# Salvage low-dose-rate $^{125}$I partial prostate brachytherapy after dose-escalated external beam radiotherapy

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## Abstract

**Purpose:** To report outcomes on 5 patients treated with salvage partial low-dose-rate (LDR) 125-iodine ($^{125}$I) permanent prostate seed brachytherapy (BT) for biopsy-proven locally persistent prostate cancer, following failure of dose-escalated external beam radiotherapy (EBRT).

**Material and methods:** A retrospective review of the Fox Chase Cancer Center prostate cancer database identified five patients treated with salvage partial LDR $^{125}$I seed implant for locally persistent disease following dose-escalated EBRT to 76-84 Gy in 2 Gy per fraction equivalent. All patients had post-EBRT biopsies confirming unilateral locally persistent prostate cancer. Pre-treatment, EBRT and BT details, as well as post-treatment characteristics were documented and assessed.

**Results:** The median follow-up post-implant was 41 months. All five patients exhibited low acute genitourinary and gastrointestinal toxicities. Increased erectile dysfunction was noted in three patients. There were no biochemical failures following salvage LDR $^{125}$I seed BT to date, with a median post-salvage PSA of 0.4 ng/mL.

**Conclusions:** In carefully selected patients with local persistence of disease, partial LDR $^{125}$I permanent prostate seed implant appears to be a feasible option for salvage local therapy with an acceptable toxicity profile. Further study is needed to determine long-term results of this approach.

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**Key words:** brachytherapy, LDR, prostate cancer, recurrence, salvage, seeds.

## Purpose

Locally recurrent prostate cancer following external beam radiotherapy (EBRT) is a therapeutic dilemma. Viable residual carcinoma has been estimated to occur in 10-54% of patients two or more years following EBRT [1-3]. Patients diagnosed with locally persistent disease often seek a second local treatment to the prostate with the goal of cure. Brachytherapy (BT) is an attractive option for these patients due to its ability to deliver a high radiation dose to the prostate with a high degree of conformity [4-7]. However, there is a risk of genitourinary toxicity, specifically incontinence, which approaches 31% [8,9], and gastrointestinal toxicity, associated with injury to the rectum, ranging from 3 to 35% [7-10].

Further complicating the risk-to-benefit balance of salvage BT is the lack of outcomes data in the era of EBRT dose-escalation. Higher doses of EBRT have been shown to reduce the risk of prostate cancer recurrence in several clinical trials [11-15]. Presently, the National Comprehensive Cancer Network (NCCN) guidelines recommend EBRT doses ranging from 75.6-81 Gy depending on risk categorization [16]. The current understanding of the potential toxicity associated with salvage BT is derived from literature based on EBRT doses of 63-68 Gy [4-7]. It is well-established that radiation toxicity is directly related to dose and patients treated with dose-escalated EBRT may be at higher risk of toxicity.

At Fox Chase Cancer Center (FCCC), dose-escalated EBRT of ≥ 76 Gy has been prescribed for over two decades [17]. Furthermore, in a recent trial of hypofractionation, a prescription of 70.2 Gy in 26 fractions was used, which is the equivalent of 84.4 Gy in 2.0 Gy fractions assuming an $\alpha/\beta$ ratio of 1.5 [18]. With the goal of mitigating risk of additional toxicity for carefully selected patients with unilateral recurrence, a salvage low-dose-rate (LDR) partial prostate implant approach has been implemented. The primary objective of this paper is to report the feasibility, preliminary toxicity, and biochemical outcomes for patients treated with salvage permanent LDR $^{125}$I seed partial prostate BT in the era of dose-escalated EBRT. To our knowledge, this is the first report of

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salvage LDR prostate BT following either dose-escalated or hypofractionated EBRT.

## Material and methods

The FCCC prostate cancer database was queried to identify patients who had received primary definitive EBRT and subsequent LDR salvage BT for prostate cancer. A total of five patients treated from 2007 to 2011 were identified. Pre-treatment, treatment, and post-treatment characteristics were collected. T-stage was reported as per the American Joint Cancer Commission (AJCC) 7$^{th}$ edition based on palpation only.

