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UROLOGY - REVIEW

Salvage treatment for radio-recurrent prostate cancer: a review of literature with focus on recent advancements in image-guided focal salvage therapies

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Abstract
Biochemical recurrence of prostate cancer occurs in 25–33% of patients who undergo radiation therapy (RT). Unfortunately, greater than 90% of patients with radiation recurrence undergo androgen deprivation therapy (ADT), despite the detrimental side effect profile and the lack of supporting evidence for ADT use in local recurrence. In patients who experience recurrence after treatment with RT, options for treatment include salvage radical prostatectomy (SRP), salvage cryotherapy (SCT), salvage brachytherapy (SBT), and high-intensity focused ultrasound (HIFU). These salvage treatments provide recurrence-free survival in almost half of the patients with an acceptable safety profile. However, it is important to note that approximately 20–40% of radio-recurrent prostate cancers are isolated and local. Recent studies have shown salvage focal treatments to have encouraging outcomes with significantly less side effects. This article summarizes the outcomes of currently used salvage treatment options for radio-recurrent prostate cancer and focuses on recent advancements in image-guided focal salvage therapies.

Keywords Prostate cancer · Focal salvage therapy · Salvage prostate cancer therapy

Introduction

Prostate cancer is the second most common malignancy in men and is the second leading cause of cancer death in the United States with an estimated 29,430 deaths in 2018. Most common treatment options for clinically localized prostate cancer include radical prostatectomy (RP) and traditional radiation therapies (external beam and brachytherapy), but a significant portion of patients experience recurrence and most relapses occur within 5 years [1]. Biochemical failure after radiation therapy was initially defined by the American Society for Therapeutic Radiology and Oncology (ASTRO) and then later revised at a Consensus Conference with the Radiation Therapy Oncology Group of Phoenix, Arizona in 2005. The current ASTRO-Phoenix criteria define biochemical failure after external beam radiotherapy (EBRT) as a PSA rise equal to or greater than 2 ng/mL above the nadir PSA regardless of whether or not the patient received hormonal therapy. The date of failure is set as the date the initial PSA rise was noted, with no backdating as the previous guidelines had recommended [2].

Biochemical recurrence (BCR) after RP is around 33% while BCR after radiation therapy (RT) is between 25 and 33% [3]. Grossfield et al. show secondary cancer treatment was required in 23% of patients who underwent RP and in 34% of patients who underwent RT [4]. A distant metastases rate of 47% and a local recurrence rate of 26% was observed 5 years after biochemical recurrence; these rates are coupled with a 5-year overall survival (OS) rate of 65% and a cause-specific survival rate of 76%. Salvage therapy is a vital tool given that at least 75% of men will have clinically significant disease 5 years after an elevation in PSA is noted [5].

Agarwal et al. found that 93.5% of patients with radiorecurrent prostate cancer in their study had been treated with ADT; ADT was the most common salvage therapy used in

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both, RP and RT failure populations [6], but ADT is rarely curative and there is a well-known association of ADT with diabetes, coronary heart disease, myocardial infarction, and sudden cardiac death. In patients with comorbidities, ADT is associated with increased mortality and should be used cautiously [7]. The use of salvage ADT was associated with higher 7-year cancer-specific survival when compared to observation only in patients with a PSA doubling time of < 6 months as 41% of patients with a PSA doubling time of < 6 months had distant metastasis [8]. In fact, ADT therapy is most beneficial in settings of subclinical metastasis outside of the radiation field rather than as a tool to control local disease in the setting of failed RT [9].

Use of ADT in salvage settings is most warranted in men with high-risk disease features such as pT3b/4 and grade group ≥ 4 or those with features of pT3b/4 and early salvage RT PSA ≥ 0.4 ng/ml [9, 10]. However, the majority of radiorecurrent prostate cancers are localized to the prostate [11, 12], making patients potential candidates to local and curative treatment options. Traditionally, only salvage radical prostatectomy (SRP) was offered to these patients. With concerns of significant morbidity, this treatment strategy was not widely adopted for treatment of radiorecurrent disease. Salvage cryotherapy (SCT) and salvage brachytherapy (SBT) are also offered in select patients with recurrence after radiation. More recently, high-intensity focused ultrasound (HIFU) has been under investigation as an alternative. HIFU technology has advanced greatly in the recent years, with substantial improvement in treatment outcomes.

