

# The role of salvage brachytherapy for local relapse after external beam radiotherapy for prostate cancer

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**Abstract:** Prostate cancer is the most prevalent cancer amongst men. For localized disease, there currently exist several reliable treatment modalities including surgery, radiotherapy and brachytherapy. Our growing understanding of this disease indicates that local control plays a very important role in prevention of subsequent dissemination. Many improvements to external beam radiotherapy over recent years have decreased toxicity and improved outcomes, but nonetheless, local relapse remains common. Many salvage options exist for locally recurrent prostate cancer, but are rarely offered, partly because of the fear of toxicity. Many men with isolated local recurrence therefore do not receive potentially curative second line treatment and are instead treated with palliative androgen suppression. Selection plays an important role in determining which individuals are likely to benefit from salvage. Those at high risk of pre-existing micro-metastatic disease despite negative staging scans are unlikely to benefit. Prostate brachytherapy has evolved over the more than 3 decades of experience. Modern techniques allow more precise tumor localization and dose delivery. Better understanding of dosimetric parameters can distinguish optimal from suboptimal implants. Salvage brachytherapy can be an effective treatment for locally recurrent prostate cancer after prior external beam radiotherapy. We review the literature pertaining to both low dose rate (LDR) and high dose rate (HDR) salvage brachytherapy and discuss patient selection, optimal dose, treatment volume and toxicity avoidance.

**Keywords:** Prostate; salvage therapy; brachytherapy

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## Introduction

Localized prostate cancer can be treated radically with surgery, external beam radiation (EBRT), brachytherapy or a combination. These therapies can all be effective in the right setting but relapses are not infrequent (1). Biochemical failure after EBRT has been defined as three consecutive rising prostate-specific antigens (PSAs) or, more commonly, a value exceeding the nadir by 2 ng/mL (2). In the past, a higher post-treatment PSA was acceptable after radiation, with the belief that since the prostate was left in-situ, there

might be sparing of non-malignant PSA-producing prostate glands. More recent evidence indicates that a higher PSA nadir predicts eventual failure (3-5).

Over the past 3 decades, developments in the delivery of EBRT have moved towards increased conformality using intensity modulation (IMRT) and inverse planning to integrate computer optimization, reducing dose to nearby organs such as the bladder, rectum, and small bowel. Increased precision and image-guidance permit safer dose escalation. Several studies have shown improved biochemical control by increasing conventionally

fractionated radiation dose from 64 to 81 Gy (6-11). Hypofractionated radiotherapy, based on radiobiologic data suggesting that the prostate has a low alpha-beta ratio, delivers a larger fraction size over fewer treatments and a shorter overall treatment time, a strategy to achieve higher tumor cell kill while limiting late effects.

Despite these developments, local control remains elusive, with biochemical failures ultimately occurring in 40–60% of patients (12). Many salvage options exist for local recurrence after EBRT, including surgery, brachytherapy, and more recently HIFU, cryotherapy, and stereotactic body radiotherapy (SBRT), but are infrequently used. The previous radical dose of radiation increases toxicity from second line treatment and access to these salvage options is often limited to specialized centers with the most experience (13). Thus, androgen deprivation therapy (ADT) is by far the most widely used treatment for recurrence post-EBRT (13,14). Reports indicate that only 2% of radiation failures are managed with local salvage, the rest being either observed or treated with ADT (13).

## ADT

Although initial biochemical response to ADT is almost universal, the median duration is only 24–36 months (15). Furthermore, ADT is associated with significant morbidity and even mortality. In addition to the expected hot flashes, loss of libido, erectile dysfunction, fatigue and mood changes, there is a wide range of metabolic changes leading to osteopenia, decreased muscle mass, obesity, gynecomastia, dyslipidemia, insulin resistance, anemia, and cardiovascular events (16-19). The timing and duration of ADT in the setting of biochemical failure have been investigated to reduce side effects in these patients who have a relatively long life expectancy and are asymptomatic from their local/biochemical recurrence. Two phase III trials, Timing of Androgen Deprivation (TOAD) (20) and Early vs. Late Androgen Ablation Trial (ELAAT) (NCT00439751) have explored the timing of ADT. The TOAD trial randomized 293 patients between immediate or delayed ADT. The hazard ratio (HR) for survival was 0.55 favoring immediate ADT, despite an increase in cardiovascular events, occurring in 9% compared to 6% in the delayed arm. Results of ELAAT trial have not been published yet.

Intermittent ADT has also been investigated to minimize adverse effects of testosterone suppression. The National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) PR7 trial randomized 1,386 men with biochemical

failure after radiotherapy and no evidence of distant metastases, to either intermittent ADT (IAD) using 8-month cycles, or continuous ADT (CAD). This was a non-inferiority trial with an acceptable HR for overall survival set at <1.25. At 7 years, the adjusted HR for death was 1.03, showing IAD to be non-inferior to CAD. Furthermore, quality of life was better, with significant improvement in hot flashes, urinary symptoms and libido, and a trend for decreased fatigue. However, the trial also demonstrated that the duration of off-treatment periods decreases over time, from 20 months for the first cycle to 13 months in cycle 2, 9 months in cycle 3 and then 4–5 months for later cycles (21), indicating that PSA doubling time shortens over time. Furthermore, reduced testosterone recovery lessens the potential quality of life (QOL) benefit.

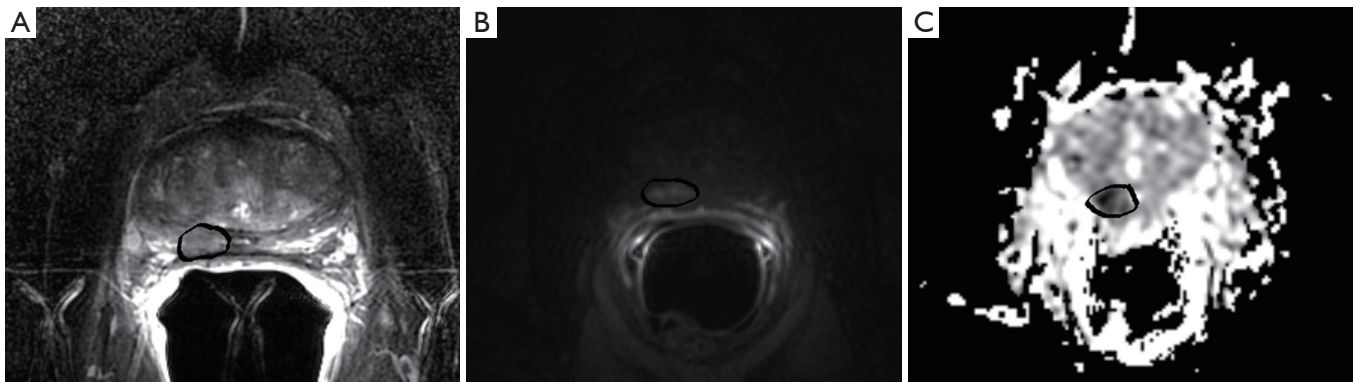
## Importance of local control and local salvage

Two decades ago, Fuks *et al.* evaluated the effect of local recurrence on the incidence of distant metastases in 679 patients. The 15-year distant metastasis free survival with local control was 77% compared to 24% in those with local failure. He concluded that local recurrence is a source for subsequent metastases and recommended complete eradication of local disease (22). Zelefsky *et al.* also assessed the importance of local tumor control on distant metastases. Biopsies on 339 patients previously treated with conformal radiation showed that those with negative biopsies had 10-year bRFS of 59% compared to 3% for positive biopsies. Multivariate analysis indicated that a positive posttreatment biopsy predicted for both biochemical failure ( $P<0.001$ ) (23) and distant metastases ( $P=0.003$ ).

We will review the appropriate work-up when considering a patient for local salvage, and the various options for local salvage, concentrating on brachytherapy and appropriate patient selection.

## Baseline imaging

Traditional staging for biochemical recurrence includes a Tc99 bone scan and CT scan of the abdomen and pelvis. However, the sensitivity of traditional imaging is less than adequate at low PSA values. Only 5% of bone scans and 12% of CTs are positive at PSA levels of 4–20 ng/mL (24,25). A review of 23 studies showed that bone metastases were detected in 2%, 5% and 16% for PSA levels <10, 10–20 and 20–50 ng/mL. Hövels *et al.* assessed the diagnostic accuracy of CT for detecting lymph nodes metastases



**Figure 1** Multiparametric MRI (mpMRI) for recurrent disease after prior 78 Gy/39 fractions 5 years earlier. 1.5T with endorectal coil. (A) T2 weighted image; (B) dynamic contrast enhancement (DCE); (C) apparent diffusion coefficient (ADC) map.

in patients with prostate cancer in a meta-analysis of 24 studies, and reported a pooled specificity and sensitivity of only 39% and 82% (26). PSMA-PET is much more promising. Pyka *et al.* compared detection rates of bone metastases in 76 patients using  $^{68}\text{Ga}$ -PSMA PET scan and  $^{99\text{m}}\text{Tc}$  bone scintigraphy. The sensitivity and specificity of PSMA-PET were 99–100% and 88–100%, while for bone scans, sensitivity and specificity were reduced to 87–89% and 61–96% (27), the range indicating the uncertainty regarding interpretation of equivocal lesions.

