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Original article

High dose rate brachytherapy for prostate cancer: A prospective toxicity evaluation of a one day schedule including two 13.5 Gy fractions

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ABSTRACT

Background and purpose: High dose-rate (HDR) brachytherapy (BT) provides a highly conformal method of dose delivery to the prostate. The purpose of this study is to prospectively determine the toxicity of the treatment protocol of 13.5 Gy × 2 fractions.

Materials and methods: From 2010 through 2017, 119 patients with low (71%) or intermediate-risk prostate cancer were prospectively treated in a single institute with HDR-BT at 13.5 Gy × 2 fractions within one day. Median follow-up time was 4.4 years.

Results: Actuarial rates of no biochemical evidence of disease, overall survival and metastasis-free survival for all patients were 96%,98% and 98%, respectively. The cumulative incidence of acute grade 2 and 3 genitourinary (GU) toxicity was 9% and 2%, respectively. The corresponding incidences of late GU toxicity were 18% and 1%. No grade ≥4 of either type of toxicity was detected. Multivariate analysis showed that having higher international prostate symptom score (IPSS; $P = 0.041$) or higher V_{200} ($P = 0.013$) was associated with a higher risk of experiencing any grade of acute GU toxicity. In addition, patients having a higher IPSS ($P = 0.019$) or a higher V_{150} ($P = 0.033$) were associated with a higher grade >1 acute GU toxicity.

Conclusions: The findings of this study show that HDR-BT 13.5 Gy × 2 as monotherapy was safe and effective for prostate cancer patients with low-intermediate risk.

Prostate cancer is the most common nondermatologic cancer among men in more developed regions [1]. Treatment options that are frequently used include radical prostatectomy, external beam radiotherapy (EBRT) and/or brachytherapy (BT). These treatment options are considered to have comparable efficacy [2]. No consensus has been reached regarding the most appropriate treatment option for localized prostate cancer. Choice of treatment options may be influenced by factors such as patient age and health at the time of diagnosis, life expectancy, tumor stage, prostate-specific antigen (PSA) levels, Gleason score, recommendation of a multidisciplinary health care team, treatment-related convenience and costs, patient values and preferences, and adverse effects.

Permanent low-dose-rate BT (LDR-BT) or high-dose-rate BT (HDR-BT) afterloading ensures the maximum radiation dose is given to cancerous tissues, while minimizing exposure to the organs at risk (OARs) [3]. LDR-BT has the relative advantage of being practically a one-time procedure, and a long-term follow-up database avails its excellent outcomes and low morbidity. LDR-BT has been a gold standard for prostate BT in low risk patients for many years. Interstitial HDR-BT allows dose escalation and minimizes the integral dose to nearby normal tissues, obviating the need to account for setup error. HDR-BT possesses the technical advantage over LDR-BT of control of the postimplant dosimetry by modulating the source dwell time and position. This important difference in dosimetric control allows HDR-BT doses to be escalated safely, in contrast with LDR-BT [4,5].

Traditionally, HDR-BT has been used as a boost in combination with EBRT. The α/β ratio for prostate cancer is considered to be low, implying that HDR-BT could be advantageous in terms of radiation biology [6]. The use of HDR-BT as monotherapy has been associated with decreased rates of acute urinary frequency, urgency, dysuria and rectal pain, compared to LDR-BT. Chronic urinary

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frequency, urgency and grade 2 rectal toxicities have also been shown to decrease with HDR-BT. In addition, a dramatic decrease was noted in the rate of sexual dysfunction with HDR-BT [7]. There are also advantages in radiation safety and protection since the patient is not radioactive when he returns home. It is even more cost-effective, as seeds do not need to be purchased per patient. In HDR-BT, treatment planning provides anatomy-based dose optimization through modulation of catheter geometry, radiation source positions, and source dwell times. The versatility of intratarget dose modulation inherent to HDR-BT can be controlled and directed to deliver higher doses to gross disease or to selectively reduce the dose to OARs. In comparison to permanent LDR-BT, HDR-BT dosimetry is "high density" because there are approximately twice as many HDR-BT dwell positions as seeds in the typical LDR-BT implant.

With regard to the treatment dose prescription, the Groupe Européen de Curiethérapie and the European Society for Radiotherapy & Oncology (GEC-ESTRO) as well as the American Brachytherapy Society (ABS) recommendations [8,9] refer to the intended minimum peripheral dose to the planning target volume. As many as nine fractions have been reported, but 54 Gy in six fractions or 38 Gy in four fractions are the most commonly used fractionation schemes [10–14]. The delivery of four to six fractions within one implant, however, is a challenge, both logistically and with regard to dosimetric reproducibility. More recently, reports have emerged using three-, two- and even single-fraction HDR monotherapy protocols, with growing data supporting the use of 26–27 Gy in two fractions, and ongoing research investigating the safety and efficacy of single fractions of 19–21 Gy [15–19].