Nevertheless, there is limited data available on the safety and efficacy of these modalities as first-line salvage treatments. In this paper, we discuss the evidence for these modalities in the salvage setting as well as the contribution of MRI to diagnosis and treatment of radiorecurrent prostate cancers.

Current salvage therapy modalities

Salvage radical prostatectomy

Mador et al. first reported salvage prostatectomy after RT in 1985 [13]. In a retrospective, international, multi-institutional analysis, Chade et al. reported the 5-year probability of being free from BCR, being free from metastases, and cancer-specific death to be 48%, 83%, and 92% [14]. However, operating in previously irradiated areas is challenging due to radiation field effects to tissue beyond the prostate leading to poor wound healing. In some cases, patients who received previous brachytherapy may have seeds placed beyond the capsule, obstructing the surgical field. These effects lead to moderate complication rates associated with SRP.

Complication rates reported after SRP ranges from 19 to 79% for urinary incontinence, 0 to 50% for anastomotic stenosis, and 0 to 19% for rectal injury. Minimally invasive SRP has Clavien > 2 complication rates of 0–33% and incontinence rates of 20–100% as reported by Matei et al. in a systematic review of 27 studies [15].

Patients should be carefully selected for surgical salvage therapy and several factors such as age, comorbid conditions, life expectancy, pre-salvage prognostic parameters such as Gleason score, clinical and pathological stage and complication rates compared to other salvage therapies should also be taken into consideration.

Salvage cryotherapy

Cryotherapy is a treatment modality that uses freezing temperatures to kill cancer cells. It results in cell membrane rupture and vascular compromise due to microthromobosis [16]. In 1995, Bales et al. first published a prospective phase 2 trial report of salvage cryotherapy after RT. Biochemical disease-free survival was defined as a PSA value < 0.3 ng/ml. 82% patients had PSA decline at 3 months and 86% patients have a PSA ≥ 0.3 ng/ml at 1 year after cryotherapy [17]. Gevorgyan et al. [18] reported 5 year BDFS > 75% for patients with Gleason score ≤ 7 or with low and intermediate risk. High risk or patients with Gleason score > 7 had 5-year BDFS of < 36%. Out of 97 patients, only one experienced a recto-urethral fistula, 66 patients experienced erectile dysfunction and 13 experienced incontinence—3 of whom required artificial urinary sphincter. Salvage cryotherapy may be an alternative option available for older patients or patients with significant comorbidities with BCR after RT as it is better tolerated than SRP while for young and healthy patients, SRP can be considered as it may offer better chance of cure [19, 20].

Salvage brachytherapy

SBT has been less commonly used for treatment of radiorecurrent disease. SBT has been shown to have a 5-year OS of 70% and cancer-specific survival of 97% and complication rates of 21–24% for genitourinary, 3.4% for fistula formation, 17% for bladder neck strictures, and 6% for incontinence. However, use of further brachytherapy especially in the salvage setting after primary RT failure is limited by the total radiation dose and toxicity [21, 22].

High-intensity-focused ultrasound

HIFU remains relatively new as a modality for cancer treatment but is gaining potential especially in the management of prostate cancer. HIFU uses high-energy ultrasound waves to destroy tissue at the focal point of a transducer without

damaging the surrounding tissues. HIFU remains unique in that it can be used in retreatment and can spare neighboring tissue while providing localized therapy. This becomes incrementally important when considering patients who have contraindications to systemic therapy, are poor surgical candidates, or have serious comorbidities.

Uchida et al., evaluated the use of HIFU in primary treatment of prostate cancer and found the overall 10-year survival and cancer specific survival rates to be 89.6% and 97.4% respectively [23]. The same study reported complications of urethral strictures (19.7%), urinary incontinence (2.3%), rectourethral fistula (0.1%), and erectile dysfunction (34.9%) after 24 months.