There have been significant refinements in imaging for detection of local recurrence, especially in the realm of prostate MRI and multiparametric MRI (mpMRI). The use of 3T magnets, and/or an endorectal coil, permits a higher signal-to-noise ratio which improves structural and functional detail (28). Prostate mpMRI includes both T1-weighted and T2-weighted anatomic imaging as well as functional imaging which distinguishes differences in cell density and diffusion of water molecules between normal and malignant tissue. The prostate imaging and reporting data system (PI-RADS) (29) has been developed to provide a uniform framework for grading the MRI sequences and reporting the likelihood of cancer. In the peripheral zone, the preferred functional sequence is DWI and the calculated apparent diffusion coefficient (ADC) map, whereas in the transition zone it is the T2 weighted image. Dynamic contrast enhancement (DCE) with Gadolinium measures perfusion parameters for rapid wash-in and wash-out on T1 imaging after rapid injection. DCE helps to resolve conflicting results between the T2 and DWI sequences. Incorporation of functional sequences improves the positive predictive value for mpMRI up to 98% compared to 68% for the T2W MRI alone (30). MR

spectroscopy, through the detection of choline peaks and choline/creatine ratios, has been used in prostate cancer detection but due its low sensitivity is no longer a required mpMRI sequence (29).

MpMRI plays an important role in the setting of local recurrence (*Figure 1*). Although a homogeneously decreased T2 signal is often seen in the peripheral zone after radiotherapy due to gland atrophy and fibrosis, the concomitant decreased vascularity contrasts to the neovascularity of recurrent tumor. While its role in the setting of primary detection may be limited, DCE is particularly useful in the setting of local recurrence (31) with a sensitivity and specificity of 0.77 and 0.89 respectively (32).

PSMA PET is also a very promising tool for detection of recurrent disease. Prostate specific membrane antigen (PSMA) is a type II membrane glycoprotein over-expressed in most localized prostate cancers.  $^{68}\text{Ga}$ -PSMA is a PSMA ligand. Eiber *et al.* assessed its utility in 248 post-prostatectomy patients with a median PSA of 2 ng/mL. Detection rates were 97% for PSA levels of  $\geq 2$  ng/mL, decreasing with lower PSA levels but still a respectable 58% for PSA 0.2 to  $<0.5$  ng/mL (33). PSMA-PET has the potential to identify local recurrence at low PSA levels while being a sensitive tool for detection of co-existing systemic disease which would disqualify a patient from definitive local salvage. Hruby *et al.* (34) assessed the role of PSMA-PET in a cohort of 419 men treated with EBRT 78–82 Gy, 48 of whom had biochemical failure without distant metastases on conventional scans. PSMA PET was positive in all 48, with 52% showing extra prostatic disease and only 17% with isolated local recurrence. PSMA PET scans will revolutionize patient selection after biochemical failure, and can identify those most likely to benefit from local salvage.

### Salvage prostatectomy

Although prostatectomy is a standard option in the *de novo* management of prostate cancer, removing the prostate after full dose radiation is associated with increased risk and toxicity. Many small single institution experiences have been reported, as well as some comprehensive systematic reviews. Overall, biochemical relapse-free survival (BRFS) ranges from 48–82% at 5 years and 28–53% at 10 years. CSS at 5 years is 65–79% and 70–83% at 10 years. In 2011 Chade *et al.* published a large retrospective series from tertiary care centers including 404 men between 1985 and 2009. With a median follow-up of 4.4 years, the 10-year BRFS, DMFS and CSS were 37%, 77% and 83% (35). Toxicity was not reported. Ward *et al.* published on 199 patients, reporting 10-year CSS rates of 65% but with rectal injury in 10%, bladder neck contracture in 22%, urinary extravasation in 15% and urinary incontinence in 44%. The most frequent toxicities reported are urinary incontinence in 19–64% and impotence in 70–100%, with anastomotic strictures seen in 7–41%, bladder neck contracture in 15–25%, rectal injury in up to 28%, and occasional rectovesical fistulae (Table 1). Despite the technical advantages and 3D magnification of robotic-assisted salvage prostatectomy, complications are reported in 47%, being major in 35% (38).

### Salvage therapies based on tissue ablation: high intensity focused ultrasound (HIFU) and cryotherapy

HIFU destroys tissue through the generation of low frequency, high energy ultrasound from a transrectal probe which heats the targeted tissue to 65–85° Celsius and induces coagulative necrosis. Salvage HIFU has demonstrated efficacy but considerable morbidity (Table 2). Crouzet *et al.* analyzed 418 patients from 9 centers across Europe and the United States. Although the median PSA nadir was 0.19 ng/mL and 5-year BRFS was 67%, 42% and 22% for low, intermediate and high-risk disease, rates of incontinence and bladder outlet obstruction were 30%, with recto-urethral fistulae in up to 10% (43). Jones *et al.* reported on 100 patients treated with HIFU post EBRT at 16 sites in North America. Of those who had post procedure biopsies, 81% were negative at 12 months but mean PSA nadir at 2 years was quite high at 1.1 ng/mL (44). and 20% developed grade 3 adverse events, including 5 rectal fistulae, 3 osteitis pubis and hematuria.

Cryotherapy uses freeze-thaw cycles to destroy tissue and has been gaining popularity. Cryoprobes and thermocouple

sensors are placed under ultrasound guidance with a warming device in the urethral catheter to limit urinary toxicity. Argon and helium freeze the tumor to minus 40° Celsius. Whole gland cryotherapy is associated with urinary incontinence in 15%, retention in 2%, and recto-urethral fistula in <3% (46) (Table 3). Ismail *et al.* reported on 100 cases of salvage whole gland cryotherapy. The 5-year BRFS for low, intermediate and high risk groups was very similar to those for HIFU. Focal cryotherapy may reduce toxicity (48). Li *et al.* reported on 91 patients with a BRFS at 5 years of 47%. Late toxicities included fistulae (3%), urinary retention (7%) and incontinence (6%) (49). In a comparison of hemi gland to whole gland cryoablation, BRFS at 5 years was 54% for hemi-gland and 86% for whole gland, but the latter was associated with worse toxicity.

### SBRT

There have also been a few studies assessing the role of SBRT for salvage post EBRT but none have a follow up greater than 2 years (Table 4). Doses range from 30 Gy in 5 fractions to 36 Gy in 6 fractions. PSA nadirs are reported as low as 0.16 ng/mL at 2 years. Early tolerance appears acceptable with grade 3 complications under 10% (51–54). Longer follow up is required.

### Brachytherapy

Low dose rate (LDR) or high dose rate (HDR) brachytherapy deliver very high doses of radiation in an ultra-conformal manner. By applying radiation internally, brachytherapy reduces the integral dose in comparison to EBRT, while permitting incomparable dose escalation. Brachytherapy is generally used as monotherapy for low and intermediate risk prostate cancer. In the high risk setting, Level One evidence has established brachytherapy in combination with ADT and pelvic EBRT (3) as the standard of care for upper tier intermediate and high risk disease (55). The role of brachytherapy in the salvage setting is less well defined but multiple small series and two multi-institution phase II trials have shown efficacy. The NCCN guidelines recognize either LDR or HDR as an option for local recurrence after prior radiotherapy (56).

### LDR brachytherapy

LDR brachytherapy involves implanting radioactive seeds, generally <sup>125</sup>I or <sup>103</sup>Pd, directly into the prostate. A pre-operative transrectal ultrasound is generally performed to

