Review Article

Management strategies for radio-recurrent prostate cancer: a comprehensive review

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Abstract: Radiation- (radio-)recurrent prostate cancer poses a significant challenge in clinical management due to its complexity and varied treatment responses. The recurrence of prostate cancer following radiotherapy necessitates a nuanced management strategy that considers disease stage and aggressiveness, patient health status, and prior treatment modalities. Androgen deprivation therapy (ADT), a cornerstone in the management of regional or distant relapse, often initiates the therapeutic cascade, effectively suppressing tumor growth by targeting androgen signaling. Second-line antiandrogen therapies such as abiraterone and enzalutamide, in conjunction with ADT, exhibit considerable clinical efficacy by delaying disease progression and ameliorating symptoms. However, in the absence of regional or distant disease, local relapse after radiation may be best managed with local salvage therapy. Salvage radical prostatectomy (SRP) may be considered in select cases of local recurrence, providing a potentially curative option. Salvage radiation therapy (RT), such as stereotactic body RT (SBRT), low-dose-rate (LDR), or high-dose-rate (HDR) brachytherapy (BT) is another viable option for localized recurrences. Other local treatments, such as cryotherapy, high-intensity focused ultrasound (HIFU) and irreversible electroporation (IRE) have been applied as salvage local therapy for radio-recurrent prostate cancer with promising results. Notwithstanding, exploring new avenues for improved outcomes and personalized treatment strategies as well as clinical trials investigating novel therapeutic agents and combination therapies remain imperative for these men. This comprehensive review aims to examine the current landscape of therapeutic approaches and emerging strategies for managing radio-recurrent prostate cancer.

Keywords: Radiation-recurrent prostate cancer (radio-recurrent prostate cancer); androgen deprivation therapy (ADT); prostatectomy; salvage local treatment

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Introduction

Globally, prostate cancer is the most commonly diagnosed cancer among men (1). The high incidence can be attributed, in part, to the use of prostate-specific antigen (PSA) testing, which facilitates the early detection of prostate cancer (2). Early diagnosis has shifted the emphasis towards more personalized and patient-focused treatments (2,3). Primary radiation therapy (RT) is commonly selected as a potentially curative treatment option that offers low morbidity and preserves health-related quality of life, which are important considerations for many men (2,3).

Diagnosing and managing locally recurrent prostate cancers after primary RT presents unique challenges

stemming from the biochemical alterations in tissues that have been exposed to radiation (4). Ten-year follow-up of patients in the phase III RTOG 0521 trial looking at a combination of androgen deprivation therapy with docetaxel and external beam RT (EBRT) with androgen deprivation therapy and EBRT alone demonstrated that in a population of high-risk prostate cancer patients, 40% of patients experience a rise in PSA post-radiation. It is important to note that this over-represents the actual rise in PSA post-radiation in the general population and that this is not directly indicative of treatment failure as PSA rise is often expected (5). Additionally, studies such as RTOG 0815 that investigated patients with long and short courses of ADT after RT have demonstrated a biochemical recurrence (BCR) rate of 25% over 10 years. Together, data such as these demonstrate that PSA can rise post-radiation from the recovery of testosterone, increase in PSA is not entirely indicative of BCR, thereby posing a difficult challenge for urologists in regards to determining when to treat (6). Existing literature such as the above on the recognition of radiation- (radio-)recurrent prostate cancer as well as various salvage treatments for radio-recurrent prostate cancer has reported a spectrum of oncologic outcomes, with the efficacy rates ranging between 30% to slightly over 50%, largely dependent on the progression of disease during the treatment decision phase (7-9). A standardized approach to evaluation and treatment of radio-recurrent prostate cancer has not been established. Considering the significant number of patients opting for primary RT, this presents a pressing area for research. The objective of this review is to explore the latest research and perspectives on radio-recurrent prostate cancer with an emphasis on patient selection and available treatments.

Diagnosis of radio-recurrent prostate cancer

Imaging

Imaging evaluation of radio-recurrent prostate cancer has traditionally included computed tomography (CT) scan of the abdomen/pelvis, prostate magnetic resonance imaging (MRI), and bone scan (10) with a focus on detecting metastatic disease and evaluating the local extent of tumor. In recent years, there has been increasing utilization of positron emission tomography (PET) CT scans. A study by Fanti *et al.* explored the efficacy of PET CT scans with (11) C-choline for assessing lymph node (LN) metastases and/or other distant lesions. The scans had a sensitivity and specificity of 87% each for overall relapse and a sensitivity and specificity of 61% and 97% respectively for local relapse (11). Gallium (Ga)-68 prostate-specific membrane antigen (PSMA) PET CT has been increasingly utilized for its ability to better identify locally radio-recurrent prostate cancer while ruling out distant metastases. In a study of 50 patients, Pfister *et al.* found that Ga-68 PSMA PET CT scans had sensitivity and positive predictive value (PPV) of 100% while accuracy was 100% (92.89–100%) for detecting local recurrence (12). Another study by Rasing evaluated 41 patients who were considering focal salvage therapy and found that combined MRI and PSMA PET led to a high PPV of 97.6% relative to prostate biopsy (13). A recent study also pointed out the usefulness of MRI and PMSA PET CT in staging (pT3 detection) and assessing LN metastasis in 113 patients who underwent salvage radical prostatectomy (SRP) for recurrent cancer after RT (14). Further studies on the utility of these imaging modalities are necessary to improve the detection of locally recurrent prostate cancer after primary RT.

Biopsy

Prostate biopsy is recommended before initiating salvage therapy. Interestingly, Crook *et al.* found that 30% of positive biopsies taken within 2 years post-RT eventually converted to negative biopsies within 24–30 months (15). In contrast, Shipley *et al.* noted the prognostic value of biopsy timing, noting that positive biopsies taken 2 years post-RT were indicative of lower 5-year disease-free survival (DFS) rate compared to negative and indeterminate biopsies in pooled institutional analyses (16). In an evaluation of 99 patients who were biopsied due to rising PSA after radiation for prostate cancer, Zagars *et al.* found that 86 cancer recurrence of which 72% were local alone (17). Based on such findings, prostate biopsy is recommended for patients with rising serum PSA levels 1–2 years after RT.

