Salvage Therapy Options for Local Prostate Cancer Recurrence After Primary Radiotherapy: a Literature Review

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Abstract
Purpose of Review While recurrence after primary treatment of prostate cancer (PCa) is not uncommon, there is currently no consensus on the most appropriate management after radiation treatment failure. This article seeks to explore the currently utilized modalities for salvage treatment for radiorecurrent PCa. We focused our review on the oncologic outcomes and reported toxicity rates in the latest studies examining salvage radical prostatectomy (SRP), salvage cryotherapy (SCT), salvage high-intensity focused ultrasound (HIFU) and re-irradiation.

Recent Findings There does not appear to be any significant difference in overall survival for more invasive salvage radical prostatectomy compared to the minimally invasive salvage approaches. Additionally, there seems to be a trend towards lower morbidity rates associated with minimally invasive and focal salvage treatment.

Summary We are encouraged by the results presented in this review and find that there is clearly a role for emerging minimally invasive and focal therapies as durable options for salvage treatment in patients with radiorecurrent PCa.

Keywords Radiation recurrent prostate cancer · Salvage radical prostatectomy · Salvage cryotherapy · Salvage high-intensity focused ultrasound · Salvage radiation therapy

Introduction
Prostate cancer (PCa) is the most commonly diagnosed cancer in men, with an estimated 161,360 new cases in the USA in 2017 [1]. Radical prostatectomy (RP) and radiotherapy (RT) with or without androgen deprivation therapy (ADT) are the most frequently utilized primary managements for localized PCa. In fact, one third of all newly diagnosed patients select RT, external beam radiation therapy (EBRT), or brachytherapy (BT), as their primary treatment option [2, 3]. However, even with improved radiation technology and higher radiation dose regimens, biochemical relapse occurs in 30–60% of patients treated with RT [4, 5].

Currently, there exists no consensus on the most appropriate management after RT failure. While there is a diverse array of salvage treatment options, only an estimated 2–3% of patients who present with recurrence after RT receive local salvage therapy, with the remaining 97–98% managed with observation or palliative treatment with ADT alone [6, 7]. However, ADT is not a benign treatment as patients often experience significant side effects such as sexual dysfunction, bone density loss, fatigue, anemia, hot flashes, and increased cardiovascular morbidity. Many of these patients, especially those who present with strictly local or organ-confined recurrence of disease are suitable for potentially curative salvage therapies.

In this review, we analyze the most commonly employed definitions of biochemical failure after RT, explore the potential causes of local recurrence post-irradiation, discuss the methods for evaluation after biochemical relapse, and evaluate...
the most recent information regarding current modalities used for salvage therapy.

Definition of Failure of RT

Historically, failure of PCa treatment was determined primarily by local progression observed on digital rectal exam (DRE), biopsy confirmation, or on discovery of distant metastases. However, in 1997, after a conference in San Antonio, Texas, the American Society of Therapeutic Radiology and Oncology (ASTRO) released the first consensus statement outlining guidelines for using prostate-specific antigen (PSA) to define biochemical failure after EBRT. Under these criteria, a serum PSA level should be obtained every 3–4 months for 2 years post-completion of RT, and in 6-month intervals thereafter. The ASTRO concluded that if three consecutive rises in PSA above the nadir are observed, there is sufficient evidence to declare biochemical failure [8]. While these recommendations provided valuable direction for investigators examining the efficacy of RT, it was not without shortcoming.

Firstly, using the ASTRO criteria, determination of the time of failure required backdating to the midpoint between the nadir PSA post-irradiation and the first observed rise in PSA. Additionally, the recommendations were created for EBRT monotherapy but began to be applied broadly to define failure of EBRT with ADT, BT, and even non-radiation therapies such as RP and cryotherapy (CT) [9–11]. Moreover, with no precise cutoff for PSA elevation and variable time of follow-up, the criteria posed limitation for effectively estimating event-free survival and had no correlation with clinical outcome [12]. Lastly, due to the phenomenon of benign PSA spike post-RT [13], the ASTRO guidelines lacked specificity for recurrence.