In a multi-institutional analysis of 418 patients with radiorecurrence treated with HIFU, Crouzet et al. demonstrated a 7-year overall survival rate of 72%, cancer-specific survival of 82%, and metastasis-free survival of 81% [24]. Their work shows that HIFU has similar survival rates to salvage surgery in radiorecurrent patients, but with a much lower rate of severe complications. They also demonstrated that patients with PSA ≤ 4 had 67% 5-year BDFS while those with PSA ≥ 10 ng/mL had only 22% 5-year BDFS. Frequent complications include incontinence (19%), bladder outlet obstruction/stenosis (15%), and rectourethral fistulas (0.6%). This study highlighted the importance of offering HIFU treatment earlier rather than later in the course of disease. In another study, Dason et al. performed HIFU salvage therapy in 24 patients with radiorecurrence. They discovered a median 2 and 5-year BDFS of 66.3% and 51.6%, respectively. Only one patient required intervention for urethral stricture. In salvage setting, HIFU shows promising results with lower complication rate especially for suboptimal surgical candidates for salvage RP.

The role of imaging in radiorecurrent prostate cancer

Multiparametric prostate MRI (mpMRI) is increasingly used before prostate biopsies in patients with suspicion of prostate cancer. mpMRI increases the diagnostic yield of prostate biopsies and accurately localizes prostate cancer resulting in better risk stratification of patients with prostate cancer [25, 26]. In patients with biochemical recurrence after RT, mpMRI was found to be superior in detecting local recurrence while 11c-choline PET is superior in detecting distant metastases [27]. mpMRI-guided biopsies have been shown to be effective for both native and recurrent prostate cancers [28]. Over the years, it has become the most reliable imaging biomarker after both, RT or RP [29].

Alongside having a negative predictive value of 95%, mpMRI can localize suspicious lesions to improve biopsy accuracy. As demonstrated in Fig. 1, this enhanced visualization combined with MRI's higher tissue contrast resolution and overall image resolution allows for better detection and localization of lesions, paving the way for partial gland therapies for prostate cancer [30].

Improvements in the imaging modalities for metastatic prostate cancer have aided urologists in identification of appropriate salvage candidates by ruling out metastatic disease with increased certainty. Newer PET scans have been reported to have higher diagnostic accuracy than

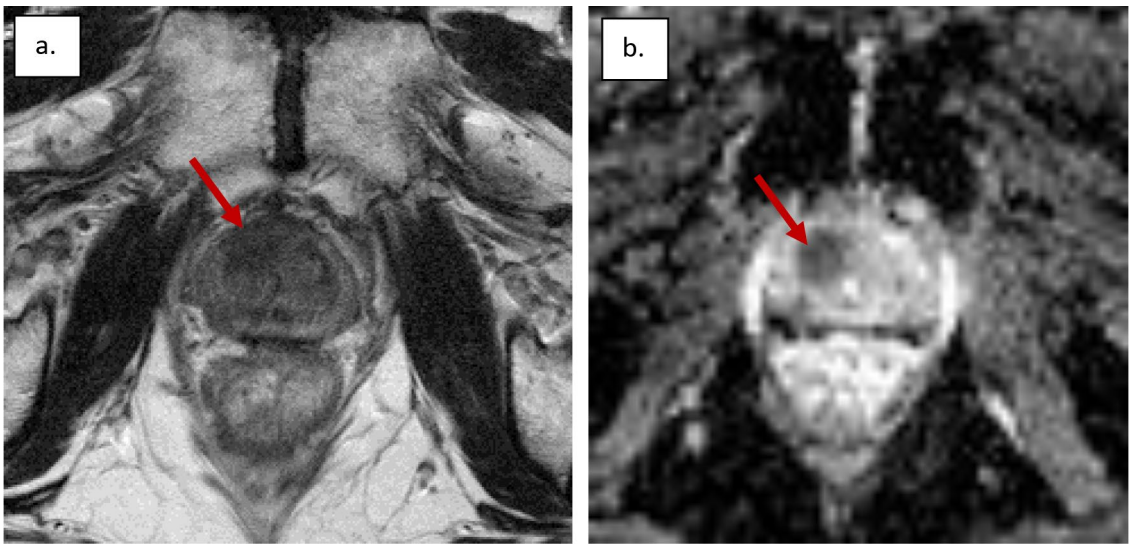

Fig. 1 76-year-old man with rising PSA after external beam radiation therapy for prostate cancer. Prostate MpMRI demonstrating **a** T2-weighted imaging with hypointense area in right anterolateral prostate. **b** Diffusion-weighted imaging demonstrating restricted diffusion in same location. Patient underwent biopsy and was shown to have Gleason 8 (4 + 4) prostate adenocarcinoma

