

Outcomes of patients with localized prostate cancer treated with combined external beam radiotherapy and high-dose-rate brachytherapy boost: A single-center retrospective study

Research Article

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Abstract:

Background: Temporary prostate brachytherapy, in combination with external beam radiotherapy (EBRT), is an established and evolving treatment technique for non-metastatic, intermediate and high-risk prostate cancer. This study aimed to evaluate the outcomes of patients with localized intermediate and high-risk prostate cancer treated with combined EBRT and high-dose-rate brachytherapy boost (HDR-BT) at a single centre.

Patients & Methods: A retrospective review of patients who underwent EBRT and HDR-BT treatment between January 2015 and December 2020. Patient and tumor characteristics, treatment outcomes (Kaplan-Meier analysis), and toxicities were analysed.

Results: 127 patients with intermediate (28.3%) or high-risk (71.7%) prostate cancer were included. Median follow-up was 42 months. Five-year bDFS, CSS and OS rate was 77.5%, 98.1% and 93.0%, respectively, with no significant difference between risk groups. The most frequent toxicity was acute grade 1 urinary obstruction (7.9%). One patient experienced acute and late grade 3 urinary obstruction. No grade ≥ 4 were observed.

Conclusions: Combined EBRT and HDR-BT demonstrated favourable disease control rates and manageable toxicities in patients with localized intermediate and high-risk prostate cancer. The 5-year bDFS rate was consistent with previous studies, supporting the effectiveness of this treatment approach. The low incidence of toxicities highlights the conformality and biological efficiency of HDR-BT boost. This treatment strategy provides an effective, safe and convenient option for this group of patients. To the best of our knowledge, this is the first report of the use of helical tomotherapy based intensity-modulated radiation therapy in combination with prostate HDR-BT (81.1% of cases).

Keywords: brachytherapy • high dose rate • intensity modulated radiotherapy • prostate cancer • radiotherapy

1. Introduction

Prostate cancer is the second most common cancer in men worldwide^[1]. Treatment modality depends on factors such as prognostic risk group, extent of the disease, obstructive urinary symptoms, prostate volume, existing comorbidities, preference, and treatment availability.

For patients treated with ionizing radiation, brachytherapy has an important role, either as monotherapy or as a dose boost in combination with external beam radiotherapy (EBRT)^[2]. Dosimetric studies have demonstrated that brachytherapy, whether in the form of high-dose-rate brachytherapy (HDR-BT) or low-dose-rate brachytherapy (LDR-BT) (permanent seed

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implants), results in notably reduced radiation doses to normal tissues such as the rectal and bladder walls, in comparison to external techniques like intensity-modulated arc therapy (IMAT), proton therapy, or carbon ion therapy, and that the lowest dose to normal tissues was obtained with HDR-BT^[3, 4].

HDR-BT refers to a dose delivered at a rate exceeding 1200 cGy/h, often surpassing 100 cGy/min. This rapid delivery of radiation leads to radiobiological impacts comparable to those observed in highly hypofractionated EBRT methods like stereotactic body radiotherapy (SBRT) and is believed to be selectively more damaging to cells with low α/β ratios, such as late-responding normal tissues or prostate cancer^[2, 5, 6]. The short treatment time also provides a possible advantage in using HDR-BT to treat more rapidly dividing cancers when compared to LDR-BT^[7].

Moreover, HDR-BT offers greater accuracy and conformity in delivering the planned dose, as the planning process is performed in real time, with the delivery catheters in place, and allows for more reliable dosing outside the prostate to treat extraprostatic extension and seminal vesicle invasion. Pelvic EBRT with HDR-BT dose escalation (biologically equivalent doses >268 Gy, calculated with an α/β ratio of 1.2) has shown a strong dose–response relationship for intermediate- and high-risk prostate cancer patients, with improved locoregional control at 10 years and decreased biochemical and clinical failures, as well as distant metastasis^[8, 9]. These advantages make HDR-BT, combined with EBRT, an optimal choice to offer as a boost for patients with intermediate- and high-risk disease^[10].