To address these limitations, the ASTRO and the Radiation Therapy Oncology Group (RTOG) met in Phoenix, Arizona, in 2006 to revise the definition of biochemical recurrence using updated data. This “Phoenix definition” established biochemical failure for EBRT ± ADT as a PSA elevation of ≥2 ng/mL above the nadir PSA post-therapy (PSAn) [14]. With this definition, biochemical failure could be determined without the need for backdating. However, as the Phoenix definition was designed for primary treatment with EBRT ± ADT, different criteria defining failure after other therapy regimens have emerged.

For example, the Stuttgart definition, named for the location of its conception in Stuttgart, Germany, in 2008, delineates the standard for biochemical failure after treatment of high-intensity focused ultrasound (HIFU) as a PSA determination 1.2 ng/mL above the nadir [15]. Additionally, a single PSA value of ≥0.2 ng/mL with subsequently confirmed rise has been applied as the definition for biochemical recurrence after RP due to strong predictive value of disease progression [16]. Nevertheless, because it is a strong predictor of systemic progression and PCa specific mortality, the Phoenix definition is currently the most widely utilized standard for biochemical failure.

Factors that Predict BF After RT

The significant heterogeneity in the clinical behavior of PCa makes it difficult to anticipate patient response to treatment and to prescribe perfectly appropriate primary or salvage therapy regimens. However, investigators are in constant search for the best predictors for failed treatment. In 1997, Zagars et al. performed a multivariate regression analysis of 938 men treated with EBRT and stratified recurrence risk into six categories using three disease characteristics: tumor, node, metastasis (TNM) stage, Gleason score, and pretreatment serum PSA levels [17]. Indeed, these three factors are still held as strong predictors for biochemical failure. In 2010, the National Comprehensive Cancer Network established treatment recommendations for local recurrence risk categories (“Very Low”–“Very High”) that utilized the same elements [18]. Therefore, errors in staging, particularly downstaging cancer that is more advanced, which occurs in over one third of cases of PCa [19], can have significant impact on the rates of therapy failure.

With respect to post-treatment factors, PSAn and biopsy are also prognostic indicators of biochemical progression. A PSAn ≤0.5 ng/mL has been demonstrated to carry the lowest risk of BF [20]. Similarly, post-RT biopsy has been shown to be an independent predictor of biochemical outcome, as a higher percentage of positive core biopsies portends eventual BF [21–23]. Additionally, PSA kinetics, specifically a PSA doubling time (PSA-DT) less than 3 months, can predict the risk of metastatic versus local failure [24].

RT failure is similarly dependent on dose scheduling of radiation provided over the treatment course. Dose-escalated regimens are associated with better biochemical disease-free survival rates (BDFS), as recent studies demonstrate greatest outcome benefit from total radiation doses >80Gy [25–27]. Recent advances in conformal radiation techniques, such as intensity-modulated RT (IMRT) and stereotactic body RT (SBRT), have also permitted for hypofractionation of therapy regimens; conventional therapy divides the total radiation dose into 1.8–2 Gy fractions over 7–9 weeks, whereas hypofractionated therapy allows for the delivery of 2.5–10 Gy fractions over 2–5 weeks. However, while hypofractionation techniques have permitted higher dose radiation delivery over shorter treatment schedules, it has not been shown to improve rates of BF [28, 29] and benefits must be balanced with increased rates of unacceptable
Using this information, researchers have developed novel nomograms predicting biochemical recurrence and distant metastases based on data from patients treated with diverse types and doses of radiation, therefore giving clinicians the ability to form more specific and evidence-based treatment regimens for patients. Similar to risk stratification categories, these nomograms utilize pretreatment PSA, Gleason score, and TNM stage as well as factors such as age, PSA-DT, percentage of positive core biopsies, lymph node invasion, radiation doses, and the use of ADT [30–32].

