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REVIEW

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# Emerging focal ablation therapies for radio-recurrent prostate cancer: a comprehensive review of diagnostic imaging, ablative techniques, and patient outcomes

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## Abstract

Prostate cancer is among the most common malignancies in men, with the majority of cases manifesting as localized disease. Standard treatment options include radiation therapy, radical prostatectomy, and active surveillance. Despite effective primary treatments, recurrence remains a clinical challenge, with limited salvage options that balance efficacy and side effects. Emerging focal ablative therapies for radio-recurrent prostate cancer represent a promising alternative for patients with biochemical recurrence following definitive radiation therapy, offering an option to avoid salvage prostatectomy or whole-gland re-irradiation. A comprehensive literature review was conducted using PubMed, Medline, and Cochrane databases to identify studies on focal ablative therapies for recurrent prostate cancer following radiation therapy. Search terms included "recurrent localized prostate cancer", "high-intensity focused ultrasound", "cryotherapy", "irreversible electroporation", and "photodynamic therapy". Selected studies were evaluated based on outcomes and safety data relevant to salvage ablation. Advanced imaging techniques such as multiparametric MRI and prostate-specific membrane antigen positron emission tomography/computed tomography have improved the detection and localization of recurrent prostate cancer, facilitating precise delivery of ablative therapies. Preliminary evidence suggests that focal therapies may provide oncologic control similar to whole-gland treatments while reducing adverse effects. However, variability in functional outcomes, particularly concerning urinary and sexual health, underscores the need for careful patient selection and rigorous follow-up. Focal ablation therapies represent a promising option for recurrent prostate cancer, potentially enhancing the quality of life without compromising cancer control. Further research, especially randomized controlled trials, is necessary to establish their long-term safety and efficacy.

## Keywords

Ablation; Cryotherapy; High-intensity focal ultrasound; Irreversible electroporation; Photodynamic therapy; Prostate cancer; Recurrence

## 1. Introduction

Prostate cancer is the second most common cancer in men and the second leading cause of cancer deaths in men globally, following lung cancer [1]. Fortunately, over 80% of patients present with localized disease, primarily treated with radiation therapy (RT), radical prostatectomy, or active surveillance [2–5].

For patients seeking to avoid the side effects of surgery and the uncertainty associated with active surveillance, RT is a key treatment option seeking to target the tumor(s) while sparing surrounding tissues. Traditional approaches to RT include brachytherapy and external-beam RT [6]. In prostate cancer, brachytherapy involves placing small radioactive implants into the prostate to release radiation over time, while external-beam RT uses external radiation focused on the prostate, often aided by imaging, and potentially combined with androgen deprivation therapy [4, 7, 8]. Despite primary treatment with RT, biochemical recurrence (BCR) of prostate cancer occurs in 10–15% of patients within 5 years [9–11]. Biochemical recurrence after radiation therapy is most commonly defined using the Phoenix criterion, which specifies a PSA rise of $\geq$2 ng/mL above the post-treatment nadir. This threshold, though imperfect, remains the standard definition in clinical trials and guidelines [11]. Among these patients, salvage options include androgen deprivation therapy, salvage radical prostatectomy, continued surveillance, or additional local therapy. In this setting, salvage re-irradiation (re-RT) with external beam radiation or brachytherapy may be considered in highly selected cases, though it is limited by concerns of


  

cumulative toxicity. While re-irradiation with brachytherapy and external beam radiation are also potential options in the management of radiorecurrent prostate cancer, they are beyond the scope of this review, which highlights the surgical ablative options rather than re-irradiation. Salvage prostate ablation is another option after prostate cancer recurrence following RT, but there is insufficient consensus in current guidelines regarding the appropriate extent of ablation for salvage therapy. This review focuses specifically on men with localized radiorecurrent disease, defined by BCR following definitive RT, with intraprostatic recurrence confirmed via advanced imaging and, when feasible, biopsy.

Ablation therapies, including cryotherapy, high-intensity focal ultrasound (HIFU), irreversible electroporation (IRE), and photodynamic therapy (PDT) offer a minimally invasive option for recurrent prostate cancer, with benefits like reduced toxicity and tissue preservation [12]. Their effectiveness, however, depends on accurately localizing the cancer within the prostate. Nevertheless, improved knowledge and discussion of these modalities are vital for improving treatments available to patients with recurrent localized prostate cancer following RT.