The goal of the present study was to determine the outcomes of patients with localized intermediate- and high-risk prostate cancer treated with combined EBRT and HDR-BT boost at a single institution.

2. Patients and Methods

An institutional retrospective study was conducted on the medical records of all patients diagnosed with localized prostate cancer who received combined EBRT and HDR-BT boost treatment between January 2015 and December 2020. Patients eligible for inclusion had a histological diagnosis of adenocarcinoma of the prostate and were classified as intermediate- or high-risk prostate cancer according to the prognostic risk groups described by D’Amico et al.^[11]. Data on patient and tumor characteristics, as well as treatment variables were collected, including disease control outcomes and toxicities for each patient. Ethical approval for the study was obtained before its initiation.

2.1. External Beam Radiotherapy

To accurately define the target volume and plan external beam therapy, a computed tomography (CT) simulation was performed with patients in the supine position. Scans were obtained with 3 mm slices, ranging from L2 to mid femur, using knee and feet positioners for immobilization and with a comfortably full bladder. Laxatives were prescribed as necessary to ensure the rectum was empty during the imaging process.

The clinical target volume (CTV) was defined by contouring the prostate and seminal vesicles. In cases where whole pelvic radiation therapy (WPRT) was prescribed, reproducible international guidelines were followed to contour CTV of the pelvic lymph nodes, including the internal iliac, external iliac, obturator, and presacral regions^[12]. Patients who were treated with two applications of HDR-BT (see section *HDR Brachytherapy*) received 4500 cGy (180 cGy per daily fraction) WPRT using three-dimensional conformal radiation therapy (3DCRT) with electronic portal imaging. Those treated with one application of HDR-BT received either 4500 cGy WPRT or 3750 cGy (250 cGy per daily fraction) to the prostate and seminal vesicles, using helical tomotherapy-based intensity-modulated radiation therapy (H-IMRT) with fan beam CT imaging (FBCT).

2.2. HDR Brachytherapy

HDR-BT boost was administered using a remote after-loading system with an Iridium-192 source (average photon energy of 380 keV) and intraoperative transrectal ultrasound (TRUS)-based planning. The procedure was performed under general anesthesia in the dorsal lithotomy position. Rigid catheters were inserted transperineally to the base of the prostate under TRUS guidance via a stepper-based system with a grid template. The prostate, rectum, and urethra were contoured using Oncentra Prostate® treatment planning software. Planning target volume (PTV) was defined by contouring the prostate, including any extracapsular extension. The urethra was contoured using the urethral catheter (16-French Foley catheter) as the landmark on imaging, and the rectum was defined as the anterior rectal wall along the length of the prostate. After contouring was completed, optimization of catheter positions, dwell times, dwell positions, and dose distribution was performed to meet the dosimetric constraints using anatomy-based inverse planning. Initially, the prescribed dose was 1900 cGy to the isodose covering PTV, administered in two applications (950 cGy per application) delivered 2 weeks apart. However, based

on published results demonstrating acceptable outcomes with single fraction dose escalation, *Groupe Européen de Curiethérapie* and the European Society for Radiotherapy and Oncology (GEC/ESTRO) recommendations, and in consideration of practical logistics and significant savings in resources, the prescription dose was subsequently revised to 1500 cGy in a single application^[13, 14]. As per international recommendations, planning objectives were applied to PTV (D90 >100%, V100 >95%, V125 <70%, V150 <40%, V200 <14%), urethra (D0.1cc ≤120 EQD2, D10 ≤120 EQD2, D30 ≤105 EQD2), and rectum (D2cc ≤75 EQD2)^[14].