A study by Rasing *et al.* highlighted the robust PPV of PSMA and MRI and suggests that prostate biopsies may be avoided in patients with rising PSA values with a median time of 7 years post-RT (13). Another study by Takeda *et al.* mapped the areas of the prostate most likely to show recurrence of tumor after prior RT to the distal apex, seminal vesicles (which are not always included in a biopsy), and periurethral region (18). Recently, MRI-guided targeted biopsies have been shown to help better determine patients who can forgo prostate biopsy, if salvage focal ablation is planned (19). Despite these studies, declaring

Table 1 Summary of ADT case series studies in radio-recurrent prostate cancer

Study	Study design	Number of patients	Primary treatment for prostate cancer [number, %]	Median follow-up duration (months)	OS results	CSS results
Garcia-Albeniz *et al.*, 2015 (23)	Retrospective (CaPSURE)	2,096	RP [1,437, 69%]	54	Immediate ADT: 85.7% (5-yr), 69.8% (10-yr)	Immediate ADT: 95.8% (5-yr), 83.1% (10-yr)
			RT [659, 31%]		Deferred ADT: 87.7% (5-yr) 69.3% (10-yr)	Deferred ADT: 92.8% (5-yr), 84.5% (10-yr)
Fu *et al.*, 2017 (24)	Retrospective (HCSRN)	5,084	RP [2,676]	NR	HR =0.62, 95% CI: 0.48–0.8	HR =0.65, 95% CI: 0.47–0.90
			RT [3,218]			
Duchesne *et al.*, 2016 (25)	Prospective	293	RP or RT	60	Immediate ADT: 91.2% (5-yr)	NR
					Deferred ADT: 86.4% (5-yr)	
Klayton *et al.*, 2011 (26)	Retrospective	432	RT only	95	PSA-DT <6: 47% (7-yr)	PSA-DT <6: 61% (7-yr)
					PSA-DT >6: 53% (7-yr)	PSA-DT >6: 85% (7-yr)

ADT, androgen deprivation therapy; OS, overall survival; CSS, cancer-specific survival; RP, radical prostatectomy; RT, radiation therapy; yr, year; NR, not reported; HR, hazard ratio; CI, confidence interval; PSA-DT, prostate-specific antigen doubling time.

recurrence following radiation without prostate biopsy must be scrutinized and should be assessed via carefully designed clinical trials.

Patient selection

Although determining ideal candidates for salvage therapy is pivotal, there is no consensus on patient selection. In this regard, various clinical parameters can be used to help patients understand the likelihood of success of local salvage therapy. A review by Touma *et al.* found that patients with a PSA less than 10 ng/mL, clinical stage T1c or T2, and a Gleason score (GS) less than 8 showed improved recurrence-free survival (RFS) rates after SRP (20). Additionally, data has demonstrated that there is an association between shorter PSA-doubling time (DT) and increased risk of distant metastases or cancer-related deaths (20). More recently, Mandel *et al.* evaluated selection criteria for SRP using the European Association of Urology (EAU) guideline. This included patients with GS ≤7, no LN involvement, serum PSA level less than 10 ng/mL, and initial clinical stage of T1 to T2. Patients meeting these criteria exhibited a 5-year RFS rate of 73.9% with significantly reduced rates of LN and distant metastases (21).

Salvage therapeutic modalities for radio-recurrent prostate cancer

Currently accepted therapeutic modalities in local and systemic radio-recurrent prostate cancer include androgen deprivation therapy (ADT). For local recurrence, salvage procedures including radical prostatectomy (RP), re-irradiation, cryotherapy, and high-intensity focused ultrasound (HIFU) have been utilized (2). Review of these therapeutic options are discussed below.

Salvage ADT

ADT remains a treatment option for radio-recurrent prostate cancer (22). Nonetheless, its therapeutic impact, especially as a monotherapy, is uncertain (*Table 1*). A study from the CaPSURE database that evaluated 2,096 patients with BCR post-RT or RP, demonstrated no substantial benefit for immediate ADT compared to deferred introduction either at the manifestation of metastatic disease or 2 or more years post-BCR. With a median follow-up of 54 months, the hazard ratio (HR) for mortality was 0.91 [95% confidence interval (CI): 0.52–1.60] (23). The estimated 5-year overall survival (OS) was 85.7% as compared to 87.7%, and the 10-year OS was also similar at 69.8% and 69.3%. In addition, a retrospective assessment of 5,804 men with BCR post-primary therapy showed that salvage ADT correlated with a reduced OS or cancer-specific mortality in the post-RT group, with HR values of 0.62 and 0.65, specifically for patients with a PSA-DT of less than 9 months (24).

Furthermore, recent data from randomized prospective trials such as Duchesne's TOAD study, involving 293 men

Table 2 Summary of SRP case series studies in radio-recurrent prostate cancer

Study	Study design	Number of patients	Median follow-up duration (months)	Pathologic organ confined disease (%)	PSM (%)	Lymph-node involvement (%)	BCR-free survival (%)	MFS (%)	CSS (%)	OS (%)
Chade *et al.*, 2011 (28)	Multi-center, retrospective	404	52.8	55	25	16	37 (10-yr)	77 (10-yr)	83 (10-yr)	NR
Marra *et al.*, 2021 (29)	Multi-center, retrospective	414	36	47.1	29.7	16	56.7 (5-yr)	NR	97.7 (5-yr)	92.1 (5-yr)
Calleris *et al.*, 2023 (30)	Multi-center, retrospective	1,030 (221: EAU fully met/809: EAU not-met)	34	57.5/36.2	85.7/67.4	10.9/22.1	55/38 (5-yr)	90/76 (5-yr)	NR	89/84 (5-yr)

SRP, salvage radical prostatectomy; PSM, positive surgical margin; BCR, biochemical recurrence; MFS, metastasis-free survival; CSS, cancer-specific survival; OS, overall survival; yr, year; NR, not reported; EAU, European Association of Urology.

with BCR after prior RT or surgery, highlight the potential benefits of ADT for locally recurrent prostate cancer (25). Notably, 52% of the cohort began ADT within 2 years. Among patients presenting with high-risk features such as short PSA-DT, the median delay to initiating ADT was 12.3 months. The results favored immediate ADT, showing 5-year OS of 91.2% against 86.4% (log-rank P=0.047; unadjusted HR: 0.55, P=0.05; adjusted HR: 0.54, P=0.047; n=293). Between groups, immediate ADT was preferred with the HR of 0.30 (P<0.001) when examining the onset of castration resistance from treatment commencement.