Recent studies have also explored the utility of biomarkers as a prognostic indicator of treatment response. While the advent of serum PSA quantification allowed for considerably improved disease monitoring, the significant variability in PSA kinetics among patients introduces the need for more reliable markers [33]. Consequently, novel proteomics investigations surveying serum, urine, and tissue biopsy protein biomarkers associated with treatment failure have emerged. For example, altered expression of E-cadherin profiled on diagnostic prostate biopsy has been associated with early BF after EBRT [34]. Similarly, positive immunohistochemical staining for apoptosis regulators bcl-2 and p53 on pre-EBRT biopsy has been demonstrated as an independent variable predictive of radiation failure [35].

Additionally, the use of genomic biomarkers has led to the development of commercially available gene panels used to help predict PCa response to radiation. For example, the Prolaris test (Myriad Genetics, Salt Lake City, UT, USA), a panel consisting of 31 cell cycle progression genes and 15 housekeeping genes, has been demonstrated to significantly predict oncologic outcome in patients treated with EBRT [36]. Similar prognostic utility has been demonstrated using a 22-gene expression panel, the Decipher genetic test (GenomeDX Biosciences, Vancouver, BC, Canada), in patients receiving irradiation post-RP [37]. Lastly, the Oncotype DX Genomic Prostate Score (GPS; Genomic Health Inc., Redwood City, CA, USA) is a 17-gene assay also being investigated for its prognostic utility for PCa aggressiveness [38]. While 85 genes are included among these three panels, there is little overlap between the tests, and there are currently no studies comparing these panels in the same patient cohort. Further, while they provide prognostic information, these tests remain costly and although hundreds of tissue and serum biomarkers have been identified, no one marker has yet been determined as clinically superior to serum PSA [39].

**Imaging**

Evaluation of the distribution pattern of disease recurrence after established BF is essential to the appropriate prescription of treatment, as patients with distant metastases are suboptimal candidates for local salvage therapy. While cancer is confined to the prostate and seminal vesicles in over one third of RT relapses, almost 60% of disease recurrence presents in the bone, visceral organs, and pelvic and abdominal lymph nodes [40]. Therefore, it is critical for imaging modalities to be sensitive to distant disease even in the absence of symptomatic recurrence or significantly elevated PSA.

Transrectal ultrasound (TRUS) is an important tool for assessing local disease and guiding biopsy of the prostate. However, radiation-induced fibrosis after RT decreases the efficacy of disease identification using TRUS alone [41]. The addition of magnetic resonance imaging (MRI)-guided biopsies has been studied as an alternative to TRUS alone. The guided biopsy technique allows for improved delineation of recurrent tumor boundaries and the opportunity to create a more targeted approach when considering focal salvage treatment options [42].

Additionally, TRUS alone cannot be used to identify metastases. Currently, axial abdominopelvic computed tomography (CT) and technetium-99 radionuclide bone scan (BS) are used as the primary tools for the workup of distant disease, but these modalities do not have strong sensitivity in patients with PSA <10–20 ng/mL [43, 44]. Recently, imaging modalities such as MRI and positron emission tomography (PET) with CT have emerged as more reliable means of evaluating local and metastatic disease recurrence, even in the setting of low PSA levels. In particular, multiparametric MRI (mpMRI), including diffusion weighted MRI (DWI) and dynamic contrast-enhanced MRI (DCE-MRI), demonstrates excellent ability to differentiate fibrosis and superior detection of, and sensitivity for, local disease recurrence as compared to TRUS and can possibly circumvent the need for biopsy [45–47]. Additionally, whole-body DWI MRI has been explored as a potential tool for investigation of metastasis but has been shown to have lower sensitivity for bone metastases as compared to PET/CT [48].

The ProstaScint scan (Cytogen Corporation, Princeton, NJ), which uses Indium (111In) capromab pendetide as a radiolabeled monoclonal antibody to prostate-specific membrane antigen (PSMA), offers one potential means of identifying sites of metastasis. However, it has a relatively poor specificity at low volumes of prostate cancer due to the limitations of single photon emission computed tomography (SPECT) imaging [49].