2.3. Follow-up

Patients were initially assessed 3 months after treatment, followed by biannual evaluations during the subsequent 5 years and annual check-ups thereafter. At each visit, serum prostate specific antigen (PSA) was measured. Biochemical failure was defined according to the Phoenix biochemical failure, definition as a PSA level 2.0 ng/mL above the nadir value^[15]. If metastatic disease was suspected, imaging modalities such as CT scans, magnetic resonance imaging (MRI), bone scintigraphy with 99mTc-labeled diphosphonates, or positron emission tomography (PET)-CT with Gallium-68 prostate-specific membrane antigen (68Ga-PSMA) were utilized for further evaluation. Relevant follow-up data were gathered from all available sources, including face-to-face office visits, telephone interviews, and medical records.

2.4. Definitions of Disease Control

Three primary outcomes were used to assess treatment efficacy: biochemical disease-free survival (bDFS), prostate cancer-specific survival (CSS), and overall survival (OS). Time zero was defined as the date of first or single brachytherapy implant. bDFS was defined as the time until the occurrence of biochemical failure, the date of last follow-up, or death. CSS and OS were defined as the time until death from prostate cancer and death from any cause, respectively.

2.5. Toxicities

The toxicities associated with the treatment were reported using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Adverse events that occurred within 3 months of completion of

radiotherapy were classified as early toxicities, while those that occurred subsequently were classified as late toxicities.

2.6. Statistical Analysis

The Kaplan–Meier method was used to determine the rates of bDFS, CSS, and OS. Statistical analysis was performed with Statistical Package for the Social Sciences (SPSS) software (version 29). Univariate analysis was utilized to evaluate the predictive value of various factors, including clinical T-stage (American Joint Committee on Cancer, 7th edition), Gleason score, initial PSA, D'Amico risk group, age, and ionizing radiation dose, to predict outcomes. Odds ratios (ORs) were calculated, and a *p*-value of ≤0.05 was considered statistically significant.

3. Results

A total of 127 patients with a median age of 66 years (range 52–78) were included in this review (patient and disease characteristics are presented in Table 1). Most patients had a Gleason score of 7 (70.9% [24.4% were 3 + 4 and 46.5% were 4 + 3]), while 8.7%, 15.0%, 4.6%, and 0.8% had a score of 6, 8, 9, and 10, respectively. Pretreatment PSA ranged from 2.90 to 81.21 ng/L, where 37.0%, 30.7%, and 32.3% presented with a PSA of <10, ≥10–<20, and ≥20 ng/L, respectively. The clinical T-stage in this cohort of patients was T1c (17.3%), T2a (10.2%), T2b (7.9%), T2c (44.9%), T3a (16.5%), T3b (1.6%), and T4 (1.6%). Three patients (2.4%) had previous transurethral resection of the prostate (TURP). In all, 28.3% and 71.7% had intermediate- and high-risk localized prostate cancer, respectively, and were treated with EBRT, HDR-BT boost, and hormone therapy. Mean follow-up time was 42 months (range 1–86 months). Most patients (81.1%) received a single implant HDR-BT boost of 1500 cGy and were treated with H-IMRT, while 24 patients (18.9%) received two 950 cGy implants and were treated with 3DCRT. Seventy-four patients (58.3%) received WPRT during EBRT. Overall, dose constraints were respected as per protocol. External beam and brachytherapy treatment characteristics are outlined in Table 2.

3.1. Disease Control

Median PSA nadir was 0.05 (interquartile range [IQR], 0.046–0.096) ng/mL, which was achieved after a median

Table 1: Characteristics of patients and tumors.

Characteristic	Value
Total number of patients	127
Age (years)	
Median	67
Range	53–78
Pretreatment PSA	
Range (ng/mL)	2.90–81.21
PSA <10 ng/mL	47 (37.0)
10 ≤ PSA < 20 ng/mL	39 (30.7)
PSA ≥20 ng/mL	41 (32.3)
Tumor stage	
T1c	22 (17.3)
T2a	13 (10.2)
T2b	10 (7.9)
T2c	57 (44.9)
T3a	21 (16.5)
T3b	2 (1.6)
T4	2 (1.6)
Gleason score	
≤6	11 (8.7)
7	90 (70.9)
8–10	26 (20.5)
D'Amico risk group	
Intermediate	36 (28.3)
High	91 (71.7)

Results are presented as frequency and percentage, *n* (%)

Table 2: Treatment characteristics.

