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## INVITED RESEARCH HIGHLIGHT

Prostate Cancer

# Salvage brachytherapy for locally recurrent prostate cancer after external beam radiotherapy

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**E**xternal beam radiotherapy (EBRT) is a standard treatment for prostate cancer. Despite the development of novel radiotherapy techniques such as intensity-modulated conformal radiotherapy, the risk of local recurrence after EBRT has not been obviated. Various local treatment options (including salvage prostatectomy, brachytherapy, cryotherapy, and high-intensity focused ultrasound [HIFU]) have been employed in cases of local recurrence after primary EBRT. Brachytherapy is the first-line treatment for low-risk and selected intermediate-risk prostate tumors. However, few studies have examined the use of brachytherapy to treat post-EBRT recurrent prostate cancer. The purpose of this paper is to analyze the current state of our knowledge about the effects of salvage brachytherapy in patients who develop locally recurrent prostate cancer after primary EBRT. This article also introduces our novel permanent brachytherapy salvage method.

There are various treatment options for patients who develop locally recurrent prostate cancer after primary EBRT. Agarwal *et al.* reported that androgen-deprivation therapy (ADT) was the most common salvage treatment (93.5%) for post-EBRT recurrent prostate cancer and that salvage brachytherapy was only performed in 0.2% of

cases.<sup>1</sup> The benefits of ADT are well-known; however, it is also associated with various adverse effects including a loss of libido, impotence, anemia, an increased incidence of skeletal fractures, and a higher cardiovascular mortality rate. Various local salvage treatment options including brachytherapy, radical prostatectomy, cryotherapy, and HIFU have been used to treat post-EBRT locally recurrent prostate cancer. Whole-gland salvage brachytherapy has demonstrated acceptable oncological outcomes; however, it can have significant side effects including incontinence, genitourinary toxicities, and gastrointestinal toxicities.<sup>2,3</sup> Recently, focal salvage brachytherapy has been used to treat post-EBRT locally recurrent prostate cancer in order to reduce the frequency of adverse events while maintaining appropriate cancer control rates.<sup>4,5</sup> However, only a few reports about focal salvage brachytherapy for post-EBRT locally recurrent prostate cancer have been published. In this article, we analyze the use of whole-gland and focal brachytherapy for post-EBRT locally recurrent prostate cancer, focusing on their clinical outcomes and toxicity. Recently, we started performing focal salvage brachytherapy based on three-dimensional cancer mapping data obtained using magnetic resonance imaging (MRI)-transrectal ultrasound (TRUS) fusion biopsy examinations. Herein, we introduce our novel permanent brachytherapy salvage method.

### SALVAGE BRACHYTHERAPY

There have been a number of reports about the use of salvage brachytherapy in cases of prostate cancer in which EBRT failed. Table 1 shows the outcome rates of salvage brachytherapy for prostate cancer.<sup>2–4,6–13</sup> In

prostate cancer, salvage brachytherapy has been reported to achieve biochemical control rates ranging from 20% to 89% (median follow-up period: 19 to 108 months). Table 2 shows the complication rates of salvage brachytherapy for prostate cancer. The frequency of genitourinary toxicities ranged from 12% to 87% and 3 to 47% for grades 1–2 and 3–4 toxicities, respectively. As for gastrointestinal toxicities, the frequency of grades 1–2 toxicities ranged from 4% to 65% and that of grades 3–4 toxicities ranged from 0% to 20%. Erectile dysfunction was seen in 2% to 95% of cases.

