

## Mini Review

# High-Dose-Rate Brachytherapy for Localized Prostate Cancer: An Opportunity for Improvement over Intensity-Modulated Radiotherapy

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## Abstract

Advances in conformal radiotherapy techniques such as IG-IMRT have improved local tumor control and survival rates while decreasing GI and GU toxicities compared to 3D-CRT. However, the question remains if further dose escalation could improve the PSA relapse-free survival rate beyond 70% for high-risk patients? Treatment of high-risk patients using IG-IMRT remains challenging as these patients may present with occult distant disease. The potential benefits of high-dose rate (HDR) brachytherapy (BT) for localized prostate cancer are two folds: dose escalation to the target with possible boosting of the regions known to contain disease; and dose sparing to the urethra, bladder, rectum, and neuro-vascular bundles. Available clinical data for the use of HDR BT a boost or monotherapy confirm that HDR BT is capable of delivering a conformal, radiobiologically effective, very high radiation dose to the targeted tumor region without compromising gastrointestinal and genitourinary dose constraints. MRI-guided HDR BT potentially allows clinicians to deliver adaptive radiation to high-risk tumor subvolumes including the dominant intraprostatic lesion, or even areas of recurrence. In addition, MRI-guided HDR offers a therapeutic advantage for those patients with visualized extra-capsular disease extension, as extra-capsular disease may be included in the radiation target volume.

**Keywords:** High-dose rate brachytherapy; Prostate cancer; Intensity-modulated radiotherapy (IMRT); Brachytherapy

## Abbreviations

PTV: Planning Target Volume; PSA: Prostate-Specific Antigen; HDR: High-Dose Rate; BT: Brachytherapy; IG-IMRT: Intensity-Modulated Radiation Therapy; GI: Gastrointestinal; 3DCRT: 3-dimensional Conformal Radiotherapy; GU: Genitourinary; LDR: Low-Dose Rate; PSI: Prostate Seed Implant; EBRT: External Beam Radiotherapy; MRI: Magnetic Resonance Imaging; CT: Computerized Tomography; DIL: Dominant Intraprostatic Lesion; MRSI: Magnetic Resonance Spectroscopic Imaging; US: Ultrasound; Pd-103: Palladium-103; I-125: Iodine-125

## Introduction

Prostate cancer is the second leading cause of cancer death in men [1]. Approximately 60% to 70% of men with newly diagnosed adenocarcinoma of the prostate present with organ-confined disease. For locoregional prostate cancer, relapses mostly happen at the original tumor location within the planning target volume (PTV) [2,3]. Furthermore, several investigators have demonstrated that local relapse is associated with a significant increase in the risk of metastatic disease [4,5], and have suggested a cause-and-effect relationship between these phenomena [5,6]. Firm clinical evidence exists supporting the contention that local tumor control can be enhanced through radiation dose escalation for localized prostate cancer [7,8]. However, bladder and rectum dose constraints are limiting factors due to dose escalation. Therefore, techniques allowing

increased conformality of radiation delivery to the prostate have been investigated [9].

It is worthwhile to revisit the risk classifications for prostate cancer [9]. The definition of low risk most often includes those patients with a Gleason score of 6 or less, a prostate-specific antigen (PSA) of 10 or less, and patients with stage T2a or less disease. Intermediate risk patients generally have up to Gleason score 7 disease with a PSA up to 20 and palpable tumor though stage T2b. High risk patients generally either have a Gleason score of 8 or above, a PSA above 20, or advanced disease beyond T2b.

The potential benefits of high-dose rate (HDR) brachytherapy (BT) for localized prostate cancer are two folds: dose escalation to the PTV with possible boosting of the regions known to contain disease; and dose sparing to the urethra, bladder, rectum, and neuro-vascular bundles. The intermediate risk subgroup of localized prostate cancer patients are expected to benefit the most from HDR BT. While dose escalation may increase local control for patients with high-risk disease, these patients likewise have a greater tendency to have occult regional or distant metastatic disease ultimately leading to treatment failure.