Characteristic	Value
External radiotherapy technique	
3DCRT	24 (18.9)
H-IMRT	103 (81.1)
External radiotherapy dose (cGy)	
4500	84 (66.1)
3750	43 (33.9)
WPRT	
Yes	74 (58.3)
No	53 (41.7)
Number of HDR-BT applications	
One	24 (18.9)
Two	103 (81.1)

Results are presented as frequency and percentage, *n* (%)
3DCRT: 3-dimensional conformal radiation therapy; H-IMRT: helical tomotherapy-based intensity-modulated radiation therapy; HDR-BT: high-dose-rate brachytherapy.

of 18 months since radiotherapy completion. Eighteen patients (14.2%) developed biochemical failure, nine (7.1%) of which developed distant metastasis. Of these, 11 (61.1%) were high-risk patients, while seven (38.9%) were of intermediate risk. Five-year bDFS was 77.5% (Figure 1) and was not statistically significantly different between high- and intermediate-risk patients (log-rank $p = 0.53$). Median time to biochemical recurrence was 28 months (0.3–5.2 years).

Five-year CSS and OS were 98.1% and 93.0%, respectively. Ten patients (7.9%) died of disease progression from metastatic prostate cancer, eight of which were high-risk patients. Five patients died from other causes.

Univariate analysis showed no factors including initial PSA, Gleason score, T-stage, risk group, age, and dose fractionation were associated with a difference in disease control.

3.2. Toxicity

The incidence of toxicities is summarized in Table 3. There were no grade 4 or 5 toxicities, and there was one (0.8%) acute grade 3 and two (1.6%) late grade 3 toxicities in our patient population. The most frequently reported toxicity was acute grade 1 urinary tract obstruction (7.9%), followed by acute grade 1 dysuria (6.3%). One patient had acute and late grade 3 urinary tract obstruction requiring TURP. Univariate analysis showed that no significant patient, disease, or treatment factors – including number of HDR-BT applications, EBRT technique, dose, and treatment volume – predicted the occurrence of toxicities.

4. Discussion

High radiation doses improve the biochemical and clinical results for prostate cancer patients^[8,9]. Currently, the most effective and resource-efficient method to deliver high ionizing radiation dose to the prostate and seminal vesicles (with pelvic lymph node irradiation, as indicated), while greatly sparing surrounding organs at risk, is the combination of image-guided intensity-modulated EBRT and prostate brachytherapy^[2-4]. The radiobiological advantages of rapid dose delivery, great accuracy, and dose conformity with significant sparing of the urethra, and the ability to treat extraprostatic extension and seminal vesicle invasion make HDR-BT a particularly attractive choice for radiotherapy boost when compared to LDR-BT, photon SBRT, proton therapy, and heavy ion therapy.

The present study investigated the outcomes of patients with localized intermediate- and high-risk prostate cancer treated with combined EBRT and HDR-BT boost at a single institution. Our findings demonstrate favorable disease control rates and infrequent and manageable toxicities, supporting this organ-preserving treatment approach for this patient population.

The 5-year bDFS rate of 77.5% observed in our study is consistent with previous publications, indicating

Table 3: Treatment-related toxicities.

Adverse events	Grade				
	1	2	3	4	5
Acute					
Dysuria	8 (6.3)	0	0	0	0
Haematuria	0	5 (3.9)	0	0	0
Urinary urgency/frequency	4 (3.1)	0	0	0	0
Urinary tract obstruction	10 (7.9)	1 (0.8)	1 (0.8)	0	0
Rectal bleeding	6 (4.7)	0	0	0	0
Anal pain	0	0	0	0	0
Late					
Dysuria	2 (1.6)	0	0	0	0
Haematuria	4 (3.1)	4 (3.1)	0	0	0
Urinary urgency/frequency	6 (4.7)	0	0	0	0
Urinary tract obstruction	4 (3.1)	3 (2)	2 (1.6)	0	0
Rectal bleeding	4 (3.1)	0	0	0	0
Anal pain	0	0	0	0	0

Results are presented as frequency and percentage, *n* (%)

the effectiveness of combined EBRT and HDR-BT boost in achieving disease control. It is noteworthy that the bDFS rate was not significantly different between high- and intermediate-risk patients, suggesting that this treatment strategy is equally effective across risk groups. In addition, our study reported 5-year CSS and OS rates of 98.1% and 93.0%, respectively, highlighting the favorable long-term outcomes of this treatment approach.