The first detailed data regarding the outcomes of salvage brachytherapy for prostate cancer were reported by Grado *et al.* in 1999. In that study, 49 patients who underwent brachytherapy after EBRT failure, which was defined as two successive increases in the patient's prostate-specific antigen (PSA) value from the posttreatment PSA nadir, were followed-up for a median period of 64 months, and their 5-year biochemical disease-free survival rate was 34%.<sup>2</sup> Recently, Aaronson *et al.* reported that the 3-year biochemical disease-free rate (Phoenix definition) was 88% among patients who were followed-up for a median period of 30 months.<sup>11</sup> The biological disease-free rate reported by Grado *et al.*<sup>2</sup> was lower than that reported by Aaronson *et al.*<sup>11</sup> however, this might have been partly due to the fact that these studies used different definitions of biochemical failure (BF). Improvements in imaging techniques like MRI, which has resulted in more appropriate patient selection for salvage brachytherapy, might also have contributed to the discrepancies between the findings of the latter studies.

In most previous studies, salvage brachytherapy was performed using low dose

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**Table 1: Outcome rates of salvage BRT series**

Author	No patients	Adjuvant ADT %	Median follow-up	BRFS (time point) %	Definition of failure	Whole gland or focal	Dose BRT
Wallner <i>et al.</i> <sup>6</sup>	13	NR	36 months	51 (5 years)	Metastasis-free	Whole gland	<sup>125</sup> I: 170 Gy
Grado <i>et al.</i> <sup>2</sup>	49	NR	64 months	34 (5 years)	Two rises above nadir	Whole gland	<sup>125</sup> I: 160 Gy <sup>103</sup> Pd: 170 Gy
Beyer <sup>7</sup>	17	47	62 months	53 (5 years)	ASTRO criteria	Whole gland	<sup>125</sup> I: 120 Gy <sup>103</sup> Pd: 90 Gy
Wong <i>et al.</i> <sup>8</sup>	17	71	44 months	75 (4 years)	ASTRO criteria	Whole gland	<sup>125</sup> I: 120–126 Gy <sup>103</sup> Pd: 103–112 Gy
Nguyen <i>et al.</i> <sup>3</sup>	25	0	47 months	70 (4 years)	Phoenix criteria	Whole gland	<sup>125</sup> I: 137 Gy
Lee <i>et al.</i> <sup>9</sup>	10	52	19 months	89 (2 years)	ASTRO criteria	Whole gland	HDR: 6 Gy×6 Gy fractions
Burri <i>et al.</i> <sup>10</sup>	37	84	86 months	54 (10 years)	Phoenix criteria	Whole gland	<sup>125</sup> I: 128.8 Gy or <sup>103</sup> Pd
Aaronson <i>et al.</i> <sup>11</sup>	37	17	30 months	88 (3 years)	Phoenix criteria	Whole gland	<sup>125</sup> I: 108–122 Gy
Moman <i>et al.</i> <sup>12</sup>	31	NR	108 months	20 (5 years)	Phoenix criteria	Whole gland	<sup>125</sup> I: 145 Gy
Jo <i>et al.</i> <sup>13</sup>	15	0	29 months	NR	ASTRO criteria	Whole gland	HDR: 11 Gy×2 Gy fractions
Peters <i>et al.</i> <sup>4</sup>	20	40	36 months	60 (3 years)	Phoenix criteria	Focal	<sup>125</sup> I: 144 Gy

BRFS: biochemical recurrence-free survival; NR: not reported; ADT: androgen-deprivation therapy; BRT: brachytherapy; HDR: high dose rate

**Table 2: Complications of salvage BRT series**

	Urinary incontinence (%)	GU toxicity (%)		GI toxicity (%)		ED (%)
		Grades 1–2	Grades 3–4	Grades 1–2	Grades 3–4	
Wallner <i>et al.</i> <sup>6</sup>	31	36	NR	36	4	NR
Grado <i>et al.</i> <sup>2</sup>	6	12	14	4	2	2
Beyer <sup>7</sup>	24	24	NR	NR	0	NR
Wong <i>et al.</i> <sup>8</sup>	6	53	47	65	6	NR
Nguyen <i>et al.</i> <sup>3</sup>	0	NR	20	NR	20	NR
Lee <i>et al.</i> <sup>9</sup>	0	86	14	14	0	95
Burri <i>et al.</i> <sup>10</sup>	NR	43	11	NR	NR	85
Aaronson <i>et al.</i> <sup>11</sup>	2.7	2.7	0	5.4	2.7	NR
Moman <i>et al.</i> <sup>12</sup>	NR	87	3	55	0	NR
Jo <i>et al.</i> <sup>13</sup>	0	NR	0	NR	0	NR
Peters <i>et al.</i> <sup>4</sup>	20	30	5	15	0	65