This review emphasizes the role of diagnostic imaging in precisely localizing prostate cancer recurrences, along with preablative patient evaluation, ablative techniques, and follow-up protocols in managing radio-recurrent prostate cancer.

## 2. Literature review

A literature search of all English-language articles in PubMed, Medline, and Cochrane databases until 2024 was conducted. This article is a narrative review that synthesizes key findings from recent literature on focal ablative therapies for radio-recurrent prostate cancer. A comprehensive, but non-systematic, search of the literature was conducted using PubMed and expert recommendations. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were not followed, and no formal risk-of-bias assessment was performed. We conducted a search using the following terms: "recurrent prostate cancer" OR "prostate cancer recurrence" OR the "recurrent prostatic neoplasms". These were combined with treatment-related terms, including "high intensity focused ultrasound" OR "HIFU" OR "cryotherapy" OR "cryoablation" OR "reirradiation" OR "salvage radiotherapy" OR "ablation" OR "irreversible electroporation" OR "photodynamic therapy" OR "PDT". Boolean operators were used to ensure comprehensive retrieval of relevant studies. All abstracts and full-text papers were reviewed by two independent reviewers (JW and JF). A total of 135 articles were initially identified. After reviewing for relevance, 129 articles were excluded because they did not meet the inclusion criteria relevant to the studied topics. A further 62 studies were included based on the following criteria: (1) studies addressed salvage focal ablation for radio-recurrent prostate cancer, (2) reported relevant oncologic or functional outcomes, (3) used modern imaging (Prostate-Specific Membrane Antigen Position Emission/Computed Tomography (PSMA PET/CT) or Multiparametric Magnetic Resonance Imaging (mpMRI)), or (4) were recommended by field experts (*e.g.*, JF) based on relevance and quality.

## 3. Results

### 3.1 Detection of recurrence and selection for ablative therapy

Imaging modalities including computed tomography (CT) or magnetic resonance imaging (MRI) with contrast enhanced imaging and prostate-specific membrane antigen (PSMA) positron emission tomography (PET)/CT are vital to identify BCR and to allow for exact targeting of tumor(s) using ablative therapies. Following the detection of recurrent tumors, confirmation occurs with targeted prostate biopsies. A discussion of these imaging modalities, prostate biopsy, and the factors that influence recommendation for patients to undergo ablation follows below.

#### 3.1.1 Imaging

Cross-sectional imaging modalities, including CT, MRI, and PSMA PET/CT, have become essential in identifying recurrent prostate cancer and guiding targeted treatment strategies [13–15]. While abdominal and pelvic contrast enhanced CT scans remain a widely accessible and cost-effective option for evaluating metastatic spread to bone and visceral organs, its utility declines at lower prostate-specific antigen (PSA) levels, where CT imaging is less effective in detecting small-volume recurrence [16]. However, CT imaging continues to play an important role in helping to identify larger recurrent masses, particularly in cases of elevated PSA, providing critical data for treatment planning.

Multiparametric MRI (mpMRI), with its combination of T1- and T2-weighted sequences along with diffusion-weighted imaging and dynamic contrast enhancement, offers superior anatomic resolution and tumor characterization [17, 18]. This multimodal approach allows for the detection of clinically significant cancers, even in cases of BCR. In the Prostate MR Imaging Study (PROMIS) trial, mpMRI demonstrated a sensitivity of 93% for detecting clinically significant cancers, highlighting its continued importance in the posttreatment setting [19].

Building on these advancements, PSMA PET/CT represents a major leap forward in prostate cancer diagnostics. Traditional PET imaging, which uses radiotracers like Fluorine 18-labeled fluorodeoxyglucose ($^{18}$F-FDG), often struggles to detect less glycolytic or more aggressive prostate cancers [13, 17]. This limitation has been overcome with PSMA ligands, which bind specifically to PSMA on prostate cancer cells and can be visualized using PET or CT. PSMA PET, particularly when combined with mpMRI, significantly enhances diagnostic and prognostic accuracy, providing superior performance in high-risk staging, BCR, and castration-resistant prostate cancer [17, 20]. Notably, PSMA PET has demonstrated the ability to detect 84% of lesions even with a low PSA rise (<2.0 ng/mL), underscoring its effectiveness in detecting recurrence in challenging clinical scenarios [21].