### *External beam radiotherapy techniques*

All patients received primary EBRT with 3-dimensional conformal radiation therapy (3DCRT) or intensity-modulated radiation therapy (IMRT). The 3DCRT [19,20] and IMRT [21] techniques have been previously described. In 3DCRT, a small pelvic four-field plan was treated to a dose of 46 Gy in 23 daily fractions with three subsequent field reductions to block the rectum and bladder, and achieve a total dose to the prostate of 78 Gy in 39 daily fractions. Intensity-modulated radiation therapy was delivered using the step-and-shoot technique with an 8 to 9 beam arrangement. On the IRB 02-602 clinical trial, patients were randomized to receive conventionally fractionated IMRT to 76 Gy in 38 fractions (2.0 Gy per day) versus hypofractionated IMRT to 70.2 Gy in 26 fractions (2.7 Gy per day) to the prostate. Assuming an $\alpha/\beta$ of 1.5, the latter dose-fractionation scheme would be biologically equivalent to 84.4 Gy in 2.0 Gy daily fractions.

### *Post-treatment biopsy*

Post-treatment biopsies were performed for one of the following indications: as a two-year endpoint as indicated by the FCCC IRB #02-602 protocol, for a suspicious rising PSA, biochemical failure or for a suspicious palpable abnormality on digital rectal exam (DRE). All patients received extended core biopsies of both lobes of the prostate with at least 12 cores obtained. A pathologist with special expertise in urologic oncology reviewed the biopsy materials. A four-tier classification scheme was used: benign, atypical, carcinoma with treatment effect, carcinoma without treatment effect [22]. Whenever possible, each slide was assigned a Gleason score (GS).

### *Patient selection*

Patients were eligible for salvage partial prostate BT if they had suspicious findings on their planned 2-year biopsy and subsequent re-biopsy showing persistent or progressive disease. Patients with a rising PSA or abnormal DRE with biopsy-proven unilateral adenocarcinoma were also eligible. Androgen deprivation therapy (ADT), with luteinizing-hormone-releasing-hormone (LHRH) agonist was prescribed at the discretion of the treating oncologist, generally for GS 7 and/or high bulk disease. Androgen deprivation therapy was implemented on the day of the implant and continued for a 6-month duration.

### *Brachytherapy technique*

All patients underwent a pre-implant MRI-based volume study, to estimate the treatment volume and prostate length. The activity and number of seeds required were determined by the physician-contoured target volume. On the day of the procedure, patients were brought to the operating room, given general anesthesia and placed in extended dorsal lithotomy position. A Foley catheter was inserted and 50 ml of contrast and 100 ml of water was instilled into the bladder then clamped. A trans-rectal ultrasound (TRUS) volume study at 5 mm intervals from the prostate base to apex was performed by the radiation oncologist. The clinical target volume (CTV) was defined as the right or left half of the prostate and contoured by a single radiation oncologist (MKB), and transferred to the VariSeed (Varian Medical Systems, Inc., Palo Alto, CA, USA) planning system. A 3-mm to 5-mm expansion was used to create a planning target volume (PTV), to account for contouring inaccuracies, except posteriorly where no margin was used. A real-time plan with proposed needle and seed-spacer sequences was produced manually to provide optimal coverage with sparing of the urethra. A typical plan consisted of 5 to 9 needles (Fig. 1). The intraoperative real-time sleeved seed technique has been previously described [23]. Using a FCCC modified Best $^{125}$I seed loader (Best Medical International, Inc., Springfield, VA, USA), the seeds and spacers were positioned according to plan and inserted into the sleeve (hollow suture material), which were loaded into the applicator needles. The needles were inserted through a transperineal approach under ultrasound guidance, using the axial and sagittal views to confirm accurate needle and seed placement prior to deployment. Once all the seeds were placed, cystoscopy was performed by the urologist to ensure the absence of seeds from the bladder and urethra.

The median radioactive seed activity for $^{125}$I was 0.33 mCi. A total dose of 110 Gy was prescribed to 100% of the volume. Post-implant CT and MRI scans for Day 0 dosimetry was used to contour the CTV, which again was the appropriate right or left half of the prostate. Further dosimetric calculations were performed 30 days post-implant to ensure coverage and seed stability. Given the prior external beam radiation dose, all attempts were made at the time of implant to spare the rectum and urethra, with the goal of limiting rectal $V_{100\%}$ to less than 1 cc and urethral $V_{150\%}$ to 0 cc.