**Table 1** Published results for salvage prostatectomy

Study	Number	Period	Median follow-up in years	BRFS	DMFS	CSS	Toxicity
Bianco <i>et al.</i> (36)	100	1984–2003	5.0	55% 5-year	NR	73% 10-year, 60% 15-year	Major complications: 33%; rectal injury: 15%, incontinence: 58%; after 1993: major 13%, rectal injury 2%
Chade <i>et al.</i> (37)	404	1985–2009	4.4	48% 5-year, 37% 10-year	83% 5-year, 77% 10-year	92% 5-year, 83% 10-year	NR
Ward <i>et al.</i> (38)	199 (138 RP and 61 CP)	1967–2000	7.0	58% 5-year, 48% 10-year	NR	79% 5-year; 65% 10-year, 77% (RP) vs. 38% (CP)	Bladder neck contracture: 22%; urinary incontinence: 44%; urinary extravasation: 22%; rectal injury 5% (RP)
Chade <i>et al.</i> (35)	Review	1980–2011	–	47–82% 5-year, 28–53% 10-year	NR	70–83%, 10-year	Anastomotic stricture: 7–41%; rectal injury: 0–28%; major complications: 0–25%; erectile dysfunction: 80–100%
Rosoff <i>et al.</i> (39)	Review	1980–2012	–	37–55% 5-year	–	70–83%, 10-year	Urinary incontinence: 19–64%; Impotence: >70%
Mandel <i>et al.</i> (40)	55	2007–2012	3.0	49% 5-year	69% 5-year	89% 5-year	Incontinence at 1-year: 26%; impotence: 100% (8 nerve sparing); 1 abscess, 1 lymphocele, 1 anastomotic stricture, 1 mechanical ileus and 3 rectovesical fistulae. Fistula repair failed in 2/3 requiring urinary diversion
Yuh <i>et al.</i> (41)	51	2004–2012	3.0	57% 3-year	NR	NR	Complication rate 47%; impotence: 77% incontinence: 55%; major complications 35%; bladder neck contracture: 16%; deep vein thrombosis/Pulmonary embolism: 4%; urosepsis: 4%; rectourethral fistula: 1
Corcoran <i>et al.</i> (42)	21	1995–2010	5.7	57% at median follow-up	NR	86% at median follow-up	NR

RP, radical prostatectomy; BRFS, biochemical recurrence-free survival; DMFS, distant metastases free survival; CSS, cancer-specific survival; CP, cystoprostatectomy; NR, not reported.

assess factors such as pubic arch interference, prostate size, and urethral position. Images are taken for planning the ideal needle and seed positions, as well as the number of seeds required. The subsequent procedure is generally performed under spinal or general anesthesia, under ultrasound and fluoroscopic guidance (57). Post procedure imaging is essential for Quality Assurance and is recommended to be performed either day 0 or 1, or at day 30, generally with CT imaging, but the addition of MRI aids contouring accuracy (58).

Initial reports of salvage brachytherapy date back to the 1990s. Grado *et al.* (59) and Beyer *et al.* (60) reported 5-year bRFS of 33% and 53%. Since then much progress has been made on patient selection, dose prescription and volumes (Table 5), resulting in improved efficacy and decreased toxicity. BRFS is as high as 90% at 3 years (62), and 75% at 4–5 years (61,66,67). Burri *et al.* reported long term outcomes with a 10-year biochemical recurrence free survival rate of 54% (64).

Given these multiple reports of satisfactory efficacy,

**Table 2** Published results for salvage high intensity focused ultrasound (HIFU)

Study	Patients	Period	Median follow-up in years	Outcomes			Toxicity
				BRFS	DMFS	CSS	
Crouzet <i>et al.</i> (43)	418	1995–2009	3.5	5-year: LR 58%, IR 51%, HR 36%	81% 7-year	82% 7-year	GU incontinence G2/3 19–32%; bladder outlet obstruction 30–15%; recto-urethral fistula: 9–0.6%; improved rates with use of post-RT parameters
Jones <i>et al.</i> (44)	100	2009–2012	3.0	70% PSA Nadir <0.5 at 1-year			G3 toxicity in 20 men, 5 rectal fistulas, 3 osteitis pubis, 1 hematuria
Murat <i>et al.</i> (45)	167	1995–2006	1.5	3-year: LR 53%, IR 42%, HR 25%	Local control with negative biopsy in 73%		No rectal complications; urinary incontinence: 50%; artificial sphincter: 11%

HIFU, high-intensity focused ultrasound; BRFS, biochemical recurrence free survival; DMFS, distant metastases free survival; CSS, cancer specific survival; LR, low risk; IR, intermediate risk; HR, high risk; GU, genitourinary; PSA, prostate-specific antigen.

**Table 3** Published results for salvage cryotherapy

Study	Patients	Period	Median follow-up in years	Outcomes			Toxicity
				BRFS	DMFS	CSS	
Williams <i>et al.</i> (47)	176	1995–2004	7.5 (mean)	47% 5-year, 39% 10-year	87% 5-year, 82% 10-year	NR	–
Ismail <i>et al.</i> (48)	100	2000–2005	2.8 (mean)	5-year: LR: 73%, IR: 45%, HR: 11%	NR	NR	Incontinence: 13%; LUTS 16%; erectile dysfunction: 86%; perineal pain 4%; urinary retention 2%; recto-urethral fistula 1%
de Castro Abreu <i>et al.</i> (46)	25 whole gland CRYO (STC), 25 focal CRYO (SFC)	2003–2010	2.6 for SFC 4.4 for STC	5-year: SFC 54%, STC 86%	NR	NR	SFC: no incontinence; STC: 13% incontinence; STC: 1 rectal fistula
Li <i>et al.</i> (49)	91 SFC	2002–2012	1.3	72% 3-year, 47% 5-year	Positive biopsies after SFC in 4/14 who underwent biopsy		Rectourethral fistula: 3%; urinary retention: 7%; incontinence: 6%; impotence: 50% of those previously potent
Izawa <i>et al.</i> (50)	131	1992–1995	4.8	5-year 40%	NR	5-year 79%	NR

CRYO, cryotherapy; BRFS, biochemical recurrence-free survival; DMFS, distant metastases free survival; CSS, cancer-specific survival; LR, low risk; IR, intermediate risk; HR, high risk; STC, salvage total cryotherapy; SFC, salvage focal cryotherapy; LUTS, lower urinary tract symptoms; NR, not reported.

the Radiotherapy Oncology Group (RTOG; now NRG) undertook a multi-institution phase 2 trial on salvage LDR brachytherapy to investigate safety with a primary endpoint of late grade 3 or higher treatment-related GI/GU toxicity. The prescribed dose to the whole prostate was 140 Gy with <sup>125</sup>I and 120 Gy for <sup>103</sup>Pd. Ninety-six men were accrued, the majority treated with <sup>125</sup>I. The recently reported primary endpoint based on analysis of 87 eligible patients with a minimum follow up of 23 months showed that treatment-related grade 3 GI/GU adverse events were seen in only

14%, with no grade 4 or 5 toxicity.

Nguyen *et al.* prospectively treated 25 men with biopsy-proven relapse at least 2 years post EBRT. Patients received salvage MRI-guided <sup>125</sup>I LDR brachytherapy to a minimum peripheral dose of 137 Gy. At a median follow-up of 47 months BRFS was 70%. In stark contrast to the recently reported RTOG results, 30% developed grade 3 or 4 GI or GU toxicity and 13% required a colostomy or urostomy due to fistula (67). Potential reasons for this difference will be explored below, under “Patient Selection/Toxicity”. Amongst

**Table 4** Published results for SBRT

Study	Patients	Period	Median follow-up in months	BRFS	Median pre-salvage PSA	Median PSA nadir (ng/mL)	Dose	Toxicity
Vavassori <i>et al.</i> (51)	6	2007–2008	11	20% 0.7-year	3.65	NR	30 Gy/5 fr	2pts transitory perineal pain; no GI/GU toxicity >G2
Fuller <i>et al.</i> (52)	29	2009–2014	24	82% 2-year	3.1	0.16 at 2-year	34 Gy/5 fr	G2 + GU: 18%; 1 G3 hemorrhagic cystitis; 1 obstruction requiring cystoprostatectomy; No G2+ GI toxicities
Leroy <i>et al.</i> (53)	23	2011–2014	23	54% 2-year	2.5	0.35 at 0.7-year	36 Gy/6 fr	G3 cystitis 9%; G3 neuritis 4%; G2 proctitis 9%; G2 urethral stenosis 9%
Zerini <i>et al.</i> (54)	22	2008–2013	21	41% 1.8 year	3.9	NR	30 or 20 Gy/5 fr	Acute G2 GU 2 patients; acute G2 GI 1 patients; late G2 GU 1 patient

SBRT, stereotactic body radiotherapy; BRFS, biochemical recurrence-free survival; DMFS, distant metastases free survival; CSS, cancer-specific survival; PSA, prostate-specific antigen; G, grade; GI, gastrointestinal; GU, genitourinary; fr, fraction.

the many retrospective series, outcomes for both efficacy and toxicity vary greatly and depend largely on patient selection.

#### Patient selection

Patient selection is important for ensuring successful treatment and minimizing toxicity. As demonstrated through the differences in the various retrospective trials, patient selection can drastically affect outcomes. Grado *et al.* (59) reported 34% 5-year BRFS but 34% of those treated had high grade disease at initial diagnosis and 55% at salvage. Median baseline PSA was 26 ng/mL and 22% had pre-salvage PSA over 10 ng/mL. Beyer *et al.* (60) found that only 30% of men with high grade cancers were free of second relapse at 5 years *vs.* 83% for those with low or moderate grade. Similarly, for PSA <10 ng/mL at time of salvage, the 5-year BRFS was 65% compared to 37% for those with PSA >10 ng/mL. This is supported by the more recent experience of Burri *et al.* (64) who found on multivariate analysis, that a pre-salvage PSA <6 ng/mL was predictive of improved BRFS.