Together, mpMRI and PSMA PET/CT enable the precise localization of recurrent prostate cancer, facilitating the application of targeted ablative therapies and improving patient outcomes through more individualized treatment strategies.

### 3.1.2 Prostate biopsy

While mpMRI and PSMA PET/CT provide crucial insights into recurrent prostate cancer following RT, pathologic confirmation via biopsy remains essential for confirming diagnosis and grading clinically significant disease [15]. Traditionally, transrectal ultrasound-guided systematic biopsies have been the reference standard, employing a 12-core nontargeted approach [22]. However, this method is often criticized for missing significant cancers, especially in key areas like the apex and anterolateral peripheral zone and can lead to both overtreatment of indolent disease and undertreatment of aggressive tumors [23, 24]. The transperineal biopsy has seen increased clinical adoption as an alternative, offering improved access to anterior lesions, and reducing the risk of infection compared to transrectal approaches, making it an increasingly favored method for recurrent prostate cancer evaluation [25].

Recent advances in mpMRI have enabled more precise targeted biopsies of lesions identified at imaging, improving the detection of clinically significant cancer compared to standard systemic biopsies [19, 26–28]. A combined approach, using both targeted and systematic biopsies, has been shown to further enhance cancer detection [23, 29]. This dual strategy is particularly valuable in cases of BCR, where accurate identification of residual or recurrent disease is paramount for planning ablative therapies.

In recurrent prostate cancer, biopsy is not only crucial for assessing the prostate but also for sampling other potential sites of involvement, such as the seminal vesicles, which are often implicated in advanced disease [30]. Routine sampling of the seminal vesicles, particularly in cases of rising PSA following radiotherapy, ensures a comprehensive assessment of disease progression and allows for precise targeting during subsequent ablative treatments.

### 3.1.3 Candidates for ablation

Candidates for focal ablation in the recurrent setting typically present with either unifocal or multifocal recurrence. Focal ablative therapies target either specific lesions or entire regions harboring cancer and are often considered for patients with a single tumor or multiple foci confined to one-half of the prostate. While initial studies on focal therapy were largely limited to low-volume localized cancers, there has been growing interest in its use for intermediate-risk disease [31, 32]. According to the American Urologic Association (AUA), ablation may be considered in select, appropriately informed patients—ideally within the context of a clinical trial—with intermediate-risk prostate cancer, as evidence for treating high-risk disease with ablation is lacking, and low-risk cancers should preferentially be managed with active surveillance. Clinicians should not recommend whole-gland or focal ablation for high-risk prostate cancer outside of a clinical trial [33]. Salvage ablation strategies often mirror those employed in the treatment of primary prostate cancer. The index lesion approach targets the largest and most aggressive tumor while leaving smaller lower-risk tumors untreated, under the premise that they are less likely to influence long-term disease progression. Alternatively, region-targeted therapy treats a larger area surrounding the tumor, increasing the potential for a cure while preserving critical structures. Hemiablation, in which half of the prostate is treated, remains a common approach in focal therapy [34]. Historically, whole-gland ablation was favored in salvage settings due to limitations in imaging and biopsy techniques. However, advancements in targeted biopsy, mpMRI, and PSMA PET/CT now enable more precise identification of localized recurrences, making focal ablation a viable option. A stepwise clinical decision pathway for evaluating patients with biochemical recurrence and determining suitability for focal ablation is shown in Fig. 1.

## 3.2 Preablative workup

Before considering secondary therapies such as ablation for recurrent prostate cancer, a comprehensive diagnostic workup is crucial to accurately classify the disease and guide treatment. Monitoring PSA following radiotherapy poses challenges as RT preferentially destroys cancer cells more effectively than benign prostate tissue, which can still produce PSA [9]. Biochemical failure is commonly defined using either the American Society for Therapeutic Radiology and Oncology (ASTRO) definition (three consecutive PSA rises following nadir) or the Phoenix criteria (PSA $\geq$2 ng/mL above the nadir) [33, 35]. However, debate continues over the use of PSA as a reliable marker for long-term outcomes, with some studies suggesting that PSA screening does not consistently predict overall survival (OS) benefits [36].