### *Follow-up*

Patients returned for follow-up at 1 and 3 months following BT, and every 6 to 12 months thereafter. This generally consisted of a focused history, DRE (except 1 and 3 month visits), and PSA (except 1 month visit). Biochemical failure was determined using the Phoenix definition (i.e. PSA nadir + 2 ng/mL). Toxicity, including gastrointestinal (GI), genitourinary (GU), and erectile dysfunction (ED) was defined according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

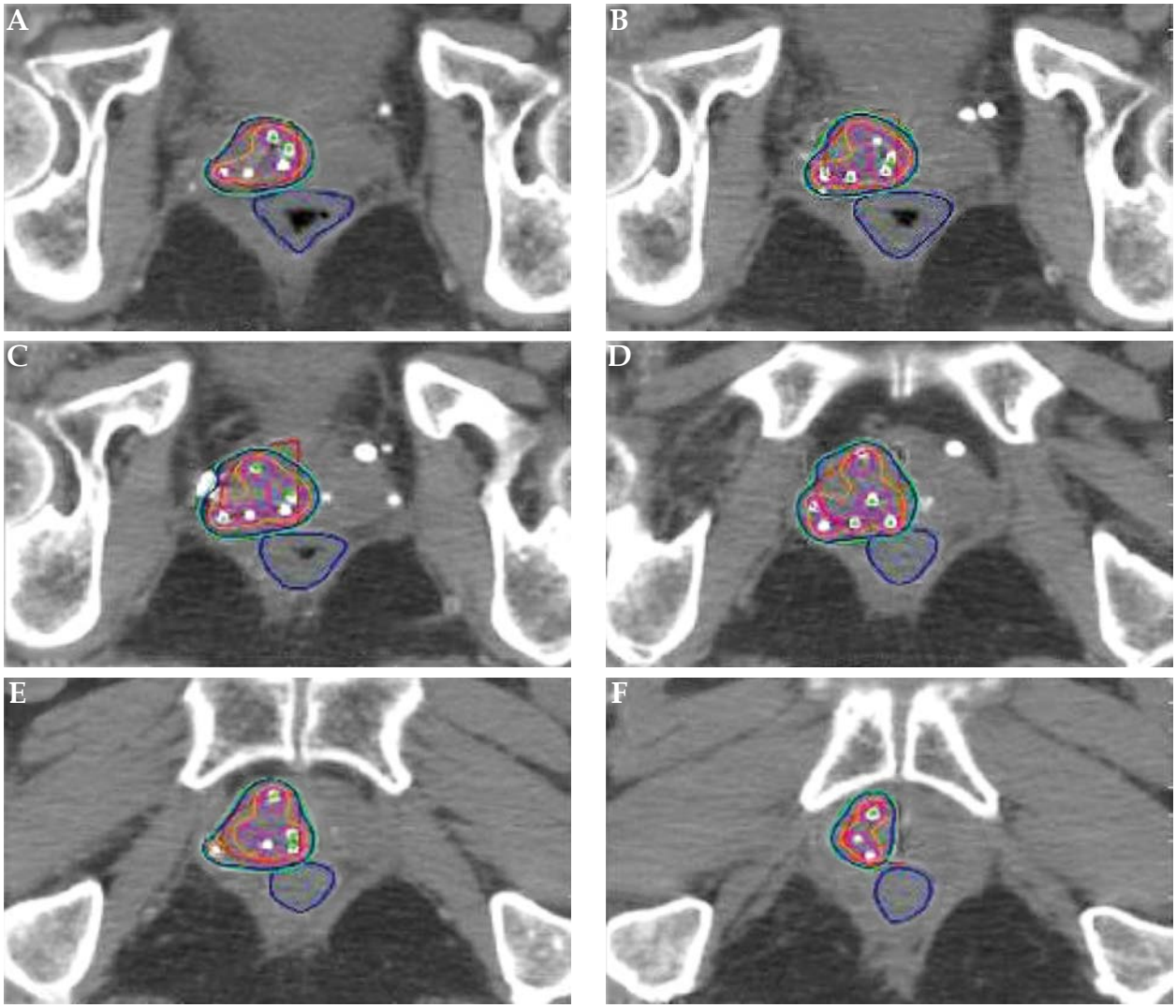


**Fig. 1.** Day 0 CT-based axial dosimetry from base (A) to apex (F) of a typical partial permanent prostate seed implant. Partial prostate volume in red. Rectal outline in blue. Isodose lines: pink – 200% (220 Gy), orange – 150% (165 Gy), blue – 100% (110 Gy), green – 90% (99 Gy)