Alternatively, studies have demonstrated strong recurrence site detection when using PET/CT with a choline tracer (11C-Choline PET/CT) [50]. Results of 11C-Choline PET/CT scans have shown to have significant impact on therapeutic strategy selection in patients with BF [51]. The use of fluoride tracers (18Fluoride and 18F-Choline-PET/MRI) has also been investigated and has shown to be optimum for the detection of skeletal metastasis [52, 53].
Salvage Radical Prostatectomy

Salvage RP (SRP) after failed RT is technically challenging due to fibrosis, loss of tissue planes and vascular damage leading to poor wound healing secondary to radiation. In addition, a study comparing primary RP to SRP found that patients receiving SRP had significantly higher median age, co-morbidity score, Gleason score, and clinical and pathological stage when compared to those receiving RP as a primary therapy [54]. These factors predispose to riskier surgical procedures with the potential for severe GU, GI, and erectile toxicities. Therefore, appropriate selection of surgical candidates is fundamental to improving survival outcomes and minimizing surgical complications.

In 2011, Chade et al. retrospectively analyzed 404 patients who received SRP for radiorecurrent PCa and found pre-salvage PSA and post-radiation prostate biopsy Gleason score to be the strongest presurgical prognostic factors predicting biochemical recurrence (BCR) and metastasis after SRP (with the most favorable outcomes in patients with PSA <4 ng/ml and Gleason score ≤7) [55]. Additional predictive parameters, such as percentage of positive biopsy cores, PSA-DT >12 months prior to SRP, and type of primary RT, have also been reported in smaller series [56, 57].

Table 1 shows the results of recent SRP series [54–66]: BCR after SRP ranged between 0 and 58%. This variance is likely explained by differing definitions of BF and the range in median follow-up (4.6 to 68 months). While these disparities limit comparative potential, data suggest that biochemical control declines over longer periods of follow-up as studies with follow-up >40 months had BCR ranging between 43 and 58% [55, 60, 63].

Recent studies have also explored the utility of pelvic lymph node dissection (PLND) in combination with SRP on long-term survival outcomes after salvage for failed RT. Using Cox proportional multivariate regression analysis and adjusting for variables for 364 patients undergoing SRP, Pokala et al. found that while there was no effect on overall survival (OS), PLND significantly improved cancer-specific survival (CSS), with a hazard ratio of 2.7 (p = .01) for those that did not receive PLND. However, increasing nodal yield (>10 vs 0–5 nodes) did not improve either OS or CSS, suggesting that while PLND may be beneficial for CSS, extended dissection may not be necessary [57].

Considering toxicity after RP, the risk of surgical complications such as urinary incontinence, rectal injury, bladder neck contracture (BNC), and erectile dysfunction (ED) are significantly greater in those undergoing SRP as opposed to RP as a primary treatment [54]. Of the studies listed in Table 1, rates of urinary incontinence range between 20 and 78%, BNC and rectal injury are less frequent, with BNC rates ranging between 0 and 42% and rectal injury rates between 0 and 9%, respectively. ED is the most common surgical complication.
complication, with some studies reporting up to 100% erectile toxicity. However, it is important to note that in many of these studies, few patients have retained potency without medical therapy after primary RT and most have residual sexual dysfunction prior to SRP.

While the recent use of minimally invasive techniques such as laparoscopic or robot-assisted prostatectomy has been presumed to improve complication rates due to better visualization, reduced blood loss, and shorter length of hospital stay after surgery, there are not many studies directly comparing open SRP to minimally invasive approaches. One recent study found significantly lower rates of BNC in patients who underwent minimally invasive SRP at one medical center [67]. These results are supported by another small study that showed a trend towards higher incidence of surgical complications among those who received open SRP [66]. While promising, larger multi-center studies with longer follow-up are needed to establish clinically applicable significance.

Several select centers still use SRP as a curative treatment option after radiation failure. Careful consideration should be taken into which patients are appropriate for surgical salvage therapy. Age, comorbid conditions, life expectancy, and the pre-salvage prognostic parameters outlined above should be evaluated and reported surgical complication rates should be compared to those of other salvage modalities (Tables 2, 3, and 4) prior to SRP.