Establishing a reasonable threshold for PSA-DT for ADT initiation requires additional studies. A study analyzing 432 men with T1–3N0M0 prostate cancer and PSA failure after completion of intensity-modulated RT (IMRT) found that the 7-year cancer-specific survival (CSS) was 61% for individuals with a PSA-DT of less than 6 months, contrasting with 85% for those exceeding this cutoff (P=0.0001) (26). Thus, PSA-DT with cutoff of 6 months has emerged as an important determinant for commencing ADT in prostate cancer patients with BCR. This delineation aligns with benchmarks set in the TOAD trial, where ADT initiation factors encompassed the emergence of symptoms, detection of metastases on standard imaging, or a PSA-DT of 6 months or less.

It is important to note that for the use of salvage ADT, patient selection is critical and may help identify those that would receive a benefit in initiation of therapy. Trials such as the ELAAT trial and TOAD trial investigated the optimal timing of ADT initiation in post-RT PSA rise. Combined pooled analysis demonstrated no difference in all-cause mortality but improvement in time to local progression with immediate ADT. One important notion to consider is that ELAAT involved significantly older men with a higher comorbid all mortality risk while TOAD incorporated higher risk patients that may have benefited from immediate ADT (30% of patients with a relapse-free interval of less than 3 years) together leading to no difference in all cause mortality demonstrated. Thus, when deciding to use salvage ADT it is important to balance the benefit of initiating androgen deprivation with the competing risks of age and comorbidities particularly in those with a high risk of all-cause mortality (27).

SRP (Table 2)

SRP is an effective management option for men with localized radio-recurrent prostate cancer. Nonetheless, current insights on SRP are entirely based on retrospective studies (*Table 2*). In a retrospective multi-institutional cohort analysis conducted by Chade *et al.*, a total of 404 patients treated with SRP were examined (28). The median follow-up period was 4.4 years, the median age was 65 years, and the median PSA was 4.5 ng/mL. Crucially, a decade after undergoing SRP, the probabilities of BCR-free survival, metastasis-free survival (MFS), and CSS were 37%, 77%, and 83%, respectively. Patients with a pre-SRP PSA of 4 or less and a pre-SRP prostate biopsy Gleason grade of 7 or less had survival rates of 64% at 5 years and 51% at 10 years. In another multicenter study of 414 patients treated with SRP, the 5-year BCR-free survival, CSS, and DSS rates were 56.7%, 97.7%, and 92.1%, respectively. Pathologic stage of pT3 or higher and GS of 8 or higher were the most important factors associated with BCR (29). A

recent multicenter retrospective study showed better MFS, PSA-free survival, and OS in the favorable prognosis group according to EAU criteria compared to other groups (30). Also, in a systematic review, SRP was associated with 5- and 10-year BCR-free survival rates of 47% to 82% and 28% to 53%, respectively. Pre-SRP PSA level and prostate biopsy International Society of Urological Pathology (ISUP) grade were strong predictors of organ-confined disease, progression, and CSS (31). Regarding morbidity, compared to primary open RP, SRP has significantly higher risk of anastomotic stricture (48% *vs.* 5.8%), urinary retention (25.3% *vs.* 3.5%), urinary fistula (4.1% *vs.* 0.06%), abscess (3.2% *vs.* 0.7%), and rectal injury (9.2% *vs.* 0.6%) (32). Functional outcomes are also unfavorable compared with primary open RP, with higher rates of urinary incontinence (21–90%) and erectile dysfunction (ED) in nearly all patients (21,31).

Gontero *et al.* reported on the feasibility of the robotic SRP in a multicenter study of 395 prostate cancer patients that recurred after non-surgical treatments (33). While the robotic SRP resulted in reduced blood loss and shorter hospital stay, the overall complication rate was comparable between the open and robotic approach. Interestingly, the post-operative continence rate was higher in the robotic SRP group compared to open SRP (64.61% *vs.* 47.15%).

In summary, SRP can achieve good oncological outcomes in patients with locally recurrent prostate cancer after radiation, with most favorable results in patients with low co-morbidity, pre-SRP PSA <10 ng/mL, initial biopsy ISUP grade group ≤2/3, initial clinical stage T2 or lower, no LN involvement and no evidence of distant metastasis (29-31). However, significant functional side-effects including high rates of urinary incontinence and sexual dysfunction as well as increased complications such as rectal injury must be weighed against the oncologic benefits.

Salvage re-irradiation

Salvage brachytherapy (BT) (*Table 3*)

Low-dose-rate (LDR) BT

LDR BT is an acceptable salvage procedure for patients who recur after primary EBRT. Smith *et al.* studied 108 patients from two institutions (34). With the median follow-up of 6.3 years, the 5- and 10-year BCR-free rates were 63.1% and 52.0%, respectively. In multivariate analysis, higher grade group and elevated PSA level at diagnosis were associated with worse outcomes. Grade 3 toxicity occurred in 16.7% with genitourinary (GU) events in 15.7% and gastrointestinal (GI) events in 2.8% of patients. The NRG RTOG 0526 phase 2 trial led by Crook, investigated transperineal ultrasound-guided LDR BT for patients with local recurrence post-EBRT (35). One hundred patients were registered from 20 institutions, primarily with low-to-intermediate-risk profiles including PSA less than 10 ng/mL prior to salvage BT. With the median follow-up of 54 months, 92 patients underwent the salvage BT with ADT in 16% of the cohort. Late grade 3 GU and GI toxicities were 13% and 1%, respectively, with no grade 4 or 5 events. In an update of this study, the by Crook *et al.* revealed that with a median follow-up extending to 6.9 years, 10-year OS was 70% and 10-year failure rates were local 5%, distant 19%, and BCR 46%. DFS was 61% at 5 years and 33% at 10 years (36).