GU: genitourinary; GI: gastrointestinal; ED: erectile dysfunction; NR: not reported; BRT: brachytherapy

rate techniques; however, there have been two reports about the use of high-dose rate (HDR) techniques. Lee *et al.* treated 21 patients who developed locally recurrent prostate cancer after EBRT using HDR brachytherapy. Although the median follow-up period was only 19 months, the 2-year biochemical disease-free rate was 89%. No grades 3–4 gastrointestinal toxicities occurred, and grade 3 genitourinary toxicities were only seen in 14% of cases. Thus, it was concluded that HDR salvage brachytherapy is feasible and safe.<sup>9</sup> Jo *et al.* treated 11 patients using HDR salvage brachytherapy (2 fractions of 11 Gy) and reported that no grade 3 or more severe adverse events occurred.<sup>13</sup>

Salvage brachytherapy is usually delivered to the whole of the prostate gland. Although this results in an acceptable biological disease-free rate, it has also been reported to cause grades 3 and 4 adverse events.<sup>2,3</sup> Wong *et al.* described the treatment outcomes of 17 patients who received combined whole gland salvage

brachytherapy and short-term ADT for locally relapsed prostate cancer after EBRT. They found that grades 3 and 4 genitourinary toxicities developed in 7 patients (41%) and 1 patient (6%), respectively.<sup>8</sup> In addition, it has been demonstrated that the frequency of toxicities is significantly higher after salvage brachytherapy than after brachytherapy for primary disease.<sup>14</sup> Treating focal lesions of the prostate might be one-way of reducing the risk of adverse events. In 2014, Peters *et al.* reported a retrospective analysis of 20 patients who received focal salvage brachytherapy for locally recurrent prostate cancer. After a median follow-up period of 36 months (range: 10–45), BF had occurred in six patients (30%). Furthermore, grade 3 genitourinary toxicities developed in one patient (5%), and grade 1 urinary incontinence was seen in 4 patients (25%). As a result, it was concluded that focal salvage brachytherapy achieves acceptable outcomes in terms of the biochemical response, its toxicity profile, and the patients' quality-of-life.<sup>4</sup>

### OUR NOVEL DOSIMETRIC CRITERIA FOR SALVAGE BRACHYTHERAPY BASED ON THREE-DIMENSIONAL CANCER MAPPING

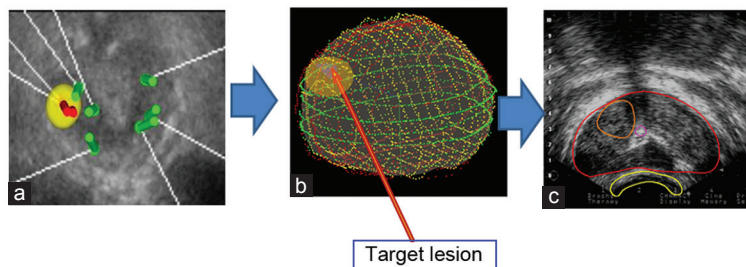
In patients who develop recurrent prostate tumors after EBRT, we have started performing permanent salvage brachytherapy based on three-dimensional cancer mapping data obtained from MRI-TRUS fusion biopsy examinations. After BF (Phoenix definition) occurs, the patient undergoes CT and bone scans as primary examinations to confirm the absence of lymph node and distant metastases. In addition, 3T multi-parametric MRI (Achieva 3T, Philips Medical Systems, Best, The Netherlands) is performed. When a cancer focus is suspected to be present in the prostate on MRI, the patient undergoes transrectal MRI-TRUS fusion biopsy as a candidate for salvage brachytherapy. A systematic biopsy is performed at 8–10 sites depending on the volume of the prostate and at 1–2 sites in each of the target lesions detected on MRI. In patients in whom cancer

is detected during the biopsy, the cancer lesions are mapped using Urostation® based on three-dimensional positional information about the cancer-positive cores, and appropriate dosimetric patterns are determined for the subsequent salvage brachytherapy.