**Salvage Cryotherapy**

In 2009, Pisters et al. released a study that compared the treatment outcomes of SRP and salvage cryotherapy (SCT) for radiorecurrent PCa. The study concluded that SCT resulted in significantly inferior biochemical disease-free survival (BDFS) and overall survival when compared to SRP [68]. However, cryotherapy technology has since advanced. First generation cryosurgical systems like those employed in the Pisters et al. study relied on probes cooled by liquid nitrogen, which created frozen sections that were difficult to control and monitor. In addition to the introduction of advanced guiding ultrasound probes, the development of current third generation cryoablation machines that are argon/helium-based and apply the Joule-Thompson principle, have permitted improved target freezing precision and have resulted in superior biochemical control with reduced toxicity [69]. In fact, studies exploring effects of physical parameters, such as prostate gland length and iceball size, on urinary toxicity suggest that future refinement of SCT technique can promote better long-term morbidity [70].

Table 2 summarizes the oncologic and toxicity outcomes of recent SCT series [69–80, 101, 102]. While no standard guideline has been adopted for which patients are most appropriate for SCT, in 2010, Spiess et al. introduced a pretreatment
A nomogram designed to select optimal candidates for SCT based on initial PSA, clinical stage, and biopsy Gleason score as predictors of oncologic progression [71]. Indeed, lower pretreatment PSA (PSA <5 ng/mL) has also been found to be associated with lower rates of recurrence [72, 80, 81], underscoring the importance of early RT failure identification and prompt SCT initiation. Many recent studies have also exposed the utility of post-SCT PSA nadir in predicting long-term oncologic outcome. Although PSAn <0.4 ng/mL has been suggested as the best objective indicator of biochemical control after SCT [82], other studies have found that a less stringent PSAn <1 ng/mL is similarly prognostic [70, 80].

Many of the studies presented in Table 2 excluded patients with prior ADT treatment. Nevertheless, pre-SCT hormone therapy exposure can have a significant effect on oncologic outcome for post-radiation SCT, as patients who were ADT naïve were found to have a superior 5-year biochemical progression-free survival when compared to those who had been receiving ADT [79]. Interestingly, this study also found that patients who received pre-SCT ADT were less likely to suffer urinary retention and incontinence but more likely to have ED.