Partial gland LDR BT aims to treat only the region of the prostate where cancer has recurred. Theoretically, this method spares the surrounding tissues and leads to fewer side effects. Kunogi *et al.* evaluated 12 patients who underwent focal partial salvage re-implantation after experiencing local recurrence following initial LDR BT using iodine^{125} seeds (37). The study showed a promising 4-year BCR-free survival rate of 78%. Remarkably, this study reported no grade 3 GU or GI toxicities, nor any deaths post-salvage re-implantation. Another retrospective study on 20 patients who underwent focal salvage LDR BT following primary RT reported the 3-year BCR-free survival rate of 60% after a median follow-up of 36 months (38). Side effects were minimal with only one patient experiencing a grade 3 GU toxicity, specifically urethral stricture. No complications greater than grade 4 were noted. An encouraging aspect of this study was the potency preservation in all five patients who were potent prior to undergoing the salvage treatment.

High-dose-rate (HDR) BT

Investigators from Scripps Clinic and the University of California-San Francisco (UCSF) reported on 52 patients treated with salvage HDR BT after definitive RT for prostate cancer (39). With a median follow-up of nearly 60 months, 5-year BCR-free survival rate was 51%. The incidence of grade 3 GU toxicity rate was only 2% with the late grade 2 GI toxicity occurring in 4%. Wu *et al.* studied 129 patients who had salvage whole-gland HDR BT after initial definitive RT from 1998 to 2016 at UCSF (40). Most patients initially presented with stage T1–2 (73%) and GS 6–7 (82%), with a median disease-free interval (DFI) of 56 months. The median PSA at the time of salvage therapy was 4.95 ng/mL. Notably, with a median follow-up of

Table 3 Summary of salvage BT case series studies in radio-recurrent prostate cancer

Study	Study design	No. of patients and BT type	Median follow-up duration (months)	BCR-free survival (%)	MFS (%)	CSS (%)	OS (%)	Treatment toxicity
Smith *et al.*, 2021 (34)	Multi-center, retrospective	108 LDR	75.6	63.1 (5-yr) 52.0 (10-yr)	NR	90.5 (5-yr) 77.8 (10-yr)	80.9 (5-yr) 56.7 (10-yr)	Gr 3: 16.7% (GU 15.7%, GI 2.8%)
Crook *et al.*, 2019 and 2022 (35,36)	Multi-center, prospective	100 LDR	80.4	54 (10-yr)	81 (10-yr)	NR	70 (10-yr)	NR
Kunogi *et al.*, 2016 (37)	Single-center, retrospective	12 LDR (focal)	56	78 (4-yr)	NR	NR	NR	No Gr 3 GU/GI toxicity
Peters *et al.*, 2014 (38)	Single-center, retrospective	20 LDR (focal)	36	60 (3-yr)	NR	NR	NR	1 Gr 3 GU toxicity No greater than Gr 4 toxicity
Chen *et al.*, 2013 (39)	Single-center, retrospective	52 HDR	59.6	51 (5-yr)	NR	NR	92 (5-yr)	2% acute and 2% late Gr 3 GU toxicities/4% Gr 2 GI late events
Wu *et al.*, 2021 (40)	Single-center, retrospective	129 HDR	68	85 (3-yr) 71 (5-yr)	NR	NR	NR	19 (15%) strictures requiring dilation
Wojcieszek *et al.*, 2016 (41)	Single-center, retrospective	83 HDR	41	76 (3-yr) 67 (5-yr)	NR	NR	93 (3-yr) 86 (5-yr)	13% Gr 3 GU toxicity with no Gr 2 or 3 GI toxicities
Henríquez López *et al.*, 2019 (42)	Multi-center, retrospective	44 LDR 75 HDR	52	Overall: 71 (5-yr) LDR: 79 (5-yr) HDR: 65 (5-yr)	NR	LDR: 96.5 (5-yr) HDR: 93 (5-yr)	NR	23.5% Gr 3 or more toxicity
Murgic *et al.*, 2018 (43)	Single-center, prospective	15 HDR (focal)	36	61 (3-yr)	NR	NR	NR	Only 1 Gr 3 GU toxicity
Maenhout *et al.*, 2017 (44)	Single-center, retrospective	17 HDR (focal)	10	Only 1 patient showed a BCR	NR	NR	NR	1 Gr 3 urethral stricture at 2 years after treatment
van Son *et al.*, 2020 (45)	Single-center, retrospective	50 HDR (focal)	31	51 (2.5-yr)	75 (2.5-yr)	NR	98 (2.5-yr)	2% Gr 3 GU toxicity, no Gr 3 GI toxicity

BT, brachytherapy; BCR, biochemical recurrence; MFS, metastasis-free survival; CSS, cancer-specific survival; OS, overall survival; LDR, low-dose-rate; yr, year; NR, not reported; Gr, grade; GU, genitourinary; GI, gastrointestinal; HDR, high-dose-rate.

68 months, 3- and 5-year DFS rates were 85% and 71%, respectively. Stricture requiring dilation developed in 15% (n=19), and the incidence of fistula was higher in this group (16%, 3/19) than in patients who did not develop a stricture requiring dilation (1%, 1/110) (P=0.001). Wojcieszek *et al.* analyzed 83 patients with local recurrence post-RT and underwent salvage HDR BT (41). With a median follow-up of 41 months, 3- and 5-year OS rates were 93% and 86%, respectively. The 3- and 5-year biochemical DFS (BDFS) were 76% and 67%, respectively. The incidence of grade 3 GU toxicity was 13%, with no occurrence of grade 2 or 3 GI toxicities. Another retrospective study examined 119 patients treated with salvage BT (LDR, n=44; HDR, n=75) after primary radiotherapy (42). The 5-year PSA RFS rate for the entire cohort was 71%. There was no statistically significant difference in the RFS between the

two groups (P=0.06). However, variables significantly associated with progression included a short time to biochemical failure from the primary RT and post-salvage nadir PSA. Complications were similar across both groups, including urinary incontinence, urethral stricture, and hematuria. Grade 3 or higher toxicity was observed in 23.5% of patients. While urethral stricture was more common in the LDR group, urinary incontinence necessitating pads was more prevalent in the HDR group.