The goal of salvage brachytherapy is to use highly conformal, high-dose radiotherapy to eradicate locally recurrent disease in the absence of co-existing micrometastatic disease. There are several absolute requirements when considering a patient for local salvage, and additional desirable features that should be considered on an individual basis but are not mandatory.

#### Biopsy proof of recurrent disease

Prostate biopsy must confirm locally recurrent disease, at

least 24–30 months after initial radiotherapy. Given the well-established time required for histologic resolution of disease after radiotherapy, earlier biopsies are unreliable (72–74). Furthermore, early biochemical failure (<18 months after radiotherapy) may be indicative of co-existing metastatic spread and correlates with increased prostate-cancer mortality (75,76). Biopsy specimens should be reviewed by an experienced GU pathologist. Radiation induced changes, especially in the first 2–2.5 years, may be interpreted as positive for residual cancer when in reality they represent an indeterminate state evolving towards eventual resolution (*Figure 2*). The radiation-induced cytoplasmic and nuclear changes have been well characterized and can be recognized by an experienced GU pathologist (77). The identification of residual viable tumour, with no or minimal radiation effect, is critical for demonstrating local recurrence (78).

As discussed above, mpMRI with Gadolinium can be useful in detecting sites of recurrence for biopsy. All suspicious areas should be confirmed pathologically.

#### Systemic staging

The traditional staging including abdominal/pelvic CT scan and a bone scan to rule out distant spread are mandatory. Additional staging with <sup>68</sup>Ga PSMA-PET for earlier detection of metastatic disease is desirable if available, and will certainly play an important role in the future. Positivity with PSA values as low as 0.5–1.0 ng/mL is 50–60% and as high as 90% by the time the PSA reaches 2–3 ng/mL (33). The role and utility of PSMA PET has not been

**Table 5** Published results for salvage LDR brachytherapy

Study	Year of report	Period	n	Selection (PSA/GS)	Interval (years)	DT (months)	Follow-up (years)	BRFS	MPD/PD/D90	Toxicity	Specific toxicities
Grado <i>et al.</i> (59)	1999	1990–1996	49	PSA 2–79; Med: 5.6; GS ≥8: 34%; PSA >10: 20%	3.5	NR	5.3	33% 5-year	<sup>103</sup> Pd—37 pts, median MPD 120 Gy; <sup>125</sup> I—12 pts median MPD 160 Gy; D90—NR	Pre CTCAE, not graded	Urinary retention requiring TURP in 15%; colostomies 2%
Beyer <i>et al.</i> (60)	1999	1989–1994	17	PSA 0.3–27; Med: 2.2; GS ≥8: 30%; PSA >10: 25%	NR	NR	5.2	53% 5-year	<sup>125</sup> I—15 pts, 120 Gy MPD; <sup>103</sup> Pd—2 pts, 90 Gy MPD; D90—NR	Pre CTCAE, not graded	Urinary incontinence 24%
Wong <i>et al.</i> (61)	2006	1991–1998	17	PSA 4–35; Med: 12; 30% GS 8–9	NR	NR	3.7	75% 4-year	<sup>125</sup> I: 5 pts, PD 126 Gy, D90 127 Gy, 4 pts, PD 120 Gy, D90 139 Gy; <sup>103</sup> Pd—4 pts, PD 103.5 Gy, 4 pts, PD 112.5 Gy; D90—119 Gy	G2 GU: 41%; G2 GI: 35%; G3 GU: 41%; G4 GU: 6%	G3 GU obstruction (7 pts); GU urge incontinence (2 pts); Urinary diversion (1 pt); G3 rectal bleeding (1 pt)
Aaronson <i>et al.</i> (62)	2009	1996–2007	24	PSA 0.3–10; Med: 3.4; GS ≥8: 3	4.1	20	2.5	89.5% 3-year	<sup>125</sup> I—144 Gy to GTV, 108 Gy to remaining gland; D90—NR	G2 GU: 29%; G3 GI: 4%	G3 rectal bleeding (1 pt); G2 urethral stricture (1 pt); G2 hematuria (5 pts); G2 urinary incontinence (1 pt)
Lee <i>et al.</i> (63)	2008	1998–2005	21	Med PSA 3.8; Med GS 7	7.1	NR	3.0	38% 5-year	<sup>103</sup> Pd —PD 90 Gy, 12 received concurrent ADT	G2 GU 19%; G2 GI 5%	NR
Burri <i>et al.</i> (64)	2010	1994–2008	37	PSA 1.7–35; Med: 12.6; 35% HR	5.2	NR	7.2	54% 10-year	<sup>125</sup> I—1 pt, PD 135 Gy; <sup>103</sup> Pd—36 pts, PD 110 Gy; median D90 122 Gy	G2 46%; G3 11%	G2 GU obstruction (9 pts), G2 GU urgency incontinence (2 pts), G2 diarrhea (2 pts); G3 GU obstruction (2 pts), G3 hematuria—1 pt; G4 prostatectomy fistula (1 pt)
Moman <i>et al.</i> (65)	2010	1994–2009	31	Mean PSA 11.4 13% GS ≥8	5.0	13	9.2	20% 5-year	<sup>103</sup> Pd—PD 145 Gy; D90—196 Gy	G2 GU 45%; G3 GU 20%; G3 GI 6%	G3 GU urethral strictures and fistulae; G3 GI: both fistulae
Vargas <i>et al.</i> (66)	2013	1989–2011	69	PSA >10; 13%; GS ≥8: 37%	7.5	NR	5.0	74% 5-year, 22% CRPC	<sup>125</sup> I—D90 of 100 Gy	G3 GU 9%; G4 GI/GU 0%; G3 GI 0%	5 pts with hematuria, of which 2 required fulguration and 1 had hyperbaric oxygen; 1 pt with necrotic tissue treated with hyperbaric O <sub>2</sub>

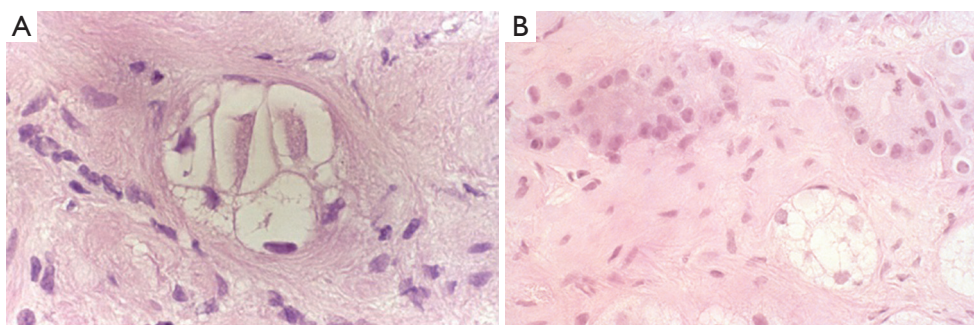
**Table 5** (continued)



Table 5 (continued)

Study	Year of report	Period	n	Selection (PSA/GS)	Interval (years)	DT (months)	Follow-up (years)	BRFS	MPD/PD/D90	Toxicity	Specific toxicities
Nguyen <i>et al.</i> (67)	2007	2000–2005	25	PSA 1.4–11.6; Med: 5.5 GS 100% <8	5.2	9.5	4.0	70% 4-year	<sup>125</sup> I—PD 137 Gy	G3–4 GU 13%; G3–4 GI 30%	2 pts with G3 radiation proctitis tx with argon plasma; 3 pts with G4 recto-urethral fistula requiring surgery; 1 pt with G3 urethral stricture; 1 pt with G3 periprostatic abscess
Hsu <i>et al.</i> (68)	2013	2003–2009	15	psPPI post PPI; PSA 0.9–5.6; Med: 3.5; GS ≥7: 27%	5.8	NR	1.9	ASTRO 63% 3-year, Phoenix, 71% 3-year	<sup>125</sup> I: psPPI PD 144 Gy, Pd-103: psPPI PD 125 Gy (1 pt), psPPI CTV D90 142 Gy, psPPI whole gland D90 37 Gy	G2 GI 0%, G2 GU 33%, G3/4 GI/GU 0%	No severe toxicities
Peters <i>et al.</i> (69)	2014	2009–2012	20	PSA 0.3–14; Med: 4.7; GS ≥8: 10%	6.6	19	3.0	6 events	<sup>125</sup> I—PD >144 Gy to target	G3 GU 5%	G3 GU 1pt urethral stricture; G2 radiation cystitis in 1 pt; 5 previously potent patients retained erectile function
Henríquez <i>et al.</i> (70)	2014	1993–2007	56 (37 LDR)	PSA 1.1–30; GS ≥8: 14%	NR	NR	4	77% 5-year	66% treated with salvage <sup>125</sup> I LDR-BT. Dose of 145 Gy	LDR BT 24%, G3 GU 24%, no G3 GI after 24 months, G4 GI 3%	LDR-BT: 3 bladder spasms, 5 obstructive uropathy requiring TURP, 1 prostatic fistula requiring colostomy
Kollmeier <i>et al.</i> (71)	2017	2003–2015	98 (37 LDR)	Med PSA for LDR 3.7; GS ≥8: LDR 12%	6	BRFS of 39% if PSADT ≤ 12 months and 73% if ≥ 12 months	2.6	60% 3-year	<sup>192</sup> Ir—58 pts with 32 Gy in 4 fr. over 30 H in a single insertion; 2 pts received 7 Gy x4 and 11Gy x2	Acute G2 GU 57%, acute G2 GI 1%, late G2 GU 36%, late G2 GI 3%, late G3/4 GU 9%, late G3/4 GI 2%	Incontinence: 14; gross hematuria: 10; urethral stricture: 8 (HDR 8); hematuria requiring intervention: 2; TURP post branchy in 4 pts; of which 3 were complicated by fistula, incontinence or abscess and 1 subsequently required a cystectomy