conventional imaging comprised of CT and bone scan. The introduction of prostate-specific membrane antigen positron emission tomography (PSMA PET) has demonstrated promise in detection of low-PSA disease recurrence. This modality has the potential to allow for better staging of disease and even assess response to treatment [31]. With regards to biochemical recurrence, this modality is able to detect disease at low PSA levels, potentially before metastasis [31]. PSMA imaging has also been shown to identify more previously undetected and atypical lesions when compared to conventional imaging modalities, including 11c-choline PET [32].

MRI in partial gland salvage therapy

Focal therapy or partial gland therapy is the targeted destruction of cancerous tissue within an organ while preserving the benign tissue. Success of focal therapy hinges on the ability to detect cancer early and to accurately localize the lesion prior to treatment. Traditionally, imaging of the prostate and detection of cancerous tissue has been done through transrectal ultrasound. Positive systematic core biopsies confirm the presence of cancer but fail to localize the specific lesion and intervention is usually delivered to the entire gland. The same is true for patients with radio recurrence; these patients face increased morbidity due to the second whole-gland treatment.

The introduction of mpMRI has led to better visualization of the prostate and the lesions within, especially lesions commonly missed by systematic biopsy such as midline, subcapsular and anterior lesions [33]. Using MRI-guidance, the need to ablate the whole prostate can be avoided thus decreasing adjacent tissue toxicity as well as overall morbidity. Orczyk et al. demonstrated that the use of mpMRI preoperatively and postoperatively allowed for better visualization of the prostate and increased efficacy of focal therapy. Additionally, preoperative and postoperative imaging allowed better understanding of prostate anatomy after therapy in the event a future biopsy is needed [34]. While this is useful in all settings, it is especially beneficial to patients in the salvage setting given prior radiation and increased risk for toxicity. Accurately delivered focal therapy minimizes overall toxicity and complications; additionally, it affords the potential for retreatment without major complications. Recent data also shows nonsurgical salvage therapies have similar outcomes to salvage RP with no significant different in toxicity outcomes [35].

Focal cryotherapy

De Castro Abreu et al. [36] compared salvage total cryoablation (STC) to salvage focal cryoablation (SFC) in 50 patients with radiorecurrence. Their findings indicated a 20% higher biochemical failure (32% SFT vs 12% STC) in the focal therapy group. Although the study is limited by small patient numbers, they reported no new-onset recto-urethral fistula formation or incontinence due to focal therapy. Two of seven patients retained postoperative potency after SFC while none of the four patients recovered postoperative potency in STC group. Li et al. conducted a study of 91 patients undergoing focal salvage cryotherapy and found BDFS at 1, 3, and 5 years to be 95.3%, 72.4% and 46.5%, respectively [37]. Although potency was 50%, they reported similar urinary retention and fistula rates compared to whole-gland therapy studies. Focal cryotherapy in the salvage setting has limited evidence but shows improved potency and lower complication rates and morbidity when compared to whole-gland therapy.

Bomers et al. [38] performed a prospective study of ten patients undergoing MR-guided focal cryoablation for radiorecurrence. All ten patients achieved successful treatment including two patients who were retreated at 6 months and one retreated at 12 months for local recurrence. Further evaluation determined that these patients were undertreated; repeat cryoablation resolved their recurrence. Through MR-guided focal ablation, fewer needles were used, hospitalization was shorter, and complication rates were lower than studies reporting on whole-gland ablation or TRUS-guided ablation. In conclusion, STC and SFC are safe and feasible, for selected patients, SFC is a better option to minimize treatment-related comorbidities. However, studies with longer follow-ups are needed.