Given the potential advantages of single day HDR-BT, and in an attempt to make prostate HDR-BT more attractive and efficient, we conducted a prospective study of a single implant HDR-BT treatment delivered in 2 fractions of 13.5 Gy each within one day. Our hypothesis was that this prescription would be well tolerated and effective. Our primary objective was to assess acute toxicity, late toxicity and biochemical and clinical disease control rates following this treatment protocol. The secondary objective was to explore risk factors for predicting toxicity.

Methods and materials

Data acquisition

Data of all patients with prostate cancer for whom HDR-BT was used as monotherapy and had been treated in a single-institute between 2010 and 2017 were collected prospectively for this study. All research was carried out in compliance with the Helsinki Declaration and in accordance with Spanish law. The institutional review board reviewed and approved this study.

Patient selection and characteristics

All patients had a previous physical examination, an International Prostate Symptom Score (IPSS) and an International Index of Erectile Function (IIEF-5) assessment, an ultrasound (US), and a pelvic magnetic resonance (MR). Additionally, all had histological confirmation of low to intermediate-risk prostate adenocarcinoma in accordance with the National Comprehensive Cancer Network practice guidelines. The low-risk patients had clinical stage T1-T2a, Gleason 6 (3 + 3) and PSA <10 ng/mL, whereas intermediate-risk patients had at least one of the following features: clinical stage T2b or T2c, Gleason score 7 or initial prostate-specific antigen level (iPSA) 10 to $\leq$20 ng/mL. The patient eligibility criteria for the present analysis were: (1) those treated with HDR-BT as monotherapy for curative intent, without EBRT; (2) clinical TNM stage (American Joint Committee on Cancer 7th edition) [20] T1c-T2c and N0M0; (3) availability and accessibility of data on pre-treatment PSA level, Gleason score, and T classification; (4) no previous history of transurethral resection of the prostate <6 months before the implant; (5) no collagen vascular disease; and (6) minimum 6-months follow-up. Patient and treatment characteristics are shown in Table 1.

Neoadjuvant/adjuvant androgen deprivation therapy (ADT) was administered to intermediate-risk patients at the discretion of the treating physician. Neoadjuvant ADT included both luteinizing hormone releasing hormone agonist and antiandrogen, whereas adjuvant ADT included luteinizing hormone releasing hormone agonist only.

HDR-BT monotherapy treatment method

The protocol consisted of a prescribed reference dose of 13.5 Gy delivered twice to a total dose of 27.0 Gy using a single implant, with an interfraction interval of 6 h. The estimated biologic effective dose (BED) of 27 Gy from this treatment is 261 Gy (using an α/β ratio of 1.5 Gy). The BT was carried out under spinal anesthesia. The patients were placed in the dorsal lithotomy position and with trans-rectal ultrasound guidance; afterloading needles were inserted into the prostate. The median number of needles used per implant was 16 (range 14–18). The catheters were secured to the template with hollow screws (Supplementary Fig. S1). The template was sutured to patient perineum in four points and an additional fixation with a bandage was added. The distance from each needle start point to the template was measured and recorded, which allowed the verification of needle positioning before the HDR-BT fraction application. Rectal-prostatic spacers were not used. Computed tomography (CT) with 50 ml diluted bladder contrast was then carried out in all patients and images were transferred to the Oncentra prostate planning system, version 14.3.2 (Nucletron BV, Veenendall, the Netherlands). The first 50 patients underwent a CT scan before the second HDR-BT fraction. There were no needle displacements $\geq$5 mm. Therefore, the CT scan before the second fraction was considered unnecessary for further cases.

The prostate, rectum, bladder and urethra were contoured. The clinical target volume (CTV) equaled the planning target volume (PTV) and was defined as the entire prostate gland without margins. Dwell time optimisation was carried out using inverse planning. The homogeneity parameters used for dose optimization aim for prostate were V_{100} >95%, V_{125} <60%, V_{150} <30%, 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 D0.1 cc) <115%; and the dose to 1 cc of rectal wall (RD1cc) is limited to <75% of the prescribed dose (Supplementary Table T1). Table 2 shows the median values of the dosimetric data for all patients.

Endpoints and statistical analyses

National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE; version 3) toxicity grades were assigned prospectively for genitourinary (GU) and gastrointestinal (GI) toxicity at the date of each follow-up visit by the attending physician. Follow-up clinical examinations were performed at 1, 3, and 6 months for all patients, then every 3–6 months for the first 5 years, and yearly thereafter. All data analyses were done using SPSS (version 19.0) statistical software. The primary endpoints were: (1) the occurrence of acute and late GU toxicity scored by the CTCAE scoring system [21]. 'Acute toxicity' is defined as adverse events that occurred within 3 months of commencing therapy; events occurring after this were classified as 'late'. Specific erectile questions of the IIFF-5, known as the "Sexual Health Inventory For Men", were used in reporting sexual function; and (2) the biochemical

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