## Limitations of image-guided intensity modulated radiation therapy alone

The advent of image-guided intensity-modulated radiation therapy (IG-IMRT) allowed clinicians to escalate dose while

minimizing normal tissue toxicity (9), in particular gastrointestinal (GI) toxicity. Per one report, the 3-year actuarial rate of late grade 2-3 rectal bleeding was 3% for IG-IMRT (81 Gy) as compared to 17% for 3-dimensional conformal radiotherapy (3DCRT) (75.6 Gy) ( $p < 0.001$ ). Acute and late genitourinary (GU) toxicities were not significantly different between 3DCRT and IG-IMRT [10]. The actuarial PSA relapse-free survival was improved through all prognostic groups, from 81% to 98% for low-risk patients; from 60% to 87% for intermediate-risk; and from 42% to 70% for high-risk. In an attempt to improve the high-risk group's relapse-free survival rate, dose escalation up to 86.4 Gy was subsequently performed. Unfortunately, a significant increase (1% vs. 8% between 81 Gy and 86.4 Gy) in the 3-year actuarial rate of late grade 2 to 3 rectal toxicity was found ( $p = 0.008$ ) [11]. For all 772 localized prostate cancer patients who received 81 to 86.4 Gy by IG-IMRT, <1% grade 3 and 4 late GI and GU toxicities were observed, while 1.5% and 9.5% grade 2 late toxicities were recorded for GI and GU, respectively. Mohammed *et al.* recently reported a comparison of acute and late toxicities observed among IG-IMRT, monotherapy low-dose rate (LDR) prostate seed implant (PSI), and external beam radiotherapy (EBRT) + HDR BT. Three-year rates of rectal bleeding of 0.9%, 20%, and 6% ( $p < 0.001$ ) for LDR PSI, IG-IMRT, and EBRT+HDR BT, respectively, were seen.

In summary, advances in conformal radiotherapy techniques such as IG-IMRT have improved local tumor control and survival rates while decreasing GI and GU toxicities compared to 3D-CRT. However, the question remains if further dose escalation could improve the PSA relapse-free survival rate beyond 70% for high-risk patients? Treatment of high-risk patients remains challenging as these patients may present with occult distant disease. Improvement in imaging techniques such as C11-choline PET/CT may help to identify those patients who would benefit from local dose escalation [12].

### HDR for localized Prostate Cancer: EBRT+HDR or HDR monotherapy

HDR prostate brachytherapy (BT) is one of the techniques used to deliver conformal, high dose radiation to the prostate while sparing organs-at-risk (OAR) [13]. The majority of clinical data for HDR prostate BT is related to its application as a radiotherapy boost in combination with EBRT [14,15] for intermediate and high-risk prostate cancer. Clinical data reported by Galalae *et al.* for HDR BT are promising. A 2-year biochemical disease-free survival (bDFS) of 89% and a bDFS of 63% at 5 years was reported for a series of patients with a PSA  $\geq 10$ , T stage  $\geq T2b$ , and Gleason score  $\geq 7$  [16,17]. Notably, the 5-year biochemical control rate was 85% in the group of patients who had 2-3 poor prognostic factors that received a biologically equivalent dose (BED) of greater than 94 Gy<sub>1.2</sub> [18]. The authors found dose escalation was beneficial for patients with two and three poor prognostic factors ( $p = 0.022$  and  $< 0.001$ ). Patients with only one poor prognostic factor did not benefit from dose escalation [18]. Given the often slow clinical progression of prostate cancer and time to recurrence, Martinez *et al.* importantly confirmed that a benefit to dose escalation persists out to 10 years [18,19]. Clinical studies comparing very high-dose IMRT versus combination EBRT and HDR BT have concluded that EBRT with HDR BT provides improved tumor control over EBRT alone. At three years, the bDFS

rate was 93% (EBRT with HDR BT) vs. 67% (EBRT alone) for high-risk patients [20]. Multi-institutional studies such as RTOG 0321 have since investigated HDR BT in combination with EBRT for patients with intermediate and high-risk prostate cancer in order to determine the long-term role, morbidity, and efficacy of combination treatments.

As a monotherapy for localized prostate cancer, reported clinical outcomes for HDR BT [21,22] are confined to a limited number of institutions with no multi-institutional or phase II/III studies available. Yoshioka *et al.* showed favorable 3-year PSA failure-free rates for intermediate- and high-risk groups of 89% and 77%, respectively [21]. However, the 5-year PSA failure-free rate for the high risk group was 70%, leading to open questions of whether these patients would benefit from treatment of the regional nodes and the role of androgen deprivation in combination with the brachytherapy modality. The patients reported in the data of Demanes *et al.* [22] were mainly low-risk or low-intermediate-risk (99.98%: 293 patients and 298 patients, respectively). There were only 4 patients with high-intermediate risk disease and 1 patient with high-risk disease, and highly favorable 8-year biochemical control rates of 97% were seen. It is noted that the feasibility and clinical benefits of monotherapy HDR have not been validated for the high risk group [21].