LDR, low dose rate; PSA, prostate specific antigen; GS, Gleason score; Med, Median; PPI, permanent prostate implant; psPPI, partial salvage permanent prostate implant; NR, not reported; BRFS, biochemical recurrence free survival; DMFS, distant metastases free survival; CSS, cancer specific survival; LR, low risk; IR, intermediate risk; HR, high risk; GU, genitourinary; MPD, matched peripheral dose; PD, prescription dose; GTV, gross tumor volume; CTV, clinical target volume; CTCAE, common terminology criteria for adverse events; G, grade; GI, gastrointestinal; GU, genitourinary; pt, patient; CRPC, Castrate resistant prostate cancer; ASTRO, American Society for Therapeutic Radiation and Oncology; PSADT, PSA doubling time; TURP, transurethral resection of the prostate.



**Figure 2** Post radiation biopsies, hematoxylin and eosin high power magnification ( $\times 100$ ) showing histologic changes post radiation and recurrent disease. (A) Severe radiation induced change with vacuolated cytoplasm; (B) lower right severe radiation induced change with vacuolated cytoplasm and chromatin smudging; upper left residual cancer with minimal radiation change.

reported yet in regards to selection of patients for salvage brachytherapy. Similarly, a higher PSA at the time of salvage is associated with a greater risk of co-existent metastatic disease. Salvage should ideally be undertaken before the PSA reaches 10 ng/mL (67,78,79).

#### Baseline characteristics

Higher risk features at initial treatment (PSA  $>20$  ng/mL, Gleason score 8–10 and clinical stage  $\geq T2c$ ) impart a higher risk that biochemical failure is not an isolated local recurrence. However, if other criteria are satisfied, initial high-risk disease does not rule out a role for local salvage. Recent success rates in definitive management of high-risk disease indicate that co-existing metastases may be present in as few as 10% of high risk patients at presentation (3,80,81). If other factors are favourable, including PSA doubling time and interval since prior radiotherapy, then salvage is not unreasonable. Rose *et al.* reported on 18 patients treated with salvage LDR brachytherapy and found that of 9 patients with high risk disease, only 4 recurred by 3 years, including 2 who had CRPC at time of salvage (82). However, if co-existent with a short PSA doubling time of  $<6$  months, benefit from local salvage is unlikely. For this reason, the recently reported RTOG (NRG) 0526 (NCT00450411) only included patients who had favourable or intermediate risk disease at diagnosis.

#### Functional criteria

Functional criteria are assessed to limit salvage-related toxicity. RTOG 05-26 specified that eligible patients should have an IPS score  $<15$ , with or without alpha-blockers. There should be no residual GI or GU radiation toxicity  $\geq$  grade 2 as per CTCAE criteria. Prostate volume measured on TRUS should be  $\leq 45$  cc as higher volumes are associated with decreased tolerance in terms of acute retention and

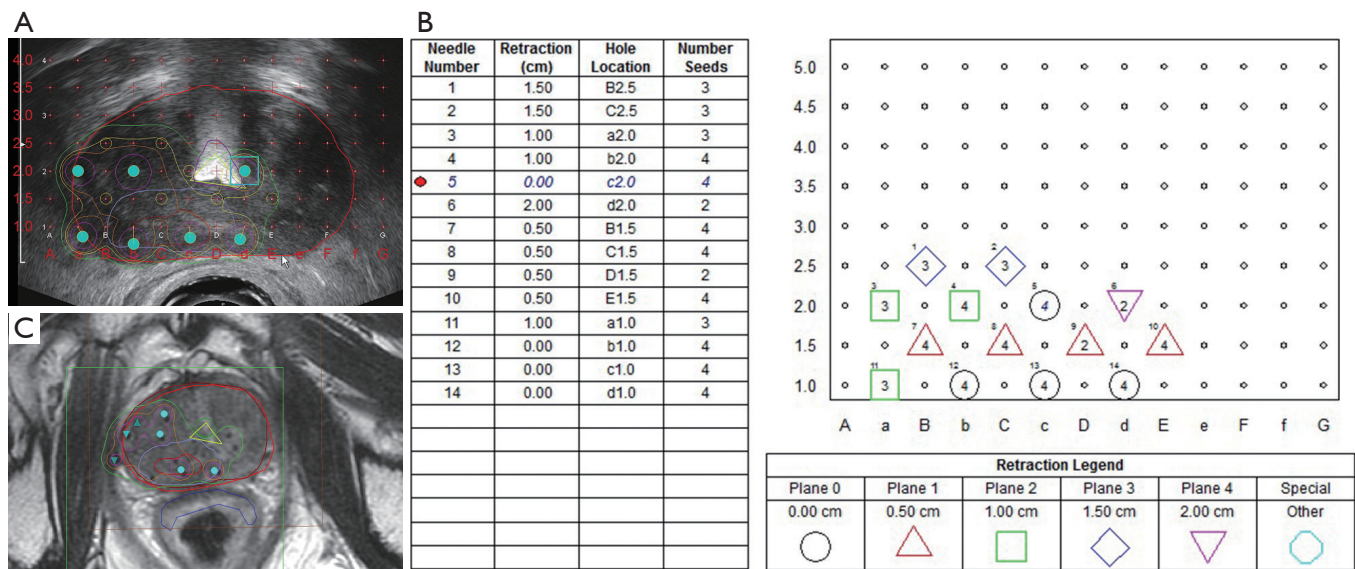
higher rectal doses. Furthermore, although not mandatory, uroflow studies can clarify voiding function in terms of peak flow, post void residual and voided volume, and are more objective than the IPSS questionnaire (83).

#### Prior EBRT dose

Early experience with salvage LDR brachytherapy involved patients who had been treated with conventional radiation doses of 60–66 Gy. Acknowledging the trend to higher doses, RTOG 0526 specified that the prior EBRT dose to the prostate could be as high as 78–81 Gy in 1.8–2 Gy fractions. There is no published experience on salvage brachytherapy after hypofractionated radiotherapy or SBRT.

#### Salvage brachytherapy dose

Dose and coverage are two quintessentially important factors for treatment success. If insufficient dose is delivered, toxicity may be reduced, but so will efficacy. Lee *et al.* (63) prescribed only 90 Gy using  $^{103}\text{Pd}$  and had no grade 3 toxicity but 5-year biochemical control was only 38%. Wong *et al.* (61) had excellent bRFS of 75% at 4 years using either  $^{125}\text{I}$  or  $^{103}\text{Pd}$ . Although there was no statistically significant association between bRFS and D90, all patients with D90  $>140$  Gy for  $^{125}\text{I}$  or  $>125$  Gy for Pd-103 achieved biochemical control, whereas 4 of 11 patients with a lower D90 experienced failure. Over the decades, a range of prescription doses has been used for salvage, 120–145 Gy for  $^{125}\text{I}$ , 90–113 Gy for  $^{103}\text{Pd}$ . Although D90 is not always reported, it is an essential dosimetric quantifier to compare efficacy and evaluate toxicities. For example, Moman *et al.* (65) treated 31 patients with salvage  $^{125}\text{I}$  brachytherapy with a prescribed dose of 145 Gy. However, the median delivered D90 was much higher, at 196 Gy, with a median V150 of 74% and V200 33%. As one could now



**Figure 3** Partial prostate salvage low dose rate (LDR) preplan (A) and needle-loading template (B) and 30-day dosimetry (C).

predict, toxicity was high, with late G3 complications seen in 26%. Rose *et al.* reported increased late toxicity with a higher D90 (P=0.04) (82).