There are several published studies on ultrasound or MRI-guided partial gland focal HDR BT. In a prospective clinical trial, Murgic *et al.* investigated 15 patients with radio-recurrent prostate cancer treated with ultrasound-guided HDR BT (43). The treatment targeted the quadrant of the prostate containing the MRI-visible recurrent lesion. With a median follow-up of 36 months, 3-year PSA failure-free rate was 61%. There was only one case of grade 3 GU toxicity, and of the 14 patients who had post-HDR MRI, 12 showed treatment response. Maenhout *et al.* examined 17 patients with confirmed locally recurrent prostate cancer (44). They were treated using MRI-guided focal HDR BT with a single 19-Gy fraction. With the median follow-up of 10 months (range, 3–40 months), only one patient developed a BCR, which was attributed to a distant nodal metastasis. One grade 3 urethral stricture occurred 2 years following treatment. van Son *et al.* initiated a prospective cohort study in 50 patients treated with MRI-guided ultrafocal salvage HDR BT for localized radio-recurrent prostate cancer (45). At the median follow-up of 2.5 years, the BDFS rate was 51%. Patients with high-risk features had a considerably lower BDFS rate (25% at 2.5 years) compared to those with lower risk features (71% at 2.5 years). There was a single occurrence of grade 3 GU toxicity and no grade 3 GI toxicity.

LDR vs. HDR BT

A systematic review and meta-analysis examined 16 studies (four prospective) for salvage HDR BT and 32 studies (two prospective) for LDR BT, with the majority (>85%) receiving whole-gland treatment rather than partial-gland (8). The adjusted pooled analysis revealed 2-year BCR-free survival rate of 77% for HDR BT and 81% for LDR BT. Five-year BCR-free survival rates were 60% for HDR BT and 56% for LDR BT, respectively. BT was associated with lower rates of severe GU or GI toxicity compared to RP or HIFU. Both HDR and LDR BT can be effective treatment options with a low toxicity profile in radio-recurrent prostate cancer. However, most published studies have small sample sizes. Therefore, salvage BT should be implemented in an experienced center through research using a prospective registry or randomized clinical trials.

Stereotactic body RT (SBRT) (*Table 4*)

SBRT is potentially a new therapeutic option for radio-recurrent prostate cancer patients with good International Prostate Symptom Sore (IPSS) sore, no urinary obstruction, good performance status, and histologically confirmed local recurrence. Several retrospective studies on SBRT have been published. Bergamin *et al.* examined a cohort involving 25 patients who were treated with focal SBRT after definitive RT (46). With a median follow-up of 25 months, the 2-year second BCR-free survival rate was 80%. Complications were minimal, with 1 patient (4%) reporting late grade 2 GU toxicity of dysuria. However, there was no reported late grade 3 toxicity. GI complications were also rare with 1 patient (4%) reporting severe grade 3 toxicity, including tenesmus and rectal ulceration. In a single center and retrospective study including 50 patients with biopsy-confirmed local recurrence with a median pre-salvage PSA of 3.9 ng/mL, the estimated 5-year second BCR-free survival rate was 60% after the median follow-up 44 months (47). This result is comparable to those of series on patients treated with RP, HIFU, and BT. Most complications involved the GU tract, with a 5-year actuarial rate of grade 3+ toxicity of 8%. No GI toxicity greater than grade 1 was noted. In a multicenter study consisting of 100 patients with biopsy-proven radio-recurrent prostate cancer treated with salvage SBRT, the median pre-salvage PSA was 4.3 ng/mL and 3-year second BCR-free survival rate was 55% after a median follow-up of 30 months (48). The rates of 3-year late grade 2+ GU and GI toxicity were 20.8% and 1%, respectively. In a recent systematic review and meta-analysis pooling five retrospective studies, 206 patients were treated with salvage SBRT and the 2-year RFS rate was 61% (8).

It is also important to note the ongoing prospective studies actively being done in order to investigate the utilization of SBRT in the salvage setting for radio-recurrent prostate cancer. NCT03253744 is a phase 1 trial aimed to identify the maximum tolerated dose of SBRT for radio-recurrent prostate cancer with 40, 42.5, and 45 Gy in 5 fractions delivered >48 hours apart. A maximum tolerated dose of 40 Gy in 5 fractions was identified with 8 patients with a 100% 2-year biochemical progression-free survival and no grade 3 toxicities at this dose (49). Further follow-up demonstrated a maximum tolerated dose of 42.5 Gy in 5 fractions with an 86% 2-year biochemical-free survival rate

Table 4 Summary of salvage SBRT case series studies in radio-recurrent prostate cancer

Study	Study design	Number of patients and RT-type	Median follow-up duration (months)	Fractionation (SD/TD)	Combined ADT	BCR-free survival (%)	Treatment toxicity
Bergamin *et al.*, 2020 (46)	Single-center, prospective	25 LINAC based	25	6–6.2 Gy/ 36–38 Gy	0/25	80 (2-yr)	Late Gr 1 GI 8%, Gr 2 GU 4%
Fuller *et al.*, 2020 (47)	Single-center, retrospective	50 Cyber knife	44	6.8 Gy/34 Gy	7/50	60 (5-yr)	8% late Gr 3 or more GU toxicity
Pasquier *et al.*, 2019 (48)	Multi-center, retrospective	100 Cyber knife	29.3	6 Gy/36 Gy in 63 patients 5 Gy/35 Gy in 37 patients	34/100	78 (4-yr)	Gr 2 or more GU toxicity 20.8%, GI toxicity 1%
Patel *et al.*, 2023 (49)	Single-center, prospective, phase 1	Intensity modulated image guided SBRT (8 patients)	35	40 Gy in 5 fractions	0/8	100 (2-yr)	1 Gr 2 toxicity, 0 Gr 3 toxicities
Patel *et al.*, 2024 (50)	Single-center, prospective, phase 1	Intensity modulated image guided SBRT (9 patients)	22	42.5 Gy in 5 fractions	1/9 (short term only)	86 (2-yr)	No Gr 3+ toxicities observed

SBRT, stereotactic body radiation therapy; RT, radiation therapy; SD, single dose; TD, total dose; ADT, androgen deprivation therapy; BCR, biochemical recurrence; yr, year; Gr, grade; GI, gastrointestinal; GU, genitourinary.

with nine patients (50). Prospective studies such as these add to the literature regarding both the feasibility of SBRT in the setting of the oncologic outcomes that can be achieved.