Focal brachytherapy

Maenhout et al. used MRI to deliver focal SBT to 17 patients. Through MRI guidance, they delivered 19-Gy single-fraction dose to a focal region rather than standard delivery to the whole-gland; this was better tolerated in regards to acute toxicity when compared to whole-gland salvage modalities [39]. At 1-year, they reported a 92% BDFS. MRI use in focal SBT allows better localization of the lesion and hence more direct aggressive treatment with lower overall radiation and lower costs and morbidity. In another study, [40] focal partial salvage permanent prostate implantation was delivered to patients with previously treated with primary permanent prostate implantation through the assistance of MRI. They reported no operative interventions, fistulas or grade ≥ 3 GI/GU toxicities; 33% had grade 2 GU toxicities. Interestingly, 2 patients had treatment failure and underwent second partial salvage permanent prostate implantation with success, achieving PSA of 0.6 and 0.7 ng/mL at 12 and 26 months. They reported 1-year, 2-year, and 3-year BDFS rates of 86.7%, 78.4%, and 62.7%, respectively. Focal SBT has been demonstrated to have excellent side effect profile with encouraging short-term oncological outcomes, but this needs further investigation.

Focal HIFU

HIFU is increasingly being used for focal or partial gland therapy in primary prostate cancer treatment, its use has also been explored in salvage settings.

Kanthabalan et al. [41] conducted a retrospective analysis of 150 men with radiorecurrent prostate cancer who underwent focal salvage HIFU. Disease localization was achieved through mpMRI and confirmed with biopsy; based on biopsy results, patients received either index lesion ablation, focal ablation, or hemiablation. A total of 91 (61%) of patients experienced composite failure, defined as local recurrence (6.7%), prostate cancer specific death (2.7%), evidence of metastases (9.5%), the need for systemic therapy (40.7%) or and/or BCR (51%). Most complications were minor, bladder neck strictures and rectourethral fistulas were reported in 8% and 2%, of patients respectively. Continence was preserved in 87.5% of patients at 2 years. It is worth mentioning that patients in this study were overall higher-risk than patients in similar studies. Like other studies, low-risk patients in this study were shown to benefit greatly from focal therapy, but this study demonstrated that even intermediate and high-risk patients had significant benefits.

Ahmed et al. also reported the outcomes of 39 patients receiving focal salvage HIFU for radiorecurrent prostate cancer at their center [42]. Patients who achieved a PSA nadir had 1-year, 2-year, and 3-year BDFS of 86%, 76%, and 42% respectively, while patients with a positive biopsy who also received ADT and achieved PSA nadir had BDFS rates of 55%, 24%, and 0% respectively. They reported a Clavien 3 or higher complication in 26%, of patients. Rectal fistula rate was reported 3.6%. The data from Focal HIFU studies are encouraging and its possible that this approach may be able to deliver comparable oncological outcomes to traditional modalities with much lower complication rates; however, further research is warranted with larger and prospective studies.

Conclusions

Patients with radio recurrence of prostate cancer are associated with unfavorable prognosis. Although ADT is an appropriate therapy in sub-clinical metastasis and used for systemic control of the disease, it is rarely curative for local disease and is associated with increased mortality in patients with comorbidities. Unfortunately, 93.5% of radiorecurrences continue to be treated with ADT regardless of stage while only 2–3% receive salvage therapy.

Radiorecurrences can be treated with SRP, SCT, SBT, or HIFU. While robotic SRP has lowered surgical morbidity, functional outcomes are still less than desirable. Any surgical approach must be exercised with caution given the previously irradiated field and risks of morbidity and complications. SBT remains limited by radiation toxicity. SCT is associated with less complications. HIFU has demonstrated strong 10-year survival rates in the primary treatment of prostate cancer and in the salvage setting. Recent studies showed that whole-gland nonsurgical modalities have similar oncological outcomes when compared to SRP.

However, recent advancements in mpMRI have led to better diagnosis and localization of clinically significant cancer in radiorecurrent disease. Prostate imaging by mpMRI have allowed enhanced delivery of intervention to specific lesions with significantly lower complication rates. Focal or partial gland therapies using image guidance has been associated with shorter hospital stays and lower overall cost of treatment. However, the long-term oncological outcomes of such approach is unknown. Further research with larger sample sizes and longer follow-ups for focal salvage therapies are needed before this approach can be widely adopted in clinical practice.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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