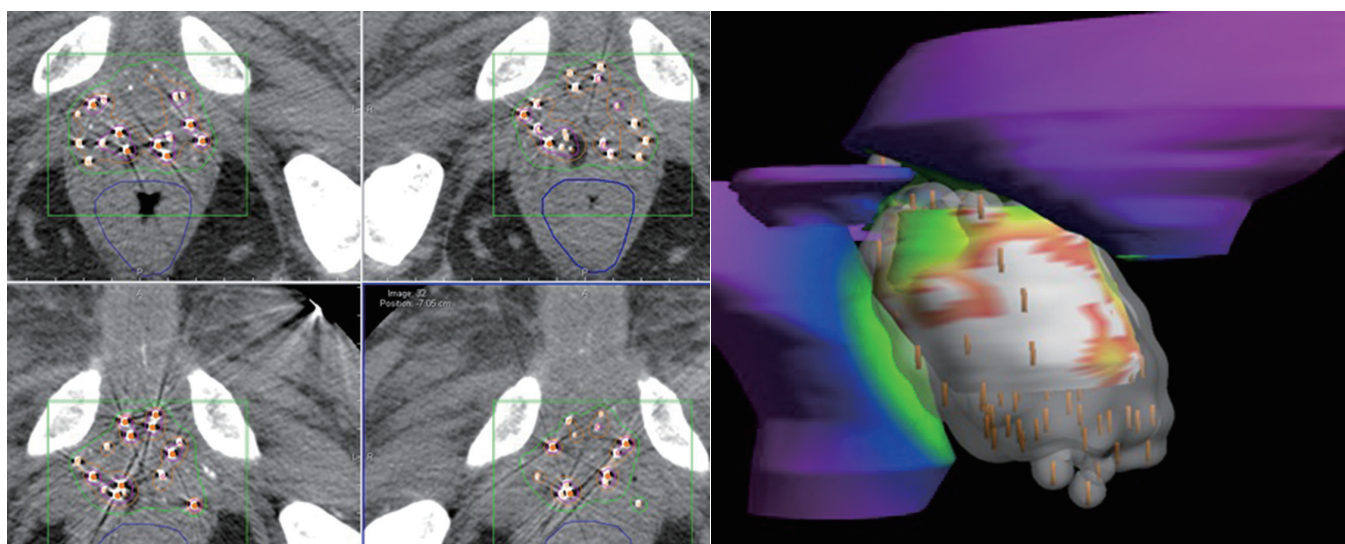
Reports by Nguyen *et al.* (67) and Aaronson *et al.* (62) with  $^{125}\text{I}$  doses of 137 and 144 Gy treating appropriately selected patients have shown promising BRFS rates of 70% at 4 years and 88% at 3 years respectively. In RTOG 0526, the prescribed doses for  $^{125}\text{I}$  and  $^{103}\text{Pd}$  were respectively 140 and 120 Gy. RTOG 0526 also used several dosimetric parameters to try to avoid overly “hot” implants. Preplans were designed to keep V150 <45% for  $^{125}\text{I}$  and <55% for  $^{103}\text{Pd}$  and V200 <10% for  $^{125}\text{I}$  and <15% for  $^{103}\text{Pd}$ . Compliance with these recommendations was high in the 20 participating centers. In the postplan evaluations, the median V150 was 50% with an interquartile range (IQR) of 43–59% and for V200 20% with an IQR of 17–27%. The RTOG doses are widely accepted as standard for salvage LDR brachytherapy.

#### Planning algorithm and volume

Initial reports on salvage brachytherapy by Grado *et al.* (59) and Beyer *et al.* (60) have concerning rates of toxicity. Grado *et al.* (59) reported post-salvage transurethral resection of the prostate (TURP) in 15% and colostomies in 2%, whereas Beyer *et al.* noted incontinence in 24%. The high urinary toxicity is likely related to the use of uniform seed loading, placing the seeds 1 cm apart, center to center throughout the prostate, resulting in a higher urethral dose (84). The Association of Physicists

in Medicine (AAPM) recommends a modified peripheral loading approach placing seeds peripherally, and removing periurethral central seeds, to improve dose homogeneity and spare the urethra. Another approach to reduce toxicity, involves maintaining high dose to the site of recurrence but reducing dose to the remainder of the gland. Aaronson *et al.* used MRI and MR spectroscopy to identify the dominant lesion and delivered 144 Gy to this site and 108 Gy to the remaining gland. At a median follow-up of 30 months, 24 patients had a 3-year BRFS of 90%. Toxicities included 1 urethral stricture, 1 grade 3 rectal haemorrhage, and 5 patients with grade 2 gross haematuria that resolved with conservative management. They concluded that salvage LDR brachytherapy provided excellent local control with acceptable toxicity (62).

More recently, the focus has shifted to partial gland brachytherapy to further reduce toxicity (Figure 3) (85–87). A few reports provide promising results. Hsu *et al.* treated 15 patients with  $^{125}\text{I}$  partial salvage using MRI/magnetic resonance spectroscopy (MRS) planning. At a median follow-up of 2 years, the 3-year BRFS was 71%. Toxicity was very acceptable with only one third developing G2 GU toxicity, no G3 or higher GU toxicity, and no G2 or higher GI toxicity. Following salvage, 87% maintained erections (2/3 with PDE5 inhibitors) (68). Peters *et al.* analyzed 20 patients treated with focal salvage  $^{125}\text{I}$  brachytherapy using mpMRI and choline PET CT (69). Prescription dose to the tumor was 144 Gy. At a median follow-up of



**Figure 4** Suboptimal whole gland salvage implant with 5.5 cc of normal tissue caudal to the apex receiving >150% of the prescribed dose. Prior external beam radiation (EBRT) 68 Gy. Grade 3 urethral stricture.

3 years, biochemical control was 70%. Grade 3 GU toxicity occurred in only one patient with a urethral stricture.

### Toxicity

The potential for increased severity of toxicity in the salvage setting is real, but efforts to control rectal and urethral doses have reduced the incidence, and focal salvage may further minimize toxicity. In the long term, patients are at risk for incontinence, retention, frequency, urethral stricture, proctitis, rectal ulcers and recto-urethral fistula (Figure 4). Late G3 or higher GU toxicity ranges from 5–25% and late grade 3 or higher GI toxicity from 5–10%. The primary endpoint of RTOG 0526 was evaluation of late treatment-related grade 3 or higher GI/GU toxicity. The hypothesis was that a frequency of  $\leq 10\%$  would be acceptable in a salvage situation but if over 20%, salvage brachytherapy would be considered too morbid. With a median follow-up of 4.5 years, there was only 14% late grade G3 GI/GU toxicity. Of 87 analyzable patients with a minimum of 23 months follow up, there was only 1 proctitis, 1 urethral fistula, and the remainder were grade 3 urinary frequency, incontinence and retention. Notably, there was no grade 4 or 5 toxicity reported. Nguyen *et al.*'s (67) prospective trial of salvage brachytherapy noted a much higher rate of 4-year grade 3 or 4 GI or GU toxicity at 30%, with 13% colostomy or urostomy. He reported that an interval of <4.5 years from EBRT to salvage brachytherapy was associated with a hazard ratio of 12 for grade 3 or 4 toxicity, and a hazard ratio of 25 for colostomy or urostomy. Interestingly, the

median time from EBRT to salvage in the RTOG 0526 trial was 7 years (IQR, 5–9 years) which may explain the markedly lower grade 3 toxicity rate of 14% and the absence of any grade 4 or 5 toxicity in this trial.

Peters *et al.* (88) published on rectal dose constraints for salvage prostate brachytherapy. He compared 30-day CT dosimetry of 20 focal salvage plans with 28 total gland implants and assessed GI toxicity through CTCAE criteria. He found that focal salvage reduced rectal dose significantly at his institution. Median reduction in rectal dose was 46 Gy for D1cc and D2cc. Severe GI toxicity in the whole gland salvage group reported by this author is by far the highest in the literature, being 41%. For comparison, grade 3 or higher late GI toxicity in the RTOG trial was <2%. Fortunately, the focal approach adopted by Peters *et al.* (88) corrected this at his institution.

### HDR brachytherapy

HDR brachytherapy is performed by implanting a scaffolding of catheters into the prostate, through which a high activity  $^{192}\text{Ir}$  source navigates to deliver the required dose. Once the catheters are positioned, images are obtained for catheter reconstruction and inverse planning. Traditionally CT-based planning has been used but currently US-based planning is making in-roads as it eliminates the risk of catheter shift with patient movement, and ensures precise dose delivery. Dosimetric coverage and constraints are reviewed before treatment is started and

duration of the source transiting through the catheters is roughly 15–20 minutes. Multiple fractions can be given per implant but require catheter position re-verification prior to each dose delivery (89,90). HDR salvage brachytherapy appears to have comparable results to LDR. Several retrospective studies and one phase II study on whole gland treatment have been reported to guide treatment (Table 6).

#### **HDR selection**

Selection criteria for salvage HDR are the same as for LDR brachytherapy. HDR has the advantage of being able to deliver dose to the seminal vesicles, or areas of extracapsular extension, but whether such patients are candidates for salvage is arguable.

