) toxicity occurred in 4 patients (9%) and none presented acute gastrointestinal (GI) toxicity. Similarly, four patients (9%) presented late GU grade-2 toxicity. No grade-3 toxicity occurred.
In terms of HRQoL, there was a statistically significant decline in Expanded Prostate Cancer Index Composite (EPIC) urinary urgency/obstructive domain at month 3 ($p = 0.047$), and returned to baseline by month 6. Mean EPIC urinary incontinence, bowel, sexual and hormonal domains did not present significant post BRT-HDR-19 Gy changes.
Patients rated their satisfaction at 6 months as "very-satisfied" (23%) or "extremely-satisfied" (77%).
Conclusions: BRT-HDR-19 Gy demonstrates excellent results in terms of toxicity, tolerance, safety, patient satisfaction and HRQoL.
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Radiotherapy for prostate cancer can be delivered as external beam radiotherapy (EBRT) or as interstitial irradiation by means of brachytherapy (BRT). In comparison with EBRT, BRT is characterized by an unparalleled dose fall-off gradient that allows for highly conformal coverage of the prostate with superior normal tissue sparing. This translates into higher tumor control with improved rates of adverse events [1].

Two types of BRT are commonly used to treat prostate cancer: low dose rate (LDR), involving the permanent implantation of radioactive seeds, and high-dose-rate (HDR), where the dose is delivered from a single high- activity radioactive source that 'steps' along catheters temporarily implanted into the prostate. Although there are few randomized trials comparing different methods of radiation delivery, available data strongly suggest that treatment with BRT, alone or combined with external beam radiotherapy (EBRT), results in higher disease control rates than achieved with EBRT alone [2,3].

LDR BRT is used more widely than HDR BRT, although advocates of the HDR technique highlight several potential advantages of this approach. The precise control over dose delivery with HDR BRT is not readily achievable with LDR BRT due to several factors: seed or strand migration, post implant prostatic swelling, and the uncertain periprostatic margin, all of which can contribute to sub-optimal dose distributions.

HDR BRT meets the objective of conformal dose escalation optimally by exploiting the radiobiological advantage of extreme hypofractionation while ensuring superior three-dimensional (3D) dosimetry.

There are a large number of reports demonstrating the efficacy of HDR BRT as monotherapy with multi-fraction schedules for localized prostate cancer and recent publications reporting excellent long-term biochemical failure-free survival support HDR as

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an innovative alternative to LDR BRT for low- and intermediate-risk disease [4,5]. However, determination of the optimal HDR BRT schedule for prostate cancer remains a challenge.

The longest follow-up for clinical results is with moderate hypofractionation (four to nine fractions) [6–8]. Nevertheless, consistent data are also reported with ultra hypofractionated protocols (one to three fractions). Two-fraction schedules, delivering doses of 24–27 Gy [9,10] appear well tolerated and are associated with low acute toxicity with similar tumor control rates, although with shorter median length of follow-up. Henceforward, the emergence of extreme-hypofractionation with only one to two treatments makes HDR logistically comparable with LDR BRT.

Moreover, in recent dates, the need to measure value in healthcare has become increasingly pressing and quality of life issues have gained prominence for treatment decision-making [11].

To date, there is published evidence on single fraction HDR BRT coming from 4 different groups [12–15]. These studies have shown good results in terms of toxicity, but there is little evidence exploring patient reported outcome measures (PROMs) and in particular HRQoL [14].

Therefore, the primary endpoint of this study was to evaluate the safety, tolerance and impact on HRQOL of the BRT-HDR-19 Gy, secondary endpoint was to measure the efficacy, in terms of cancer control and satisfaction of the patients undergoing the examined treatment protocol.

Methods

Inclusion criteria to participate in this prospective non-controlled phase II trial included: histologically confirmed prostate adenocarcinoma, life expectancy longer than 10 years, clinical stage T1–T2, Gleason score 6 or 7, PSA level <20 ng/mL and prostate volume <60 cc. Exclusion criteria were: evidence of distant or nodal metastases, previous transurethral resection of the prostate (TURP), International prostate symptoms score (IPSS) >18, inflammatory bowel disease and patients unsuitable for general or spinal anesthesia.