## Results

The median follow-up was 41 months (range: 24–60). Descriptions of the five cases from the time of initial diagnosis to last follow-up are described below and summarized in Table 1. Brachytherapy characteristics and 30 day post-implant dosimetry are summarized in Table 2. Overall, there was no increase in GI or GU toxicity following salvage BT. There was some progression of ED in three patients, evidenced by a decline in their Sexual Health Inventory for Men (SHIM) scores. Figure 2 shows the American Urologic Association (AUA) Prostate Symptom Scores over time and no trends were observed. All patients had a decline in serum PSA following salvage BT without evidence of biochemical failure.

### *Patient 1*

A 66 year old Caucasian male with presenting PSA of 5.2 ng/mL, GS 6 (3 + 3) disease in the right base, mid and apex, and clinical T2A disease on DRE. He was randomized to the hypofractionated arm of FCCC IRB #02-602, receiving 70.2 Gy in 26 fractions using IMRT. His PSA nadir was 0.2 ng/mL, 2.8 years after treatment. He had two post-treatment biopsies, the first at two years showing GS 6 (3 + 3) adenocarcinoma with radiation effect. A second biopsy at three years failed to show regression, with GS 6 (3 + 3) disease with treatment effect on the right. At the time of salvage BT, 3.4 years after EBRT, his PSA was 0.3 ng/mL. Brachytherapy and dosimetry details are shown in Table 2. At his last follow-up, five years post-salvage BT, his DRE was within normal limits and PSA was 0.1 ng/mL. He had no acute or late grade 2 or higher GI or GU toxicities throughout. There was evidence of grade 2 ED after EBRT, which was unchanged after salvage BT with SHIM scores ranging from 8-11 without interventions.

### *Patient 2*

A 66 year-old Caucasian male with presenting PSA of 5.0 ng/mL, GS 7 (3 + 4) adenocarcinoma in the right base,

**Table 1.** Patient characteristics

| Factor | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 |
|---|---|---|---|---|---|
| Age (yrs) | 66 | 66 | 52 | 46 | 57 |
| Gleason score | 7 (3 + 4) | 6 (3 + 3) | 6 (3 + 3) | 6 (3 + 3) | 7 (3 + 4) |
| PSA (ng/mL) | 5.2 | 5.0 | 8.3 | 10.4 | 4.7 |
| T stage | T2a | T2a | T2b | T1c | T2a |
| EBRT technique; dose/fractions | IMRT; 70.2 Gy/26 | 3DCRT; 78 Gy/39 | IMRT; 76 Gy/38 | 3DCRT; 78 Gy/39 | IMRT; 76 Gy/38 |
| PSA nadir (ng/mL) | 0.2 | 0.7 | 1.4 | 0.8 | 0.4 |
| Number of post-RT biopsies | 2 | 1 | 3 | 1 | 2 |
| Post-RT biopsy GS | 6 (3 + 3) | 7 (4 + 3) | † | 7 (3 + 4) | 7 (3 + 4) |
| Time to salvage BT (yrs) | 3.4 | 9 | 5.3 | 11 | 6.8 |
| PSA at salvage BT (ng/mL) | 0.3 | 2.1 | 2.6 | 2.5 | 3.1* |
| ADT | N/A | N/A | N/A | 6 months | 6 months |
| Duration of follow-up (yrs) | 5 | 4.4 | 3.4 | 2 | 2 |
| PSA at last follow-up (ng/mL) | 0.1 | 0.5 | 1.4 | 0.4 | 0.2 |
| Toxicity (≥ gr 2)‡ pre-salvage BT | ED | ED | ED | N/A | ED |
| Toxicity (≥ gr 2)‡ post-salvage BT | ED | ED | ED | ED | ED |

*PSA – prostate specific antigen, T stage – tumor stage, EBRT – external beam radiotherapy, RT – radiotherapy, GS – Gleason score, BT – brachytherapy, ADT – androgen deprivation therapy, gr – grade, ED – erectile dysfunction*
**met PSA definition for biochemical failure per Phoenix criteria (PSA nadir + 2 ng/mL)*
*†Unable to be graded*
*‡Grade 2 or higher gastrointestinal (GI), genitourinary (GU), or erectile dysfunction (ED) according to CTCAE v.3*