#### **HDR dose**

As is the case for LDR salvage, dose for HDR salvage has varied in the literature. Yamada *et al.* (90) used 32 Gy in 4 fractions in a single implant. At a median follow-up of 3 years, the 5-year BRFS and DMFS were 69% and 82% for 42 patients. Other fractionation schedules are 36 Gy in 6 fractions with two implants 1 week apart (63,92); as well as 10 Gy per fraction  $\times 3$  fractions with weekly implants (95–97). If multiple fractions are delivered per implant, a minimal interval of 6 hours between fractions is recommended. Kukiela *et al.* treated 25 patients with combined interstitial hyperthermia and HDR brachytherapy, delivering 30 Gy in 3 fractions at 21-day intervals. Hyperthermia heated the prostate to 41–43° Celsius for sixty minutes. At a median follow-up of 13 months, the 2-year biochemical control was 74% (94). Wojcieszek *et al.* assessed 83 patients treated with 10 Gy  $\times 3$ , once every 2 weeks to a total dose of 30 Gy. At a median follow-up of 41 months, the 5-year BRFS was 67% (95). Jiang *et al.* achieved 5-year biochemical control of 45% for 29 patients Treated with 3 weekly fractions of 10 Gy to the peripheral zone and PET positive area (97).

#### **HDR volume**

HDR salvage brachytherapy can be delivered to the whole gland but if the site of recurrence can be identified on mpMRI or PSMA PET, the dose can be escalated with relative ease. While most series have focused on whole gland treatments, partial salvage brachytherapy is readily achievable and is currently being investigated (NCT03246802, NCT01583920). By treating the recurrence and sparing part of the gland, toxicity may be reduced. Transrectal ultrasound and multiparametric MRI can be done prior to the procedure for off-line fusion using either rigid or deformable registration. The site of recurrence is identified on mpMRI in each of the sequences: T2, ADC and dynamic contrast

enhanced (DCE) and then combined through a Boolean addition of the abnormalities seen on each sequence, areas of low-intensity on T2W MRI, low ADC map values and high DCE map values (Figure 5) (99). Manual rigid registration can be used if required to align the sequences to account for variations in prostate position during sequence acquisition. This contour becomes the focal GTV (F-GTV) as previously described by Mason *et al.* (99).

To account for uncertainties in image registration and tumor delineation, a margin is added to create a F-PTV, cropped at the urethra and posteriorly at the prostate-rectal interface. Mason *et al.* (99) estimated the uncertainty margin in tumor delineation and registration by repeating the contours 4 times on 5 cases and found the required margin to be 2.6 to 5.2 mm with a mean of 4.2 mm. For simplification, a 4.5 mm isotropic margin was chosen for the purposes of focal dose escalation to the dominant lesion. For purely focal treatment, a 6-mm margin is recommended (100).

During the HDR procedure, the number and placement of treatment catheters are determined using a standard grid spacing of 0.5 cm and manual catheter steering. After HDR needles are placed under TRUS guidance and locked in place, a set of continuously-acquired images is obtained. Prostate, urethral and rectal volumes are contoured. The F-PTV is then transposed from the pre-procedure TRUS (101). The catheters are reconstructed and inverse treatment planning is used for dose optimization.

#### **HDR toxicity**

Toxicities in HDR brachytherapy are similar in nature to LDR brachytherapy and rates vary with fractionation as well as whole *vs.* partial gland salvage. Yamada *et al.* noted late grade 2 GU toxicity in 48% and one grade 3 incontinence. Late Grade 2 GI toxicity was noted in 8%, with no G3 or higher GI toxicities (98). Jiang *et al.* used 3 weekly fractions of 10 Gy to PET positive target volumes in the peripheral zone with 9% each late G2 GI and grade 3 GU toxicity. By sparing the urethra and respecting dose constraints, the urethral stricture rate is acceptable and should be in single digits (63,70,94,98). Yamada *et al.* reported a grade 2 stricture rate of 7% (98). Kollmeier *et al.* reviewed experience with both LDR and HDR brachytherapy and found no significant differences in toxicity. However, there were more patients with acute urinary retention and late urethral strictures (8:1) with HDR compared to LDR. After analysis of IPS scores, a higher peak in urinary symptoms was noted with LDR. However, for most patients, urinary scores returned to baseline by 24–36 months (71).

**Table 6** Published results for salvage HDR brachytherapy

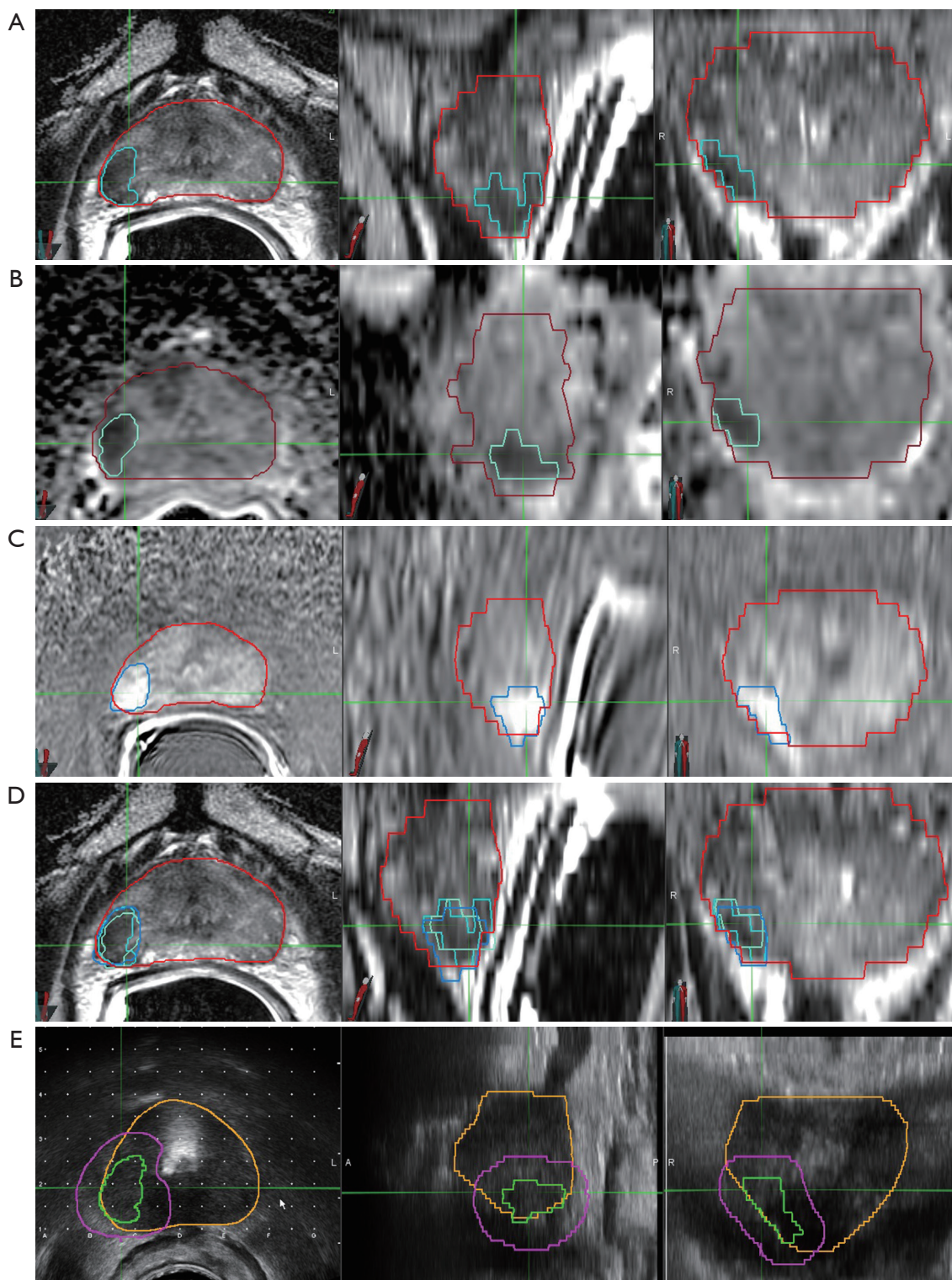
Study	Year of report	Period	n	Selection PSA/ GS	Interval years	DT (months)	Med follow-up	BRFS	Isotope and dose	Toxicity	Specific toxicities
Tharp <i>et al.</i> (91)	2008	2001–2006	7	PSA 2–36; Med: 5.5; GS ≥8: 29%; PSA >10: 14%	2.8–20.5	NR	4.8	71%, med F/U	<sup>192</sup> Ir—6 to 9 Gy/fr in 2–4 fr. interfraction interval of 6H; Seed failures received 36–45 Gy 3DCRT with HDR	4 pts with G2 urinary stricture rate, 1 G2 radiation proctitis	2 cases of incontinence post urethral necrosis in prior LDR failures
Chen <i>et al.</i> (92)	2013	1998–2009	52	PSA 0.4–26.3; Med: 5.0; GS ≥8: 52%	4.3	NR	5	51% 5-year	<sup>192</sup> Ir—36 Gy in 6 fr.	Acute G2 GU 36% GI 0%; late G2 GU 54 % GI 4%; acute G3 GU 2% GI 0%; late G3 GU 2% GI 0%	NR
Henríquez <i>et al.</i> (70)	2014	1993–2007	56 (19 HDR)	PSA 1.1–30; Med: 3.7; GS ≥8: 14%	NR	NR	4	77% 5-year	34% treated with <sup>192</sup> Ir HDR-BT; 6–13 Gy per fr. in 2–4 fr.	HDR-BT; G3 GU 21% GI 2%	HDR-BT; 4 urethral strictures, 1 proctitis
Lee <i>et al.</i> (93)	2008	1998–2005	21	PSA 1.4–9.5; Med: 5.9; GS ≥8: 15%	5.3	12.1	3	89% 2-year	<sup>192</sup> Ir—36 Gy in 6 fr., two separate HDR catheter implants, 1 week apart	G3 GU 3 pts; G3 GI 0 pts; no G4 toxicity	3 cases of macroscopic hematuria
Kukielka <i>et al.</i> (94)	2014	2008–2013	25	PSA 1.0–25.3; Med: 2.8	–	–	1.1	74% 2-year	Combined interstitial hyperthermia and HDR brachytherapy; Brachytherapy 30 Gy in 3 fr.; hyperthermia required heating prostate to 41–43 °C for 1 h	No grade 3+ GIGU toxicities	Grade 2 rectal hemorrhage: 1
Wojcieszek <i>et al.</i> (95)	2016	2003–2011	83	PSA 0.1–19.9; Med: 3.1; GS ≥8: 7%	5.6	NR	3.4	76% 3-year, 67% 5-year	3 implants, 10 Gy/ fr., q2w	Acute G2 GU 35%; acute G3 GU 1%; late G2 GU 39%; late G3 GU 13%	Acute urinary retention: 6; suprapubic cystostomy: 1; late urinary retention: 11; urinary incontinence: 1 after urological intervention