As previously discussed, emerging imaging techniques, such as PSMA PET/CT and mpMRI, are transforming the landscape of recurrence detection, enabling visualization of disease even below the Phoenix threshold. Although BCR is commonly defined by the Phoenix criterion, modern imaging techniques such as PSMA PET and mpMRI can detect local recurrence earlier, even before patients meet this biochemical threshold.

These technologies are integral to modern focal ablation strategies, providing precise localization of recurrent lesions. Given that up to half of recurrences occur outside previously treated areas, accurate imaging is essential for delivering targeted ablative therapies [37]. However, even with advanced imaging, certain factors may preclude focal therapy, including the need for candidates to have a clearly localized, targetable lesion without extensive bilateral, multifocal, or extraprostatic disease, and accurate lesion mapping with mpMRI and targeted biopsy. Contraindications include anatomy or gland size incompatible with complete ablation, inability to comply with close post-treatment surveillance, and general procedural risks, such as active infection, bleeding diathesis, or access-limiting rectal pathology [38, 39].

Ultimately, the efficacy of focal ablative interventions, to be described in the next section (Table 1, Ref. [40–42]), is directly tied to the thoroughness of the preablative workup, which ensures accurate disease characterization and optimal treatment planning.

# 4. Discussion

## 4.1 Ablative therapies

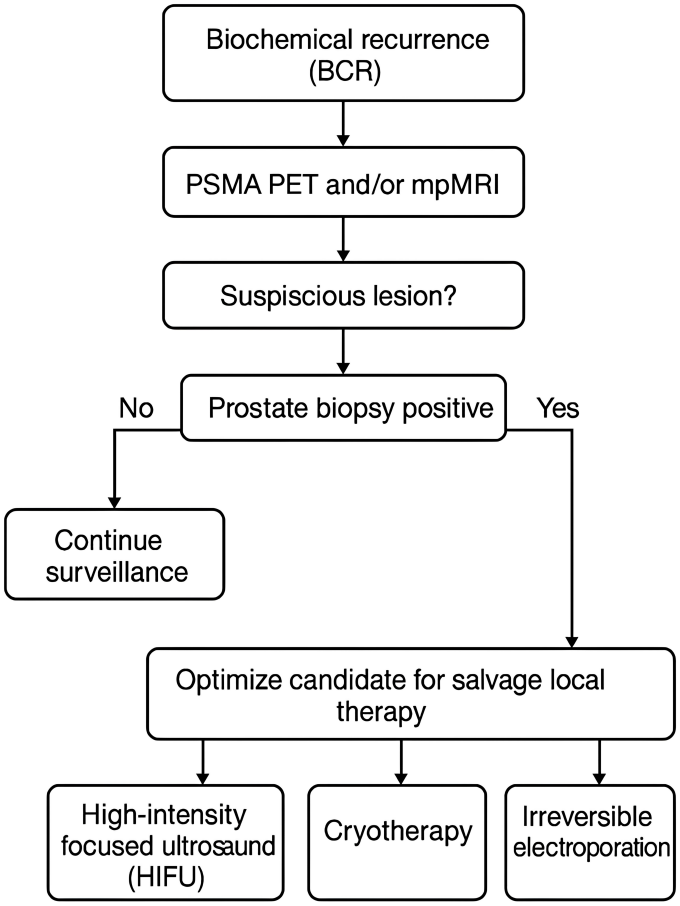


**FIGURE 1. Clinical decision flowchart for BCR.** PSMA: prostate-specific membrane antigen; PET: positron emission tomography; mpMRI: Multiparametric MRI.