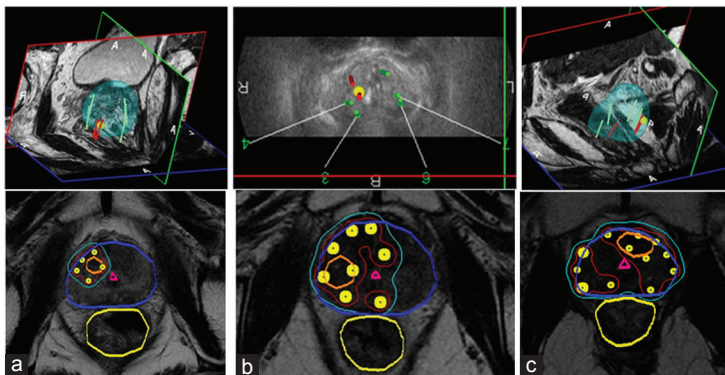
A flowchart of the dosimetric planning process is shown in **Figure 1**. During planning, a cross-sectional image of the entire prostate including the three-dimensional cancer map is prepared from 5-mm slices on Urostation®. All of our patients have been treated using the InterPlant treatment planning system (ver.3.4, ELEKTA, Sweden).

We use the following three treatment patterns, which are based on the number and distribution of biopsy-positive regions and the biopsy Gleason score (GS) (**Figure 2**):

- Focal pattern: one positive core was



**Figure 1:** Dosimetry planning based on cancer mapping. (a) The needle tracts produced during the needle biopsy are visualized on Urostation®. The red tract represents the cancer core, and the green tracts are noncancer cores. (b) Cancer mapping in the prostate using Urostation®. The region to be targeted by focal therapy is shown in yellow. (c) The three-dimensional model of the prostate constructed in (b) was reconstructed using 5-mm slices, and the DICOM data were transferred to the brachytherapy software. The DICOM data were synchronized with 5-mm cross-sectional slices obtained using ultrasonography during preplanning in order to plan the seed distribution. The lesions in the right prostate lobe diagnosed by positive biopsy are consistent with the localization of the cancer lesions on Urostation®.



**Figure 2:** Positive regions in 3 cancer lesions on Urostation® and radiation source distribution pattern. (a) Focal pattern: red cancer tracts were visualized in the prostate (mesh pattern) constructed on magnetic resonance imaging. Two cancer tracts were localized in one hemi-lobe in the targeted biopsy region. The radiation sources were distributed so that radiation was restricted to the target lesion. (b) In addition to the target lesion in the yellow region, cancer cores were detected in one of the systematic biopsies. The cancer-positive regions were localized in one hemi-lobe; thus, a hemi-focal pattern was selected. (c) A red cancer core extended over both lobes; thus, a focused pattern in which the target lesion was irradiated with a high dose was planned.

detected within one hemi-lobe during the targeted biopsy, and it exhibited a GS of <8. One of the cancer-positive regions constructed using Urostation® was the single focal lesion. The focal gross tumor volume GTV (F-GTV), which was equal to the focal clinical target volume (F-CTV), was defined as the target (focal) lesion

- Hemi-lobe pattern: positive cores were detected within one hemi-lobe during targeted/systematic biopsies and exhibited GS of <8. In addition to the target lesion(s), seeds were placed in the affected hemi-lobe. Similar to the focal pattern, the F-GTV was (were) defined as the target (focal) lesion(s). The F-CTV was defined as the hemi-lobe of the prostate

- Whole/focused gland pattern consistent with hormonal therapy: positive core(s) with GS of >7 were identified regardless of their location, or positive cores with GS <8 were detected in the bilateral lobes. When cancer foci were depicted on MRI, the F-GTV was defined as the target lesion. The F-CTV was defined as the whole prostate.