Lastly, studies investigating outcomes of focal salvage cryoablation have suggested that focal salvage cryoablation can have a significant effect on oncologic outcome, as post-radiation SCT has a 5-year biochemical disease-free survival rate of approximately 50% [76, 78, 102]. While thought to reduce the risk of severe toxicity by targeting only the tumor and sparing healthy surrounding tissue, focal SCT has not yet been dem-
<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>No. patients</th>
<th>Median age</th>
<th>Median follow-up after SRT (mo)</th>
<th>Type SRT</th>
<th>BDFS% [years]</th>
<th>GU toxicity grade 2+ (%)</th>
<th>GI toxicity grade 2+ (%)</th>
<th>Rectal fistula (%)</th>
<th>Erectile dysfunction (%)</th>
</tr>
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<tbody>
<tr>
<td>Burri et al. [88]</td>
<td>2010</td>
<td>37</td>
<td>70</td>
<td>86</td>
<td>LDR-whole gland 125-I (135 Gy) or 103-Pd (110 Gy)</td>
<td>65 [5]</td>
<td>46</td>
<td>11</td>
<td>2.7</td>
<td>75</td>
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<td>Chen et al. [89]</td>
<td>2013</td>
<td>52</td>
<td>67.5</td>
<td>59.6</td>
<td>HDR (36 Gy)</td>
<td>51 [5]</td>
<td>56</td>
<td>4</td>
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<td>35</td>
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<td>Lahmer et al. [90]</td>
<td>2013</td>
<td>18</td>
<td>69</td>
<td>21</td>
<td>PDR 192-Ir (60 Gy)</td>
<td>57 [3]</td>
<td>27.8</td>
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<td>Hsu et al. [91]</td>
<td>2013</td>
<td>15</td>
<td>68.5</td>
<td>23.3</td>
<td>Focal-partial PPI 125-I (144 Gy) or 103-Pd (125 Gy)</td>
<td>100 [1] 100 [2] 71.4 [3]</td>
<td>33</td>
<td>0</td>
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<td>Peters et al. [92]</td>
<td>2014</td>
<td>20</td>
<td>69</td>
<td>36</td>
<td>Focal 125-I (&gt;144 Gy)</td>
<td>60 [3]</td>
<td>10</td>
<td>–</td>
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<td>Henriquez et al. [93]</td>
<td>2014</td>
<td>56</td>
<td>65 (avg)</td>
<td>48</td>
<td>I-125 LDR (145 Gy) Ir-192 HDR (50.2 Gy, 6.2 Gy/fraction)</td>
<td>77 [5]</td>
<td>21 (HDR) 24 (LDR)</td>
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<td>Chang et al. [94]</td>
<td>2014</td>
<td>5</td>
<td>57</td>
<td>41</td>
<td>LDR partial 125-1 (110 Gy)</td>
<td>–</td>
<td>0</td>
<td>0</td>
<td>–</td>
<td>60</td>
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<tr>
<td>Yamada et al. [95]</td>
<td>2014</td>
<td>42</td>
<td>72</td>
<td>38</td>
<td>HDR 192- Ir</td>
<td>68.5 [5]</td>
<td>57.1</td>
<td>14</td>
<td>–</td>
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<td>Vargas et al. [96]</td>
<td>2014</td>
<td>69</td>
<td>72.5</td>
<td>60.4</td>
<td>103-Pd (100 Gy)</td>
<td>85.6 (Low risk) 74.5 (Intermediate) 66 (High risk) [5]</td>
<td>13</td>
<td>5.8</td>
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<td>Fuller et al. [98]</td>
<td>2015</td>
<td>29</td>
<td>73</td>
<td>24</td>
<td>HDR Sterotactic (34 Gy)</td>
<td>82 [2]</td>
<td>18</td>
<td>0</td>
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<td>30</td>
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<td>Rutenberg et al. [99]</td>
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<td>11</td>
<td>67</td>
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<td>EBRT (45 Gy)</td>
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<td>36</td>
<td>18</td>
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<tr>
<td>Lacy et al. [100]</td>
<td>2016</td>
<td>21</td>
<td>65</td>
<td>49</td>
<td>125-I (108-144 Gy)</td>
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<td>9.5</td>
<td>–</td>
<td>4.76</td>
<td>45.5</td>
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*BDFS* biochemical disease-free survival rate, *GU* genitourinary, *GI* gastrointestinal
utilizing the Ablatherm or Sonoblate HIFU units for salvage therapy after radiotherapy failure are delineated in Table 3 [69, 83–89, 90–92, 99, 100]. The latest prospective study, published in 2017, found a 5-year BDFS of 53%, a rate comparable to other methods of salvage therapy [90–92].

Higher pre-RT PSA, higher pre-salvage HIFU PSA, PSAn ≥ 0.5 ng/ml after salvage treatment, and shorter time to PSAn have all been implicated as factors that predict progression after salvage HIFU treatment [86, 88, 89, 98]. Additionally, the location of post-RT cancer recurrence, specifically tumor anterior to the urethra, has been described as an independent predictor of salvage HIFU failure [98], possibly due to an insufficient fixed focal length of HIFU devices. While the size of the prostate gland can diminish enough after salvage HIFU to allow access to anterior recurrence, the toxicity associated with HIFU limits multiple salvage sessions [87, 88, 99]. For example, a study by Ahmed et al. found that while the rate of rectourethral fistula after one whole-gland HIFU treatment was 2.4%, this rate rose to 33% for repeat treatment [99].

Indeed, while there exists a heterogeneity in morbidity frequencies presented in Table 3, likely due to inconsistent biochemical failure definitions and range of follow-up, reported rates of urinary incontinence and urethral stricture after salvage HIFU have been as high as 38 and 54%, respectively. However, a retrospective study comparing toxicities of salvage HIFU to those of first and second generation SCT found that both early and late SCT treatment groups experienced a significantly larger number of overall complications than the salvage HIFU group [69]. Specifically, the investigators found that patients in salvage HIFU group experienced lower rates of both mild-moderate urinary incontinence and urinary retention when compared to the SCT groups [69].