**TABLE 1. Overview of ablative therapies for radio-recurrent prostate cancer.**

| Ablative Technique | Mechanism of Action | Benefits | Drawbacks | Guideline Recommendation (AUA/NCCN/EAU) |
|---|---|---|---|---|
| Cryotherapy | Freezes tissue to induce cell death through protein denaturation, membrane rupture, and microvascular thrombosis. | Minimally invasive; effective local control; reduced toxicity. | Urinary and sexual dysfunction; potential for urethral stricture. | EAU: Considered salvage option after RT [40]; AUA/NCCN: Not routinely recommended due to limited data; use in select cases [40, 41]. |
| High-Intensity Focused Ultrasound (HIFU) | Causes coagulative necrosis through hyperthermia and cavitation at 60–90 °C. | Noninvasive; potential for urinary preservation; guided by imaging. | Limited to smaller prostates; sexual dysfunction; variable long-term data. | EAU: Considered in select salvage cases [42]; NCCN/AUA: Mentioned as investigational or limited-use option [40, 41]. |
| Irreversible Electroporation (IRE) | Uses electric pulses to create nanopores in cell membranes, leading to apoptosis. | Spares critical structures; preserves continence; nonthermal. | Erectile dysfunction; technical challenges; limited long-term data. | Not currently included in major guidelines; ongoing trials may inform future recommendations [40–42]. |
| Photodynamic Therapy (PDT) | Activates light-sensitive agents to release free radicals causing necrosis and immune activation. | Minimally invasive; localized treatment; immune-modulating potential. | Limited salvage data; depth limitations; requires special equipment. | EAU: Experimental [42]; AUA/NCCN: Not routinely recommended; investigational [40, 41]. |

*RT: radiation therapy; AUA: American Urologic Association; NCCN: National Comprehensive Cancer Network; EAU: European Association of Urology.*

### 4.1.1 Cryotherapy

Cryotherapy freezes targeted tissue to achieve cell death through protein denaturation, membrane rupture, and microvascular thrombosis [42]. Performed under general anesthesia, the procedure involves percutaneous insertion of thermo- and cryoprobes, using argon gas to reach cytotoxic temperatures as low as −40 °C, followed by a warming phase with hydrogen to complete the ablation process [43]. Initially applied to the entire prostate gland, whole-gland cryotherapy has been associated with considerable urinary and sexual side effects, prompting a shift toward partial-gland, or focal, approaches [44, 45].

Despite this shift, data on focal cryotherapy as a salvage treatment following radiotherapy remains limited, with most evidence derived from retrospective studies on whole-gland ablation [46]. In a cohort of 157 patients with localized radio-recurrent prostate cancer following treatment with whole-gland cryotherapy, Siddiqui *et al.* [47] reported a 10-year overall survival (OS) rate of 76%, with BCR-free and metastasis-free survival rates of 35% and 86%, respectively. Key predictors of survival included pre-cryoablation and nadir PSA [47]. Another study of 150 patients found a 5-year disease-free survival rate of 26% in cases with residual cancer at biopsy versus 52% in those without recurrence ($p = 0.016$) [48]. This study also highlighted that increasing the number of cryoprobes and implementing multiple freeze-thaw cycles could enhance ablation efficacy, recommending at least two cycles and five cryoprobes to optimize treatment outcomes [48].

While early studies on salvage cryotherapy focused on whole-gland ablation, achieving promising oncologic control, they also reported high morbidity, including complications such as incontinence, urethral stricture, and sexual dysfunction [49]. Efforts to reduce these side effects, including the use of urethral warmers and ultrasound guidance, have had some success, yet, complications remain a concern [50]. In response, focal cryotherapy has emerged as a targeted approach, aiming to minimize adverse effects while retaining oncologic efficacy.

Recent evidence suggests that, in appropriately selected patients, focal cryotherapy offers comparable oncologic outcomes to whole-gland ablation [51, 52]. In a study by Tan *et al.* [53], no significant difference was observed in 2-year progression-free survival rates between whole-gland and focal cryotherapy (79.8% *vs.* 76.98%; $p = 0.11$) [51]. Supporting these findings, other studies report favorable BCR rates for focal ablation in the short term, although some divergence in outcomes may occur over the long term [54, 55]. Focal therapy also appears to offer decreased morbidity; an analysis of the Cryo On-Line Data Registry (COLD) indicated lower rates of rectourethral fistula (0.09% *vs.* 0.4%) and higher rates of urinary continence (98.4% *vs.* 96.9%) and sexual function preservation (58.1% *vs.* 32.3%) compared to whole-gland treatment [51].

In conclusion, cryotherapy has evolved from whole-gland to focal approaches, potentially reducing morbidity without compromising short-term oncologic control. Continued research, particularly randomized trials, is essential to establish the long-term outcomes of focal cryotherapy and optimize patient selection.