Salvage cryotherapy

Salvage whole gland cryotherapy has been considered as an alternative to SRP, due to potentially lower risk of morbidity and comparable efficacy (*Table 5*). With the median follow-up of 4.8 years, a retrospective analysis of 131 patients treated with salvage cryotherapy for radio-recurrent prostate cancer demonstrated a 5-year DFS rate of 40% overall and 5-year DFS of 57% for patients with a pre-cryotherapy PSA level of ≤10 ng/mL and 23% for those with PSA level >10 ng/mL (51). Furthermore, for patients who had received EBRT with or without ADT, 5-year DFS rates were 58% and 23% respectively. Pisters *et al.* analyzed 279 patients in the Cryo On-Line Data (COLD) registry who had received salvage whole-gland cryoablation following radiotherapy (52). With the average follow-up of 21.6 months, 5-year BDFS rates were 58.9% and 54.5%, respectively. Post-procedure complications were acceptable, with 3.2% of patients requiring TURP. Of patients who were continent prior to the procedure and evaluable 12 months afterwards, 4.4% were using pads while 5.8% reported minimal leakage that did not need pads. The incidence of rectal fistula was 1.2%. Additionally, Pisters *et al.* compared the results of 42 patients with radio-recurrent prostate cancer treated with SRP at Mayo Clinic to 56 patients treated with salvage cryotherapy at M.D. Anderson Cancer Center (53). The median follow-up was 7.8 and 5.5 years for these two groups, respectively. SRP had a better 5-year BDFS rate than cryotherapy (61% *vs.* 21%) when failure was defined as PSA >0.4 (P≤0.001). This difference was still significant when considering two increases above post-salvage PSA nadir, with rates being 66% *vs.* 42%, respectively (P=0.001). Williams *et al.* reported on 176 patients with biopsy-proven radio-recurrent prostate cancer treated with salvage cryotherapy at the University of Western Ontario (54). With a median follow-up of 7.46 years, 5- and 10-year DFS rates was 47% and 39%, respectively. A compelling association between pre-salvage PSA levels and DFS rates was noted: patients with a PSA <5 ng/mL had a 10-year DFS rate of 64%, while those with a PSA >10 ng/mL had the rate of 6.7%. There was a correlation between pre-radiation PSA level and pre-salvage GS with recurrence. More recently, Exterkate *et al.* analyzed 169 patients with biopsy-confirmed radio-recurrent prostate cancer who underwent salvage cryotherapy (55). With the median follow-up of 36 months,

Table 5 Summary of salvage cryotherapy case series studies in radio-recurrent prostate cancer

Study	Study design	Number of patients	Median follow-up duration (months)	BCR-free survival (%)	DFS (%)	Treatment toxicity
Izawa *et al.*, 2002 (51)	Single-center retrospective	131	57.6	NR	Overall: 40 (5-yr)	NR
					Pre-cryotherapy PSA ≤10: 57 (5-yr)	
					Pre-cryotherapy PSA >10: 23 (5-yr)	
Pisters *et al.*, 2008 (52)	Multi-center, retrospective	279	21.6	58.9 (5-yr, by ASTRO criteria)	NR	4.4% incontinence rates
				54.5 (5-yr, by Phoenix criteria)		1.2% rectal fistula
Pisters *et al.*, 2009 (53)	Multi-center, retrospective	42 SRP (Mayo)	93.6 (SRP)	SRP: 61 (5-yr, by Phoenix criteria)/66 (5-yr, by ASTRO criteria)	NR	NR
		56 sCryo (MDACC)	66 (sCryo)	sCryo: 21 (5-yr, by Phoenix criteria)/42 (5-yr, by ASTRO criteria)		
Williams *et al.*, 2011 (54)	Single-center, retrospective	176	89.5	NR	47 (5-yr)/39 (10-yr)	NR
Exterkate *et al.*, 2021 (55)	Single-center, retrospective	169	36	52 (5-yr)/45 (8-yr) (by Phoenix criteria)	NR	19% new-onset urinary incontinence
						92% new-onset ED
						6.5% persistent urinary fistula
de Castro Abreu *et al.*, 2013 (56)	Single-center, retrospective	25 (focal)	31 (focal)	Focal: 54 (5-yr) (by Phoenix criteria)	NR	New onset urinary incontinence: 0% in focal/13% in total
		25 (total)	53 (total)	Total: 86 (5-yr) (by Phoenix criteria)		Recto-urethral fistula: one (4%) patient in the total group
Li *et al.*, 2015 (57)	Retrospective	91 (focal)	15	95.3 (1-yr)/72.4 (3-yr)/46.5 (5-yr) (by Phoenix criteria)	NR	3.3% recto-urethral fistula
						6.6% urinary retention

BCR, biochemical recurrence; DFS, disease-free survival; NR, not reported; yr, year; PSA, prostate-specific antigen; ASTRO, American Society of Therapeutic Radiology and Oncology; SRP, salvage radical prostatectomy; sCryo, salvage cryotherapy; ED, erectile dysfunction.

5- and 8-year biochemical RFS (BRFS) rates were 52% and 45%, respectively. Multivariable analysis revealed that PSA level at initial diagnosis, initial treatment, interval between primary treatment and salvage cryotherapy, age at salvage cryotherapy, and post-salvage PSA nadir were significant factors for BRFS. The 5-year ADT-free survival was 70%. Clavien-Dindo Grade ≥3 complications occurred in 1.2% (2/169). Overall, 19% (29/156) of patients had new-onset urinary incontinence defined as using >1 pad/day and 92% (57/62) of patients had new-onset ED. Persistent urinary fistula occurred in 6.5% (11/169).