**Table 2.** Brachytherapy characteristics and 30 day post-implant prostate dosimetry

| Factor | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 |
|---|---|---|---|---|---|
| Laterality | Right | Right | Left | Right | Right |
| Target volume | 14.1 cc | 14 cc | 9.4 cc | 10 cc | 13 cc |
| Prostate length | 3 cm | 3 cm | 3 cm | 3 cm | 4 cm |
| Number of needles | 9 | 8 | 7 | 6 | 5 |
| Number of seeds | 36 | 41 | 34 | 34 | 43 |
| Total activity | 11.85 mCi | 13.53 mCi | 11.22 mCi | 11.22 mCi | 14.19 mCi |
| $D_{90\%}$ | 125.4 Gy | 129.9 Gy | 137.6 Gy | 138.3 Gy | 100.5 Gy |
| $V_{110\ Gy}$ | 94.4% | 95.3% | 98.9% | 96.2% | 85.4% |
| $V_{140\ Gy}$ | 83.4% | 86.2% | 90.4% | 89.4% | 67.5% |
| $V_{145\ Gy}$ | 80.6% | 84.0% | 86.0% | 87.5% | 64.2% |

*cc – cubic centimeters, mCi – millicuries, $D_{90\%}$ – dose delivered to 90% of the post-implant volume, $V_{110\ Gy}$ – post-implant volume receiving 110 Gy, $V_{140\ Gy}$ – post-implant volume receiving 140 Gy, $V_{145\ Gy}$ – post-implant volume receiving 145 Gy*

mid and lateral margin and apex, and clinical T2A disease on DRE. He received primary EBRT with 3DCRT to 78 Gy in 39 fractions. His PSA nadir five years post-treatment was 0.7 ng/mL. A repeat biopsy at nine years post-treatment, at which time his PSA was 2.1 ng/mL and his DRE showed firmness on the right, demonstrated GS 7 (4 + 3) and 6 (3 + 3) disease in 3 cores on the right. He underwent salvage BT more than 9 years after completion of EBRT. Brachytherapy and dosimetry details are shown in Table 2. At his last follow-up, 4.4 years after salvage treatment, his PSA was 0.5 ng/mL and DRE was within normal limits. He had no acute or late grade 2 or higher GI or GU toxicities. He had late grade 2 ED following primary EBRT, which declined further after salvage BT with SHIM scores ranging from 5-10, for which he used a vacuum-assisted device with success.

### *Patient 3*

A 52 year old Caucasian male with presenting PSA of 8.3 ng/mL, GS 6 (3 + 3) disease in the left apex, mid, base and lateral mid and base, and clinical T2A disease on DRE. He was randomized on FCCC IRB #02-602 to the conventional fractionation arm and received IMRT to 76 Gy in 38 fractions. His PSA nadir was 1.4 ng/mL, 1.3 years after treatment. He had a total of three post-treatment biopsies. The first biopsy at two years (per #02-602 protocol) and second biopsy at four years, both showed

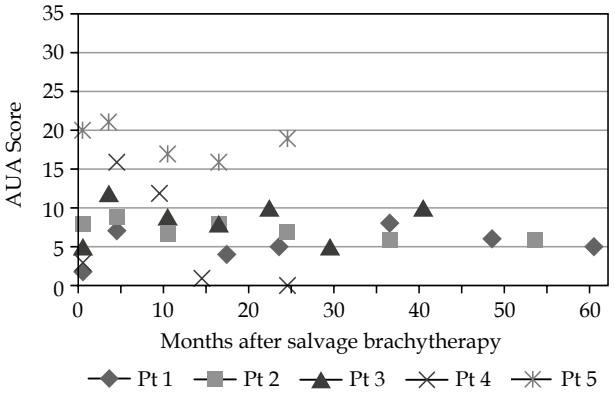


**Fig. 2.** Patient-reported American Urologic Association (AUA) scores as a function of time

prostatic adenocarcinoma with treatment effect. A final biopsy, five years post-treatment showed adenocarcinoma (unable to be graded) in 3 cores on the left. He underwent salvage BT, 5.3 years after EBRT, at which time his PSA was 2.6 ng/mL. Brachytherapy and dosimetry details are shown in Table 2. At his last follow-up, 3.4 years post-salvage treatment, his PSA was 1.4 ng/mL and DRE was within normal limits. He had no acute or late grade 2 or higher GI or GU toxicities. After primary EBRT, he experienced grade 2 ED with SHIM scores of 20 with phosphodiesterase-5 enzyme (PDE-5) inhibitors. Following salvage BT, his erectile function declined further with SHIM scores of 5-12, and was subsequently referred to the ED clinic.