### 4.1.2 High-intensity focal ultrasound

HIFU ablates tissue through hyperthermia and cavitation, causing coagulative necrosis at focal temperatures between 60–90 °C [42]. Modern HIFU devices, applied transrectally or transurethrally with MRI or transrectal ultrasound guidance, are limited to treating smaller prostates and focal lesions. Although HIFU is promising, data on its use in the salvage setting (S-HIFU) following radiotherapy remains limited and varied [56].

In whole-gland HIFU for radiation-recurrent prostate cancer, a study by Rouvière *et al.* [57] of 46 patients reported 2- and 4-year progression-free survival rates of 42% and 31%, with PSA levels and MRI tumor extent as prognostic factors. A later study by Shah *et al.* [58] showed progression-free survival rates of 72%, 40%, and 31% at 1, 3, and 5 years, respectively, improving to 86%, 47%, and 37% when patients with high PSA nadirs (>0.5 ng/mL) were excluded. Larger studies report 7-year OS rates between 72%–82% and cancer-specific survival between 82%–94%, highlighting the durability of S-HIFU outcomes in selected patients [59, 60].

In contrast to whole-gland approaches, focal HIFU for hemigland ablation offers a more targeted strategy. Baco *et al.* [61], in a study of 48 men with unilateral radiation-recurrent prostate cancer, found an OS of 83% at 12 months and 52% at 24 months, with Gleason scores serving as key prognostic indicators (82% survival for Gleason scores ≤7, compared to 34% for Gleason scores ≥8). Another series study reported composite failure in 61% of patients, with biochemical failure in 51.3%, indicating mixed outcomes that warrant further exploration [62].

Functionally, S-HIFU demonstrates improved urinary outcomes compared to salvage radical prostatectomy, with continence rates reported between 57–88% [59, 62]. However, sexual function outcomes are inconsistent [54]. One study by Jones *et al.* [63] reported that only 26% of patients retained erectile function following treatment. Despite higher rates of incontinence with whole-gland HIFU, focal therapies generally have fewer complications [58, 64], supporting the potential of a more targeted approach.

Overall, S-HIFU holds promise for oncologic control and urinary preservation in the salvage setting, though variability in sexual function outcomes and complication rates necessitate careful patient selection and counseling. More study of S-HIFU, including comparative trials, is needed to better define its role and optimize outcomes in radio-recurrent prostate cancer.

### 4.1.3 Irreversible electroporation

IRE is an emerging focal therapy that uses pulsatile electrical currents to create nanopores in cell membranes, inducing apoptosis through osmotic imbalance [42]. Typically performed under general anesthesia with endorectal ultrasound guidance, IRE ablates tissue within 5–20-mm zones, requiring a 5-mm margin from sensitive structures such as the urethra and rectum to avoid damage [65].

Early studies of IRE in the salvage setting show promise.

The Focal Irreversible Electroporation (FIRE) trial, a multicenter study of patients with radio-recurrent prostate cancer, reported favorable outcomes with a median follow-up of 29 months, with urinary continence in 93% of cases, local control in 78% of cases, and 73% free from local and systemic disease [66]. However, erectile function declined from 35% to 15%, and 16% of patients developed metastases within a median of 8 months, highlighting the need for ongoing monitoring [66].

Further evidence from a single-center study of 74 patients with radio-recurrent disease found a 5-year progression-free survival of 60% and metastasis-free survival of 91% [67]. Urinary continence was preserved in 93% of patients at 12 months, though only 23% retained erectile function. While complications were generally manageable, cases of rectal fistula and urethral sloughing were noted [67].

Overall, IRE offers promising oncologic control with manageable side effects, particularly in preserving urinary continence. Nonetheless, the decline in erectile function and potential for metastatic progression underscore the importance of patient selection and close follow-up in this novel therapy. Collectively, outcomes from cryotherapy, HIFU, and IRE are summarized in Table 2 (Ref. [47, 58, 59, 61, 66, 67]), which highlights the oncologic results across major salvage studies.

#### 4.1.4 Photodynamic therapy

PDT employs light-sensitive drugs, delivered via intraprostatic catheters, to induce targeted cell death. Upon light activation, these agents release free radicals that lead to thrombosis, coagulative necrosis, and an immune response in the treated tissue. Commonly used photosensitizers include temoporfin, 5-aminolevulinic acid (5-ALA), motexafin lutetium, padeliporfin, and padoporfin [42, 68].