Concerning partial gland focal cryotherapy, de Castro Abreu *et al.* investigated in 50 patients with biopsy-proven unilateral or bilateral radio-recurrent prostate cancer (56). Patients received salvage focal cryoablation (SFC) for unilateral disease and salvage total cryoablation (STC) for

Table 6 Summary of salvage HIFU case series studies in radio-recurrent prostate cancer

Study	Study design	Number of patients	Median follow-up duration (months)	BCR-free survival (%)	Other survival outcomes	Incontinence (%)	Obstruction/ retention (%)	Rectourethral fistula (%)	ED (%)
Crouzet *et al.*, 2017 (58)	Multi-center, retrospective	418	39.6	49 (5-yr, by Phoenix criteria)	7-yr OS:72% 7-yr CSS: 82% 7-yr MFS: 81%	42.3	18.0	2.3	NR
Jones *et al.*, 2018 (59)	Multi-center, prospective	100	12	50 (1-yr, by nadir PSA >0.05 ng/mL or positive biopsy)	NR	42.0	49.0	5.0	74.0
Kanthabalan *et al.*, 2017 (60)	Multi-center, retrospective	150	35	48 (3-yr, by Phoenix criteria)	NR	12.5	8.0	2.0	41.7

HIFU, high-intensity focused ultrasound; BCR, biochemical recurrence; ED, erectile dysfunction; yr, year; OS, overall survival; CSS, cancer-specific survival; MFS, metastasis-free survival; NR, not reported; PSA, prostate-specific antigen.

bilateral disease. No patients died of prostate cancer during the follow up period, while one patient from the STC group developed bone metastases. BCR occurred in 8 SFC patients and 3 STC patients. The 5-year BFS rates was 54% in SFC and 86% in STC. There were no incontinent patients in the SFC group. In contrast, 13% of the STC patients were incontinent. Two of seven patients undergoing SFC retained erectile function while no STC patient regained potency post-treatment. One STC patient developed a recto-urethral fistula. Li *et al.* examined 91 patients from the COLD registry who were treated with SFC for radio-recurrent prostate cancer (57). At a median follow-up of 15 months, 5-year BDFS was 46.5%. The recto-urethral fistula rate was 3.3%, urinary retention occurred in 6.6% of patients, and half of the patients who were potent before the procedure retained their ability to have intercourse a year after the SFC.

Salvage HIFU

Salvage HIFU is another option for radio-recurrent prostate cancer (*Table 6*). Data on this relatively new treatment are limited. Crouzet *et al.* reported a retrospective, multi-institutional study of 418 patients with locally recurrent prostate cancer treated with salvage HIFU after EBRT (58). The mean PSA before salvage HIFU was 6.8 ng/mL and the median PSA nadir after salvage HIFU was 0.19 ng/mL. With the mean follow-up of 3.5 years, the OS, CSS, and MFS rates at 7 years were 72%, 82%, and 81%, respectively. At 5 years, the biochemical failure-free survival (bFFS) rate was 58%, 51%, and 36% for pre-EBRT low-, intermediate- and high-risk patients, respectively. The 5-year bFFS rate was 67%, 42%, and 22% for pre-salvage HIFU PSA level ≤4, 4–10, and ≥10 ng/mL, respectively. In another retrospective study, 100 men were treated with whole gland HIFU due to recurrent prostate cancer after 2 years post-EBRT (59). At 12 months post-treatment, 78 had prostate biopsy and 81% (63/78) was negative. PSA nadir ≤0.5 ng/mL plus negative biopsy at 1 year was achieved in 50 men. Adverse events developed in 91 men through 12 months, which were grade 1 in 67, grade 2 in 80, and grade 3 in 20. Treatment-related grade 3 adverse events included recto-urethral fistulas in five men. There were no life-threatening adverse events or treatment-related deaths.

Kanthabalan *et al.* described outcomes and complications associated with partial gland focal salvage HIFU for radio-recurrent prostate cancer (60). In their retrospective registry of 150 patients, the median PSA pre-focal salvage HIFU was 5.59 ng/mL. Prior to the treatment, patients were categorized into low- (2.7%, 4/150), intermediate- (39.3%, 59/150), and high-risk disease (41.3%, 62/150) according to the D'Amico classification. Composite failure occurred in 61% and BCF occurred in 51.3%. Composite endpoint-free survival (CEFS) rate at 3 years was 40% for the entire cohort. The estimated CEFS were 100%, 49%, and 24% at 3 years in the low-, intermediate- and high-risk groups pre-salvage HIFU, respectively. The estimated BDFS rate at 3 years after salvage HIFU was 48% for the entire group

Table 7 Summary of salvage IRE case series studies in radio-recurrent prostate cancer

Study	Study design	Number of patients	Median follow-up duration (months)	Oncologic outcomes	Safety outcomes
Guenther *et al.*, 2019 (62)	Multi-center, retrospective	429 (63: recurrent disease)	Max 72	Overall recurrence rate: 41 (10%) patients (5-year recurrence rate: 5.6% for Gleason 6/14.6% for Gleason 7/39.5% for Gleason 8–10)	Complications: mild (19.7%), moderate (3.7%) and severe (1.4%) No life-threatening complications Urinary continence was preserved in all cases IRE-induced ED persisted in 3% of the evaluated cases at post-treatment 12 months
Blazevski *et al.*, 2023 (63)	Multi-center, prospective (FIRE trial)	37	29	27 (73%) patients: no local and systemic disease 4 (11%) patients: local recurrence only 6 (16%) patients: metastatic disease with a median time to metastasis of 8 months	7 (19%) patients: self-limiting urgency, frequency, or hematuria (Gr 1–2) 7 (19%) Gr 3 complications; urethral sludge requiring transurethral resection 93% of patients remained continent at post-salvage IRE 12 months ED deterioration: from 35% to 15% (4/27)

IRE, irreversible electroporation, ED, erectile dysfunction; Gr, grade.

and were 100%, 61%, and 32% at 3 years in the low-, intermediate-, and high-risk groups pre-salvage HIFU, respectively. Complications included urinary tract infection (11.3%, 17/150), bladder neck stricture (8%, 12/150), recto-urethral fistula after one HIFU procedure (2%, 3/150) and osteitis pubis (0.7%, 1/150).