### *Patient 4*

A 46 year-old Caucasian male with presenting PSA of 10.4 ng/mL, GS 6 (3 + 3) adenocarcinoma in the left base and right base, mid and apex, and clinical T1C disease on DRE. He was treated with 3DCRT to 78 Gy in 39 fractions. His PSA nadir was 0.76 ng/mL, 5.5 years after completion of treatment. A repeat biopsy at 10.4 years post-treatment, at which time his PSA was 2.46 ng/mL and there was firmness on DRE, showed GS 7 (3 + 4) adenocarcinoma in 6 cores on the right. He underwent salvage BT 11 years after EBRT. Brachytherapy and dosimetry details are shown in Table 2. He also received 6 months of ADT, beginning the day of his implant due to his GS 7 and high bulk disease. At his last follow-up 2 years after salvage treatment, his DRE was within normal limits, PSA was 0.4 ng/mL, and testosterone was 180 ng/dL. He had no acute or late grade 2 or higher GI or GU toxicities. Following primary EBRT, he had mild ED with a SHIM score of 19, not requiring interventions. After salvage BT, his SHIM scores dropped to 5 on ADT, but increased to 10 without medications by his last follow-up.

### *Patient 5*

A 57 year-old African American male with presenting PSA of 4.7 ng/mL, GS 7 (3 + 4) and 6 (3 + 3) disease in the right mid, base, lateral apex and base, and clinical T2A disease on DRE. He was randomized on FCCC IRB #02-602 to standard fractionation, and received 76 Gy in 38 fractions using IMRT. His PSA nadir at 2.3 years after completion of therapy was 0.4 ng/mL. He had two post-treatment biopsies, the first at two years (per #02-602 protocol), showing atypical small acinar proliferation. A repeat biopsy 6.7 years post-treatment showed GS 7 (3 + 4) and 6 (3 + 3) adenocarcinoma in 5 cores on the right. He underwent salvage BT 6.8 years post-treatment, at which time his PSA was 3.09 ng/mL and his DRE demonstrated a palpable abnormality. Brachytherapy and dosimetry details are shown in Table 2. He received short-term ADT for 6 months beginning the day of his implant due to GS 7 and high bulk disease. At his last follow-up 2 years post-salvage BT, his PSA was 0.19 ng/mL and testosterone was 153 ng/mL, and DRE was within normal limits. He experienced some acute grade 2 toxicities during primary EBRT, but no acute or late grade 2 or higher GI or GU toxicities following salvage BT. He had evidence of ED following primary EBRT with SHIM scores of 16-17 with use of a PDE-5 inhibitor. After salvage BT, his erectile function was unchanged, with SHIM scores of 11 without and 16 with medications.

## Discussion

The management of locally recurrent or persistent prostate cancer following EBRT is challenging. As evidence that local persistence of prostate cancer translates to the development of distant metastasis and disease-specific death mounts [24], the need for an effective salvage therapy is emphasized. Local salvage therapy is potentially curative and advisable in healthy patients with local recurrence without metastases. Re-irradiation with EBRT, however, is generally not advised due to concerns of insufficient conformity to spare surrounding normal tissues that have previously received tolerance dose. Furthermore, the mechanism of radioresistance that resulted in persistent disease can prevail if a similar EBRT approach is used for salvage. Accepted local salvage treatment options include radical prostatectomy, cryotherapy, or BT.