Research on PDT in the salvage setting for recurrent prostate cancer remains limited. The ongoing SpectraCure P18 study, conducted at Memorial Sloan Kettering in the United States, as well as other sites in the United Kingdom and Canada, aims to address this gap by evaluating interstitial PDT with verteporfin [69]. In this trial, optical fibers are transperineally inserted into the prostate under general anesthesia, and verteporfin is administered intravenously before light delivery [69]. A dose-titration model is being used to establish safe and effective thresholds while monitoring adverse effects. This study represents a critical step in assessing PDT's feasibility, safety, and efficacy as a salvage treatment option for recurrent prostate cancer.

### 4.2 Postablation follow-up

Effective monitoring following salvage ablative therapy for prostate cancer is essential to detect recurrence early. Guideline recommendations for post-focal therapy (FT) surveillance remain limited. The AUA advises follow-up with PSA, DRE, MRI, and biopsy tailored to the individual, but does not specify timing, while the EAU offers no formal protocol [70, 71]. In practice, many experts recommend a structured approach that includes targeted and systematic biopsy at 6–12 months post-treatment, accompanied by a screening mpMRI. PSA should be monitored closely, with a rise of $\geq$1.0 ng/mL over nadir at 12 months or $\geq$1.5 ng/mL at 24–36 months prompting further evaluation for recurrence [72, 73]. Imaging is recommended at 6–12 months following ablation, with some experts advocating for annual MRI for the first 5 years [74]. Advanced modalities like PSMA PET and MRI enhance the detection of recurrent lesions, facilitating timely intervention [75]. A robust follow-up strategy integrating regular imaging and biopsy is crucial for comprehensive management and improved outcomes in salvage therapy patients.

### 4.3 Limitations and implications

Our review builds on prior systematic reviews, such as Khoo *et al.* [10], by incorporating more recent studies that utilize advanced imaging modalities like PSMA PET and multiparametric MRI. In addition, we highlight emerging focal techniques such as IRE and vascular-targeted PDT that have gained traction in recent years but were underrepresented in earlier literature. Focal therapies aim to minimize treatment-related toxicity by selectively targeting the dominant intraprostatic lesion. This is in contrast to whole-gland salvage approaches, which may provide broader oncologic coverage but are often associated with increased urinary and sexual side

**TABLE 2. Key studies of focal ablative therapies in radio-recurrent prostate cancer.**

| Study/First Author | Modality | No. of Patients | PFS/DFS | OS/MFS |
|---|---|---|---|---|
| Siddiqui *et al.* [47] (2016) | Cryotherapy | 157 | 35% BCR-free at 10 yr | 76% OS at 10 yr, 86% MFS |
| Shah *et al.* [58] (2016) | Whole-gland HIFU | 50 | 72% (1 yr), 40% (3 yr), 31% (5 yr) | Not reported |
| Baco *et al.* [61] (2014) | Focal HIFU | 48 | 52% (24 mon, Gleason $\leq$7) | 83% (12 mon) |
| Crouzet *et al.* [59] (2017) | S-HIFU | 418 | Not specified | 82% OS (7 yr), 94% CSS |
| Blazevski *et al.* [66] (2023) | IRE (FIRE Trial) | 40 | 78% local control (median 29 mon) | 73% DFS |
| Geboers *et al.* [67] (2023) | IRE | 74 | 60% PFS (5 yr) | 91% MFS |

*BCR: Biochemical Recurrence; CSS: Cancer-Specific Survival; DFS: Disease-Free Survival; FIRE: Focal Irreversible Electroporation; HIFU: High-Intensity Focused Ultrasound; IRE: Irreversible Electroporation; MFS: Metastasis-Free Survival; OS: Overall Survival; PFS: Progression-Free Survival.*

effects. However, focal strategies carry the inherent limitation of potentially missing occult contralateral or multifocal disease. Compared to whole-gland salvage approaches, focal ablation strategies generally offer lower morbidity. Whole-gland cryotherapy and HIFU are associated with higher rates of incontinence, erectile dysfunction, and urethral complications. By contrast, focal cryotherapy and focal HIFU demonstrate higher continence rates (>95%) and better preservation of erectile function in selected patients (40–60%), while registry data suggest lower rates of severe complications such as rectourethral fistula. However, the trade-off is a greater risk of missing contralateral or multifocal disease, which can compromise long-term control [49–55, 58, 62, 64].