**Table 6** (continued)

Table 6 (continued)

Study	Year of report	Period	n	Selection PSA/GS	Interval years	DT (months)	Med follow-up	BRFS	Isotope and dose	Toxicity	Specific toxicities
Łyczek <i>et al.</i> (96)	2009	1999–2008	115	PSA 2.3–64.5; Med: 13; GS ≥8: 12%	NR	NR	NR	46% if PSA <6; 18% if PSA >6	3 implants, 10 Gy/fr., q 3 weeks	G3/4 GU 12%; G3/4 GI 1%	Hematuria: 6 urethral fistulae: 2; permanent catheterization: 2; urinary incontinence: 4
Jiang <i>et al.</i> (97)	2017	2003–2011	22	PSA 2.1–18.6; Med: 4.1; HR: 55%; choline PET to determine local recurrence. SUV >2.5 defined as positive	5.5	NR	5	45% 5-year	HDR: 3 weekly fr. of 10 Gy. Target volume was the peripheral zone and PET positive area	Acute G2 GU 0%; acute G2 GI 9%; late G2 GU 5%; late G2 GI 9%; late G3 GU 9%	Late urinary incontinence: 1
Yamada <i>et al.</i> (98) (phase 2 RCT)	2013	2007–2011	42	PSA >10 in 12%; GS ≥8 33%; excluded pts with PSA >10 ng/mL, baseline IPSS >15, any history IBD or rectal surgery	NR	NR	3	69% 5-year	Ir-192—32 Gy in 4 fr. over 30H in a single insertion	Acute G2 GU 40%; late G2 GU 48%; late G3 GU 10%; late G4+ GU 0%; late G2 GI 14%; late G3+ GI 0%	1 pt—G3 urinary incontinence; 3 pts—G3 urethral strictures
Kollmeier <i>et al.</i> (71)	2017	2003–2015	98 (37 LDR; 61 HDR)	Med PSA: HDR 3.9 (0.25–15); GS ≥8: HDR 27%; 42 pts on P2 RCT	6	BRFS of 39% if PSADT ≤12 months and 73% if ≥12 months	2.6	60% 3-year	Ir-192—58 pts with 32 Gy in 4 fr. over 30H in a single insertion; 2 pts received 7 Gy x4 and 11 Gy x2	Acute G2 GU 57%; acute G2 GI 1%; late G2 GU 36%; late G2 GI 3%; late G3/4 GU 9%; late G3/4 GI 2%	Incontinence: 14; gross hematuria: 10; urethral stricture: 8 (HDR 8); hematuria requiring intervention: 2; TURP post-brachy in 4 pts, of which 3 were complicated by fistula, incontinence or abscess and 1 subsequently required a cystectomy

HDR, high dose rate; LDR, low dose rate; PSA, prostate specific antigen; GS, Gleason score; Med, median; HR, high risk; NR, not reported; BRFS, biochemical recurrence free survival; DMFS, distant metastases free survival; CSS, cancer specific survival; LR, low risk; IR, intermediate risk; HR, high risk; GU, genitourinary; G, grade; GI, gastrointestinal; GU, genitourinary; pt, patient; SUV, standard uptake value; IPSS, international prostate symptom score; RCT, randomized control trial; P2, phase 2; IBD, inflammatory bowel disease; DT, doubling time; BT, brachytherapy; pt, patient; 3DCRT, 3-dimensional conformal radiotherapy.



**Figure 5** Example of contouring the dominant lesion on T2-weighted multiparametric MRI (mpMRI), dynamic contrast enhancement (DCE) and apparent diffusion coefficient (ADC). A Boolean addition of these contours is then transferred to the ultrasound (US) image and a planning target volume (PTV) margin is added for treatment planning. (A) T2 image with T2 dominant intraprostatic lesion (DIL); (B) ADC image with DIL; (C) DCE image with DIL; (D) Boolean addition of 3 DILs on T2, ADC and DCE; (E) DIL sum transferred to US image.



**Table 7** Suggested eligibility and dose constraints

Category	Recommendations for salvage brachytherapy
Eligibility	<p>Life expectancy &gt;10 years, Able to tolerate anesthesia and procedure;</p> <p>Biopsy proven local recurrence, absence of distant metastases with standard restaging;</p> <p>PSMA PET if available;</p> <p>Initially LR or IR disease: pre-salvage PSA &lt;10;</p> <p>PSADT &gt;6 Mo, ≥3 years from EBRT (preferable &gt;4.5 years);</p> <p>Minimal residual toxicity from prior EBRT (&lt; grade 2)</p>
Suggested constraints	<p>LDR whole gland salvage (validated in RTOG 0526):</p> <ul style="list-style-type: none"> <li>❖ <sup>125</sup>I: V150 ≤45%, V200 ≤10%</li> <li>❖ <sup>103</sup>Pd V150 ≤55%, V200 ≤15%</li> </ul> <p>HDR whole gland (no validated constraints for single fraction or 2 fraction treatment):</p> <ul style="list-style-type: none"> <li>❖ <sup>192</sup>Ir</li> <li>❖ Two dose levels may be preferable <ul style="list-style-type: none"> <li>◆ 10 Gy to the whole gland</li> <li>◆ Dose escalate DIL to 13.5 Gy</li> </ul> </li> <li>❖ Minimum 95% coverage with PD</li> <li>❖ Maximum urethral dose ≤115% of PD</li> <li>❖ Rectal D1cc &lt;6 Gy, D0.1cc &lt;85%</li> </ul>

LDR, low dose rate; HDR, high dose rate; PD, prescription dose; EBRT, external beam radiotherapy; PSADT, PSA doubling time; PSMA PET, prostate-specific membrane antigen positron emission tomography.

## Conclusions

There is no consensus on the best salvage treatment for failure after radiotherapy. Androgen deprivation therapy is currently the most common and most conservative approach. Although at times, it may be appropriate, it is purely palliative and exposes the patient to the many side effects of testosterone ablation. Given that a significant proportion of biochemical failures after EBRT may be attributable to local recurrence, robust local therapies are important. By eradicating residual disease, in the absence of micrometastases, a second chance at cure is possible. Several local treatments, such as salvage prostatectomy, SBRT, cryotherapy, HIFU and brachytherapy have all been used with varying degrees of success. However, all are associated with higher toxicity than when used in the primary setting.

Amongst these options, brachytherapy is an ideal salvage treatment for localized disease, delivering a high dose in a very conformal manner, minimizing dose to adjacent organs. Although most published experience concerns whole gland

salvage, focal salvage has been made possible by improved imaging and is being explored, particularly with HDR, with the potential advantage of further reduced toxicity.

Appropriate patient selection and advances in treatment planning have benefited both HDR and LDR salvage brachytherapy. Eligibility and dose constraints are summarized in *Table 7*. We await the efficacy results of the RTOG 0526 trial but in the meantime, improved imaging and image registration are changing the landscape, permitting more precise tumour targeting and treatment delivery.

## Acknowledgements

None.

## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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