The dosimetric criteria for each of the above patterns are as follows:

- Focal pattern: the minimum dose received by 90% of the F-GTV (D90(F-GTV)) and the volume of the F-GTV that receives 100% of the prescribed dose (V100(F-GTV)) range from 160 to 180 Gy and >95%, respectively
- Hemi-lobe pattern: the D90 (F-GTV) and V100 (F-GTV) range from 160 to 180 Gy and >95%, respectively. The D90 (F-CTV) and V100 (F-CTV) range from 110 to 130 Gy and >95%, respectively
- Whole/focused gland pattern consistent with hormonal therapy: the D90 and V100 values for this pattern are similar to those for the hemi-lobe pattern.

In all of the above patterns, V100 (rectum) and D90 (urethra) are set at 0% and <165 Gy, respectively.

We started performing salvage brachytherapy based on three-dimensional cancer mapping data and fusion biopsy findings in July 2012 and have since treated nine patients. The focal, hemi-focal, and focused patterns were selected in 4, 3, and 2 patients, respectively. After a median follow-up period of 17 months (range: 12–23), BF had only occurred in one patient (at 13 months after salvage brachytherapy). Grade 1 toxicities developed in 2 patients (both patients exhibited the focused pattern). Grade 2 hematuria was noted in one patient, but it was resolved within a month. No severe complications were developed. Long-term follow-up is required to investigate the frequency of recurrence after salvage brachytherapy; however, so far our results suggest that the toxicities associated with salvage brachytherapy are mild compared with those induced by whole-gland salvage brachytherapy.

## DISCUSSION

There are various local treatment options (including salvage prostatectomy, brachytherapy, cryotherapy, and HIFU)

for locally recurrent prostate cancer that develops after primary EBRT. Radical salvage prostatectomy achieves satisfactory oncological control; however, it is also associated with complications such as incontinence, anatomic stricture, and rectal injuries because the radiation causes fibrosis and poor wound healing. Chade *et al.* performed a systematic review focusing on cancer control and the functional outcomes of radical salvage prostatectomy for postradiotherapy recurrent prostate cancer. They reported that the biochemical disease-free rate ranged from 47% to 82% at 5 years and from 28% to 53% at 10 years. They also found that the most frequent complications included anastomotic stricture (7%–41%) followed by rectal injury (0%–28%) and that the frequency of severe complications (grades 3–5) ranged from 0% to 25%.<sup>15</sup> Despite improvements in surgical techniques, the frequency of adverse events after radical salvage prostatectomy is still high suggesting that such procedures should be performed by experienced surgeons.

Cryotherapy and HIFU are typical salvage options for recurrent prostate cancer that develops after primary radiotherapy. Mouraviev *et al.* reported a systematic review of the use of salvage cryotherapy to treat patients that developed locally recurrent prostate cancer after primary radiotherapy. They found that the frequency of toxicities like urinary incontinence was lower in more recent studies. However, the risk of recto-urethral fistula formation cannot be completely abrogated, and such complications need to be treated with salvage therapy.<sup>16</sup> Most previous studies examining salvage HIFU were single-institution, small, retrospective studies. Salvage HIFU was reported to exhibit a much higher complications rate than primary HIFU. In addition, Murat *et al.* reported that 11% of patients that undergo salvage HIFU required artificial urinary sphincter implantation.<sup>17</sup>

Prostate brachytherapy is a well-established first-line treatment option; however, few reports have been published about secondary brachytherapy after the failure of primary radiotherapy. It has been reported that higher toxicity rates are observed after whole-gland salvage brachytherapy than after the whole-gland primary brachytherapy (Table 2). Nguyen *et al.* reported that serious complications that required surgical intervention (e.g., colostomy or urostomy) occurred in 12% patients.<sup>3</sup> Recently, Peters *et al.* retrospectively analyzed focal salvage brachytherapy in 20 patients.