Several important limitations must be acknowledged. Biopsy of suspected local recurrence can yield false-negative results due to sampling errors and post-radiation tissue distortion, which complicates treatment planning. Second, the non-systematic approach and absence of PRISMA guidelines or risk-of-bias assessment weaken the reproducibility of the findings in this review. Furthermore, the majority of studies reviewed are retrospective, single arm or observational in nature, with substantial heterogeneity in patient selection, focal therapy technique, outcome definitions, and follow-up protocols. These limitations hinder direct comparison across studies and reduce the generalizability of findings. Furthermore, the optimal timing of salvage intervention following BCR is unclear, particularly when imaging modalities such as PSMA PET or mpMRI detect suspicious lesions without confirmatory biopsy [40]. The clinical significance of these radiographic findings in the absence of histologic evidence is uncertain and complicates decision-making. Moreover, the lack of randomized controlled trials limits confidence in comparative efficacy across modalities, and concerns persist about overtreatment, particularly in patients with indolent disease or competing comorbidities. Future prospective studies are needed to better define patient selection criteria, treatment sequencing, and long-term oncologic and functional outcomes.

Finally, ongoing prospective trials and multi-institutional registries are expected to provide additional data on long-term oncologic outcomes, functional preservation, and optimal patient selection criteria. Furthermore, while early data on focal therapy outcomes are promising, further research is needed to evaluate the cost-effectiveness, technical feasibility, and patient selection criteria across different healthcare settings. These studies will be essential in shaping future guidelines and refining clinical decision-making for men with radio-recurrent prostate cancer.

## 5. Conclusions

Focal ablative therapies offer a promising approach to managing radio-recurrent prostate cancer, with preliminary evidence suggesting a favorable balance between cancer control and preservation of quality of life. From a clinical perspective, these modalities represent a meaningful option for carefully selected men who wish to avoid the morbidity of salvage prostatectomy or repeat whole-gland radiation. Importantly, focal therapy provides improved rates of continence and sexual function preservation compared to whole-gland salvage, but this benefit comes at the cost of a higher risk of missing occult multifocal or contralateral disease. Whole-gland salvage, by contrast, offers broader oncologic coverage but with significantly greater urinary and sexual side effects. Clinicians must therefore weigh these trade-offs in patient counseling, tailoring treatment to patient priorities regarding functional outcomes versus oncologic certainty. Success with either approach relies on precise localization of recurrent lesions through advanced imaging modalities, such as PSMA PET/CT and mpMRI, as well as confirmation by targeted biopsy. Optimized follow-up incorporating PSA monitoring, periodic biopsy, and advanced imaging—is crucial to detect recurrence early and guide subsequent interventions. Continued research and clinical trials will be essential to refine these techniques, validate long-term outcomes, and establish guidelines to aid in patient selection, maximizing both efficacy and quality of life.

## ABBREVIATIONS

5-ALA, 5-aminolevulinic acid; $^{18}$F-FDG, Fluorine 18-labeled fluorodeoxyglucose; ASTRO, American Society for Therapeutic Radiology and Oncology; AUA, American Urological Association; BCR, biochemical recurrence; COLD, Cryo On-Line Data Registry; CSS, cancer-specific survival; CT, computed tomography; DFS, disease-free survival; EAU, European Association of Urology; FIRE, focal irreversible electroporation; FT, focal therapy; HIFU, high-intensity focused ultrasound; IRE, irreversible electroporation; MFS, metastasis-free survival; mpMRI, multiparametric magnetic resonance imaging; NCCN, National Comprehensive Cancer Network; OS, overall survival; PDT, photodynamic therapy; PET, positron emission tomography; PFS, progression-free survival; PROMIS, Prostate MR Imaging Study; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; RT, radiation therapy; S-HIFU, salvage high-intensity focused ultrasound.

## AVAILABILITY OF DATA AND MATERIALS

All data supporting the findings of this review are derived from the existing literature and are available within the referenced articles cited in the manuscript.

## AUTHOR CONTRIBUTIONS

JW, JSF—contributed to data collection, writing–original draft; writing–review and editing and approval of the final manuscript. JCH—contributed to review, editing and approval of the final manuscript.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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