Few men undergo salvage radical prostatectomy with even the most experienced centers performing on average five or six cases per year [25]. Patient selection and preference are most likely the predominant factors, heavily influenced by a narrow risk-to-benefit ratio. Common complications of salvage radical prostatectomy include urinary incontinence (30-73%), urethral strictures (0-30%), erectile dysfunction (29-72%), and rectal injury (0-35%), Success rates are ~50% [26,27]. Utilization of cryosurgery is scarcer, with a comparable risk-to-benefit profile, but availability and expertise appears to be limited [28,29]. In general, the toxicities of salvage BT are minimal and tolerable. Compared to other modalities, BT provides at least a similar if not better risk-to-benefit ratio, because of reduced toxicity to the urinary tract. Urinary incontinence rates following salvage prostatectomy and cryotherapy have been reported to be as high as 73-79% [26,27,30-32] compared to 6-31% with salvage LDR BT [4,8].

Several centers have reported their experience with salvage whole prostate LDR BT following EBRT to dos-

es of 63-68 Gy. In the early series by Grado *et al*. [4] and Beyer *et al*. [33], the 5-year biochemical disease-free survival rates were 34% and 53%, respectively. More recent series from Lo *et al*. [6] showed an 8-year actuarial freedom from relapse of 61.5%, whereas Aaronson *et al*. [7] reported a biochemical disease-free survival rate of 88% at 30 months. Unfortunately, there are no reports of salvage LDR BT for patients treated in the era of EBRT dose-escalation.

The goal of this technique was to provide a minimally-invasive procedure that would both limit the risk of toxicity in men treated to EBRT doses ≥ 76 Gy in 2 Gy fractions and provide equal efficacy to whole prostate salvage BT. Central to this goal was selecting patients with limited post-EBRT toxicity, and who are most likely to have unilaterally recurrent disease. All the men reported here had little or no late GU toxicity following EBRT, and thus were ideal candidates. Prior to salvage therapy, all patients had good rectal function, none required alpha-blockers, and the AUA scores were low (median 3, range: 2-20). Patients in the series had either no evidence of bilateral disease upon initial diagnosis or a microfocus of low grade GS 3 + 3 disease, which definitive doses of EBRT of ≥ 76 Gy should eradicate.

The ideal BT dose for salvage therapy is undefined. In previous studies, the median prescribed salvage BT doses for ranged from 100 to 160 Gy [4-7]. These salvage BT doses were used prior to the era of dose-escalated EBRT, and thus could only be applied to our patient population with caution. In addition, these series reported on whole prostate salvage BT, with no data to suggest appropriate doses for partial or unilateral salvage BT. Given these considerations, a prescription dose of 110 Gy was selected based upon extrapolation from the available literature, while being conservative as day 30 dosimetry is often higher. Since higher salvage BT doses can lead to worse toxicity, we limited both the volume and dose. Despite the smaller volume and lower dose in the current study, the coverage of the target volume was excellent with a median $D_{90}$ of 118%. None of the patients experienced grade 2 or higher GI or GU toxicity and all had good biochemical response with no evidence of BF to date.

High-dose-rate (HDR) BT may be a safer and more effective way of delivering partial salvage BT. The advantages of HDR are: 1) less dependence on the accuracy of needle placement compared to LDR; 2) inverse treatment planning can allow the plan to be optimized on a case by case basis; 3) the implant is temporary; therefore, there is no concern over seed migration or need to repeat post-implant dosimetry several weeks later; 4) radiation safety advantages compared to LDR, with less radiation exposure to personnel due to the remote afterloading technique, and 5) it also lends itself to fractionation, which may allow for even superior tumor control due to delivery of higher biologically effective doses.

Possible disadvantages of HDR BT are that it is a relatively newer technique with overall less experience and long-term toxicity data; it produces more dose inhomogeneities within the treatment volume, and it often requires fractionation, which is less convenient for the patient [34]. Yamada *et al*. recently published the results of their phase II study of salvage HDR alone after high dose EBRT. The biochemical relapse-free survival was 68.5% at 5 years with late grade 2 GI and GU toxicities of 8% and 48%, respectively, with minimal late grade 3 GU toxicity [35]. As such, salvage HDR BT may become a more favorable option for local salvage therapy following dose-escalated EBRT in the future.

## Conclusions

Preliminary follow-up suggests that partial salvage permanent prostate BT with $^{125}$I may be a safe and effective local salvage therapy following dose-escalated EBRT. To our knowledge, this is the first report of permanent LDR partial prostate BT. Although short-term follow-up is encouraging, further study is needed to determine the long-term toxicity and effectiveness of this approach.

## Disclosure

Authors report no conflict of interest.

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