Local staging studies included multiparametric Magnetic Resonance Imaging (mpMRI) of the prostate. Two specialists in uroradiology evaluated all MRI studies.

Brachytherapy procedure

All patients were treated with a real-time MRI-TRUS fusion BRT-HDR technique. The MRI-TRUS fusion technique has been previously reported [16,17]. Briefly, the T2 axial volumetric sequence (VISTA) is imported directly from the picture archiving and communication systems (PACS), and sent to the Oncentra® Prostate v. 4.1.6 software (Elekta AB, Stockholm, Sweden). Magnetic resonance images are reconstructed and segmented. Target volumes, including prostate, urethra, bladder, and rectum were contoured.

A transrectal sagittal volumetric ultrasound image is immediately acquired with images obtained every 0.5 degrees. A rapid reconstruction algorithm converts the series of 2D images into a 3D volume, which is then displayed in axial, sagittal, and coronal views and transferred to the fusion module. The MRI and the real-time ultrasound examination are displayed on a split-screen with the possibility of overlaying the images live in one image. A graphical user interface is used for rigid manual registration of the ultrasound and MRI. This interface allows for displacements in three dimensions as well as rotations, until both images are correctly superimposed. The contoured structures are transferred to the ultrasound dataset. These contours may be slightly modified, until a perfect match with the US images is achieved.

The prescription dose was 19 Gy. The dose was prescribed to the planning target volume (PTV) as a minimum peripheral dose.

Steel needles (Elekta, Sweden) 24 cm in length were inserted into the prostate using TRUS guidance, under general or spinal anesthesia. Dwell time optimization was performed using inverse dose–volume histogram-based optimization (DVHO). The homogeneity parameters used for dose optimization aim for prostate V100 >95%, V150 of 25–35%, and V200 <8%, where Vn is the fractional volume of the organ that receives *n*% of the prescribed dose; maximum point dose inside the urethral volume (urethral Dmax) <110%; and the dose to 1 cc of rectal wall (RD1 cc) is limited to <60% of the prescribed dose.

Following treatment, catheters were removed; the patient was awoken and discharged home once recovered from the anesthesia.

Follow-up: toxicity and HRQoL evaluation

The patients were monitored prospectively for toxicity and HRQOL. Toxicity was assessed using the CTCAE, version 3.0, and HRQOL was assessed using the Expanded Prostate Cancer Index Composite (EPIC-26) questionnaire [18], both endpoints were measured at baseline, 1, 3, 6, 12 and 24 months after HDR-BRT. The International Prostate Symptom Score (IPSS) was also completed by the patient at baseline and at each follow-up visit.

A clinically significant decrement was considered an EPIC score decrease greater than one-half of the standard deviation (SD) of the baseline value for each domain [19,20]. Patient satisfaction was evaluated using a five-category predetermined *Likert* scale question (extremely satisfied, very satisfied, moderately satisfied, slightly satisfied and not at all satisfied). The protocol was approved by the Institutional Review Board of the hospital.

Descriptive statistics were calculated (medians and ranges) to summarize the clinical and pathological characteristics of the patients. Complete data were available for all parameters included. All analyses were conducted using Stata 14.2 for Windows (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.). *p*-Value <0.05 was considered statistically significant.

Results

From January 2014 to July 2016, 43 consecutive patients with low/intermediate risk have been treated with HDR-BRT-19 Gy.

Table 1 summarizes the clinical and tumor characteristics. The median age was 71 years (range 55–78 years), median initial PSA 7 ng/mL (range 4.2–17.8 ng/mL) and median baseline IPSS was 5 (range 0–14). Forty-four percent of the patients were low-risk

Table 1
Clinical and tumor characteristics.

Characteristics	Category	*N*	Percentage (%)
Clinical stage	T1c	31	72.1
	T2a	10	23.2
	Ts	2	4.7
Gleason score	6(3 + 3)	25	58.1
	7(3 + 4)	17	39.5
	7(4 + 3)	1	2.4
Risk group	Low-risk	25	56.8
	Intermediate-risk	18	43.2
		Median	Range
Age (years)		71	55–78
PSA (ng/mL)		7	4.2–17.8
IPS score		5	0–14

PSA: Prostate Specific Antigen; IPS: International Prostatic Symptoms.

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