A newer focused ultrasound technology, transurethral ultrasound ablation (TULSA), has been evaluated in a phase I study by Anttinen *et al.* (61). In 11 patients, there was one grade 3 and three grade 2 AEs related to urinary retention and infection. There was some increase in urinary symptoms and decrease in urine flow rates. Protocol follow-up biopsy at 12 months identified cancer in 1/11 patients in the targeted ablation zone, and 2/11 had out-of-field cancer detected.

Salvage irreversible electroporation (IRE) (Table 7)

IRE is an image-guided ablative technique that triggers cell death using brief, intense electric pulses. Unique to IRE is its reported capability to spare essential structures such as blood vessels, nerves, and the extracellular matrix. Such specificity makes salvage IRE a potentially attractive salvage option for patients with radio-recurrent prostate cancer, as it offers the potential for targeted disease ablation while minimizing collateral damage to normal tissues.

Guenther *et al.* investigated the efficacy and safety of IRE (62). The patient cohort, broadly classified based on risk levels, included 25 with low-risk, 88 with intermediate-risk, and 312 with high-risk cancers. A comprehensive diagnostic evaluation using multi-parametric MRI was performed for all patients. Moreover, 199 patients underwent an additional three-dimensional (3D)-mapping biopsy before undergoing IRE. Treatment approaches were focal [123], sub-whole-gland [154], and whole-gland [134] treatments, and 63 patients were treated for recurrent disease post-initial definitive treatments. Mild, moderate, and severe adverse effects were reported in 19.7%, 3.7%, and 1.4% of the patients, respectively. None of the adverse events were life-threatening. Urinary continence was reported in all cases. IRE-induced ED was temporary in most patients and persisted in only 3% 12 months post-treatment. On the sexual health index, the IIEF-5 score temporarily decreased by 33% within the first 12 months post-IRE and improved to a 15% reduction after a year. Recurrence within the follow-up period was observed in 10% of treated men. Of these, 23 were within or adjacent to the IRE treatment field, while 18 were outside, termed as "residuals". Recurrence rate at 5 years post-IRE was 5.6% for Gleason 6, 14.6% for Gleason 7, and

39.5% for Gleason 8–10 disease. Recently, the results of a multicenter, prospective study (FIRE) on salvage IRE have been published (63). This study included 37 patients with focal recurrent prostate cancer after EBRT or BT. Median PSA was 3.5 ng/mL. Twenty-eight (75.5%) patients had intermediate risk and 9 patients (24.5%) high-risk disease. Seven patients (19%) reported self-limited urgency, frequency, or hematuria (grade 1–2). Seven patients (19%) developed grade 3 adverse events. At 12 months post-treatment, 93% of patients remained continent and erection sufficient for intercourse deteriorated from 35% to 15% (4/27). Local control was achieved in 29 patients (78%) and 27 patients (73%) were clear of local and systemic disease. Four (11%) patients had local recurrence only. Six (16%) patients developed metastatic disease with a median time to metastasis of 8 months.

Ongoing and future trials

There are multiple studies currently in progress exploring the optimal strategies for radio-recurrent prostate cancer. A noteworthy study is ROADSTER, a single institution phase I/II randomized trial (64). Patients eligible for this study have an isolated local failure (ILF) post-definitive initial RT. Diagnostic confirmation of the ILF will be confirmed using a combination of biopsy, MRI, and PSMA PET CT scans. Participants will then be randomized into two cohorts: the first will receive HDR BT in two fractions. The second cohort will first receive an intravenous treatment of Lutetium-177 PSMA RLT, which will then be followed by a single fraction of HDR BT. The key primary outcome during the phase I portion of the trial with 12 patients is feasibility, defined as 10 or more participants successfully completing the study protocol within 2 years of activation. Safety is also another endpoint. The procedure will be declared safe if zero or one patient in the second cohort experience grade 3 or higher toxicities in the initial 6 months post-treatment. Should these criteria for feasibility and safety be met, the trial will progress to phase II, which will evaluate preliminary efficacy in 30 participants. Secondary objectives encompass changes in PSA levels, early-stage toxicity rate, quality of life alterations, and variations in translational biomarkers. Furthermore, translational objectives will involve the examination of blood, urine, and tissue samples to identify markers indicative of DNA damage and immune system activation post-treatment.

As previously discussed, NCT03253744 was designed as a phase 1 trial with the goal of determining the maximum tolerated dose (MTD) when using image-guided, focal, salvage SBRT for patients with locally radio-recurrent prostate cancer (49). The identified MTD for this salvage SBRT, intended for treating isolated intraprostatic radio-recurrences, was established at 40 Gy delivered across 5 fractions. This dose achieved a 100% biochemical progression-free survival rate over 24 months, although there was one poststudy failure noted at the 33-month mark. Similarly, a follow-up study identified the MTD as 42.5 Gy delivered in 5 fractions with an 86% biochemical progression-free survival over 24 months. The overarching goal is to refine and enhance the SBRT regimen for this specific patient population. This trial is actively obtaining further follow-up to provide additional information.

Conclusions

Patients with radio-recurrent prostate cancer usually have an unfavorable prognosis. Although ADT is used for systemic control of visible and sub-clinical metastatic disease, it is not curative in case of local disease and associated with increased mortality in patients with comorbidities. While robotic SRP has improved and has relatively low surgery-related morbidity, functional outcomes still remain poor. Any surgical approach must be performed with caution considering the risks of morbidity and complications resulting from the previously irradiated field. Radio-recurrent prostate cancer can be also treated with other salvage local procedures, including radiation or ablation approaches. There is increasing interest in subtotal salvage therapies given improved localization of cancer recurrence with modern imaging and targeted prostate biopsies due to the decreased side effects associated with sub-total treatments. However, available evidence to date on these treatment options remains of low quality, and strong recommendations regarding the choice of any of these treatment options cannot be made with confidence. Further research with higher quality study design, larger sample sizes and longer follow-up are needed before salvage local treatments are routinely implemented in clinical practice. Until such studies are completed, the management of radio-recurrent prostate cancer should be individualized, taking into account the patient's overall health and priorities, the extent of recurrence, and the morbidity of salvage treatments.

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Footnote

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