As stated before, HDR-BT boost allows for highly conformal and biologically efficient dose escalation within the tolerance of surrounding organs at risk. This is reflected in our study with the low rate of reported acute and late genitourinary and rectal toxicity. Only one patient experienced acute and late grade 3 urinary tract obstruction, and no grade ≥ 4 toxicities were observed. Treatments were well tolerated, and there were no notable interruptions.

With regards to this study's limitations, being a retrospective study, it is subject to inherent biases associated with the retrospective design. In addition, we were unable to determine the incidence of erectile dysfunction, a significant adverse effect of prostate cancer treatment, due to challenges in consistent screening and potential underreporting by patients. Due to inconsistency in the reporting of hormone therapy duration, it was not possible to analyze this important treatment component in detail. Finally, the small patient population and low incidence of events may have resulted in high ORs observed in the univariate analysis, occurring by chance.

Despite these limitations, our study contributes to the existing evidence supporting the use of combined

EBRT and HDR-BT boost to treat localized prostate cancer. The favorable outcomes and manageable toxicities observed in our patient population highlight the potential of this treatment approach. Also, our study suggests that implementing HDR-BT boost can optimize the utilization of existing brachytherapy units and by adopting this approach, the workload of linear accelerators used to treat prostate cancer patients can be reduced, effectively shortening waiting times and accommodating patients with other disease sites. Still, an experienced multidisciplinary team is required for the patients to undergo these treatments safely and effectively.

5. Conclusions

In conclusion, this study provides evidence that the use of EBRT and HDR-BT boost yields excellent disease control outcomes and minimal toxicities in our population of patients with localized intermediate- and high-risk prostate cancer. These results are consistent with internationally published data, demonstrating the reproducibility and effectiveness of this treatment approach in our specific setting. From the patient's point of view, this treatment approach combines effectiveness, safety, and convenience and is a suitable option for patients who prefer a shorter treatment duration. To the best of our knowledge, this is the first study reporting the use of H-IMRT in combination with prostate HDR-BT and the first Portuguese study reporting the use of prostate HDR-BT.

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Conflict of Interest

The authors declare no conflicts of interest regarding the publication of this manuscript.

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Radiotherapy Department of the Portuguese Institute of Oncology of Coimbra, Portugal

List of Abbreviations

3DCRT: three-dimensional conformal radiation therapy
⁶⁸Ga-PSMA: Gallium-68 prostate-specific membrane antigen

bDFS: biochemical disease-free survival
 CSS: cancer-specific survival
 CTV: clinical target volume
 CTCAE: Common Terminology Criteria for Adverse Events
 EBRT: external beam radiotherapy
 FBCT: fan beam CT imaging
 GEC/ESTRO: *Groupe Européen de Curiethérapie* and the European Society for Radiotherapy and Oncology
 HDR-BT: high-dose-rate brachytherapy
 H-IMRT: helical tomotherapy-based intensity-modulated radiation therapy
 IMAT: intensity-modulated arc therapy
 IQR: interquartile range
 LDR-BT: low-dose-rate brachytherapy
 MRI: magnetic resonance imaging
 OS: overall survival
 PSA: prostate specific antigen
 PTV: planning target volume
 SBRT: stereotactic body radiotherapy
 SPSS: Statistical Package for the Social Sciences
 TRUS: transrectal ultrasound
 TURP: transurethral resection of the prostate
 WPRT: whole pelvic radiation therapy

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