Available clinical data for the use of HDR BT a boost or monotherapy confirm that HDR BT is capable of delivering a conformal, radiobiologically effective, very high radiation dose to the targeted tumor region without compromising GI and GU dose constraints. Wilder *et al.* found no significant difference in toxicities between the two treatment groups of EBRT plus HDR BT vs. EBRT alone [20]. Low Grade 3 or higher toxicities have been reported. Wilder *et al.* reported 1% GU toxicities and 0% GI toxicities [20]. Vargas *et al.* reported 5.1% Grade 3 and 1.5% Grade 4 combined GU and GI toxicities [23]. Other series report between 7% and 12% Grade 3 GU toxicities [24-26]. However, Grades 1 and 2 toxicities are significant, especially for GU cancers. A range of between 20% and 72% Grade 1 and 2 GU side effects were reported with an observed 7% of GI side effects [20,24,26,27]. Mohammed *et al.* reported a significant increase in acute Grade 2 GI or GU toxicities for patients receiving a combination of EBRT and HDR BT. Toxicities were 35%, 49%, and 55% for LDR PSI, IG-IMRT, and combined EBRT and HDR BT, respectively ( $p < 0.001$ ) [28]. Late GU toxicities Grade 2 or higher were present in 22%, 21%, and 28% for patients receiving LDR PSI, IG-IMRT, and EBRT with HDR BT ( $p = 0.01$ ). Patients receiving combination therapy were more likely to experience urethral strictures and urinary retention, while patients who received LDR PSI commonly experienced dysuria.

Firm clinical evidence exists showing that radiation dose reduction to normal tissue is linked with a reduction in acute and late toxicities [24,26,29,30]. An HDR BT boost, combined with EBRT, has shown promising clinical outcomes emphasizing brachytherapy's intrinsic benefit of providing localized, conformal dose escalation. HDR BT has a potential radiobiologic advantage over LDR PSI or EBRT (e.g. IG-IMRT) owing to prostate cancer's low  $\alpha/\beta$  ratios (the currently accepted values are 1.2-1.5 [31]). However, patients who receive HDR brachytherapy do experience increased low-to-moderate urinary frequency or urgency [23].

The use of magnetic resonance imaging (MRI) in combination

with HDR BT provides physiological and functional information that surpasses the anatomical data obtained from computerized tomography (CT) [32-36]. MRI-guided prostate BT was first described in the late 1990s [36] in which an LDR PSI was performed in a very low magnetic field (0.5 Tesla) MRI scanner. The early experience of MRI-guided BT enabled maximizing dosimetric coverage to the dominant intraprostatic lesion (DIL) with the goal of decreasing acute urinary morbidity and long-term side effects such as erectile dysfunction and proctitis [13]. MRI-guided HDR implantation for localized prostate cancer is gaining interest due to advances in MR, including high-resolution and functional imaging. MRI-guided HDR brachytherapy potentially allows clinicians to deliver adaptive radiation to high-risk tumor subvolumes including the DIL, or even areas of recurrence [32-35]. The location of the DIL may be obtained from MRI using techniques such as magnetic resonance spectroscopic imaging (MRSI) or dynamic-contrast enhanced MRI [32-35]. In addition, MRI-guided HDR offers a therapeutic advantage for those patients with visualized extra-capsular disease extension, as extra-capsular disease may be included in the radiation target volume [32]. Also, the urethra and distal urethral muscles are more easily identified on MRI than on ultrasound (US) [32], allowing for dosimetry to minimize radiation to these structures. The significant reduction of inter-observer and even intra-observer variability in prostate delineation is an additional reported benefit of MRI-guided HDR over CT-based HDR [37]. The avoidance of neurovascular and erectile tissue that has been performed with EBRT using co-registered MRI-based anatomic delineation [38,39] is expected to be feasible using MRI-guided HDR.

### The rationale for low-dose rate prostate seed implants for small tumors and high-risk tumors

The clinical outcomes for intermediate and high-risk disease when LDR PSI is performed using palladium-103 (Pd-103) [25] or iodine-125 (I-125) have been examined [40]. Using Pd-130, five-year PSA control rates of 82% and 65% were seen for intermediate and high-risk groups [25], respectively. Similarly using I-125 [40], a control rate of 70% was found for the intermediate risk group (Gleason score of 7 and PSA < 10). Contraindications to LDR PSI as a monotherapy include 1) metastatic disease, including lymph node involvement; 2) gross seminal vesicle involvement; or 3) large T2 disease that cannot be adequately implanted due to geometrical impediments to adequate tumor mass implantation [41]. The increased risk of extracapsular spread of disease being present in intermediate-risk disease has been one of the reasons that LDR PSI as a monotherapy is primarily recommended for patients with low-risk disease [27,41]. LDR PSI is often not recommended for patients with larger prostates as the anterolateral portion of the gland may be difficult to implant due to pubic arch interference, and these patients often experience increased GU morbidity [15].

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