Grade 1 urinary incontinence occurred in 4 patients (20%), but grade 3 genitourinary toxicities only occurred in one patient (5%).<sup>4</sup> These results were considered to be promising compared with the high frequencies of severe toxicities seen after whole-gland salvage therapy, which exhibits high rates of severe incontinence (up to 70%), urinary obstruction/retention (up to 50%), and rectal injuries/rectourethral fistulas (up to 10%).<sup>18,19</sup>

Gomez-Veiga *et al.* performed a systematic review focusing on the treatment of postradiotherapy recurrent prostate cancer with brachytherapy. They stated that accurately locating sites of recurrence through biopsy examinations is important for obtaining good outcomes after salvage brachytherapy.<sup>20</sup> MRI is often used to detect primary tumors. Unfortunately, the contrast between recurrent tumors and normal tissue decreases after EBRT; however, several recent reports have indicated that dynamic contrast-enhanced imaging techniques, diffusion-weighted imaging, and proton MR spectroscopy imaging are more accurate at diagnosing locally recurrent cancer.<sup>21</sup> Thus, such MRI techniques could be useful for guiding focal salvage therapy.

Arumainayagam *et al.* reported that multi-parametric MRI imaging diagnosed postradiotherapy recurrent prostate cancer with 93% accuracy during the examination of tumors with biopsy core lengths of >3 mm.<sup>22</sup> Recent studies have indicated that targeted biopsies guided by real-time three-dimensional TRUS registration systems with MRI/TRUS image fusion functions produce accurate results. For example, Ukimura *et al.* found that a novel three-dimensional transrectal ultrasound biopsy localization system achieved encouraging accuracy (<3 mm error) during the targeting of hypoechoic and isoechoic lesions.<sup>23</sup> Therefore, cancer mapping based on fusion biopsy data might be applicable to focal salvage therapy.

Focal salvage brachytherapy might reduce the frequency of adverse events while achieving acceptable cancer control. This requires the accurate localization of recurrent tumors within the prostate. As for our preliminary experience using MRI/TRUS fusion biopsy technique, long-term follow-up studies are required to investigate the frequency of recurrence after focal salvage brachytherapy; however, it has been suggested that the toxicities associated with such treatment are mild compared with those associated with therapies targeting the whole gland.

## CONCLUSION

Although focal salvage brachytherapy is not an established technique, in cases of post-EBRT recurrent prostate cancer, it might offer a way of reducing the frequency of toxicities while maintaining similar treatment outcomes compared with whole-gland therapy.

## EDITORIAL COMMENT—(BY DR JOHN W DAVIS, DEPARTMENT OF UROLOGY, THE UNIVERSITY OF TEXAS, MD ANDERSON CANCER CENTER, HOUSTON, TEXAS, USA)

Salvage therapy for prostate cancer, as reviewed by Yamada *et al.*, carries a higher burden/risk of short-term complications and long-term functional compromise. Salvage prostatectomy is the gold standard for failed radiation therapy with clinically localized (biopsy confirmed) disease. However some patients will naturally seek alternatives that can potentially avoid metastatic progression with fewer side effects. As the Yamada essay reviews, several authors have looked at brachytherapy as a viable option, with feasible side effects. In their short series of salvage brachytherapy, they demonstrate an emerging technique of MRI imaging and fusion biopsies to modified the salvage to focal versus whole gland. More studies will need to focus on the long-term effects of this methodology and comparisons to the more established methods of salvage cryotherapy.

## CONFLICTS OF INTEREST

None declared.

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