Focal HIFU treatment technique has also been explored as a feasible salvage therapy option with reduced adverse events. While a few retrospective studies have showed a trend towards acceptable toxicity rates [86, 103–105], there is a need for larger, prospective investigations.

**Re-Irradiation: Salvage External Beam Radiation Therapy and Brachytherapy**

Re-irradiation with external beam radiation therapy (EBRT) or brachytherapy (BT) following local PCa recurrence are both potential salvage treatment options. However, there exist very few reports on salvage EBRT after RT failure. In fact, the European Association of Urology (EAU)—European Society for Radiotherapy & Oncology (ESTRO)—International Society of Geriatric Oncology (SIOG) Guidelines on Prostate Cancer state that “following recurrence after previous definitive RT there is no indication for salvage EBRT as the total dose is limited and therefore the chance of cure is low” [91]. Nonetheless, in 2016, Rutenberg et al. reported on a small series of 11 patients treated with salvage EBRT after failed primary BT and found a 3-year BDFS rate of 69%, with 36% grade ≥ 2 GU and 18% grade ≥ 2 GI complications [92]. Similarly, Fuller et al. prospectively treated 29 patients with salvage stereotactic body radiation therapy (SBRT) between 2009 and 2014 and reported a 2-year BDFS of 82%, with 18% grade ≥ 2 GU complications and no GI complications ≥ grade 1 [93]. While this study was small, the data suggests that salvage EBRT is a promising approach for recurrent PCa control and additional investigation is warranted.

The results from these series and other studies reporting on salvage BT (SBT) are presented in Table 4 [92–97, 100, 104–110]. For low dose rate (LDR) SBT studies, radiation doses ranged between 100–145 Gy using 125-I or 103-Pd. For high dose rate (HDR) SBT studies, radiation dose and fractionation varied significantly (see Table 4), but all used 192-Ir implants. The diversity in SBT dose strategy may contribute to variability in study results. Biochemical control rates for these investigations ranged from 20 to 82% and rates of ≥ grade 2 GU and GI toxicities ranged between 10 and 58 and 0 and 18%, respectively.

Studies exploring focal or partial SBT are limited but have yielded favorable disease control and toxicity profiles [100, 104, 106]. However, heterogeneities in patient and tumor characteristics (e.g. unifocal vs multifocal local recurrence) make it challenging to compare these results to outcomes from whole-gland SBT series. Similar to focal SCT and focal salvage HIFU, large randomized, prospective trials are indicated before definitive recommendations can be made regarding focal SBT.

The wide variability across most SBT studies makes it difficult to come to a consensus on which dose and radiation source is most appropriate for SBT treatment. However, the results displayed in Table 4 demonstrate that multiple variants of salvage RT are both oncologically robust and well tolerated. As each patient with primary RT failure presents with distinctive disease recurrence characteristics and comorbid conditions, evidence supporting multiple types of effective salvage RT regimens allows physicians to consider diverse treatment options suited for each patient’s individual criteria.

**Future Directions**

With a current shift towards minimally invasive and focal therapy options for PCa, it is evident that as imaging technology and staging methodology continue to improve, the future of salvage therapy for locally recurring PCa with also be focused on targeted and tissue-sparing focal therapies [111]. Investigation into novel focal therapy techniques such as
electroporation [112–114] may offer a new method of therapy
to further improve outcomes after failed radiation. Initially
developed in 2005, electroporation involves creating 80–
490 nm nanopores in the cell membranes of target cells by
applying repetitive heavy current pulses with needle elec-
trodes placed in target tissue. This leads to apoptosis sec-
dondary to the loss of homeostasis due to the uninhibited flux of
ions and macromolecules. While current studies on the onco-
logic outcomes of electroporation for PCa are promising [115,
116], the safety profile and efficacy of this treatment modality
are still undefined and comparative clinical trials are necessary
prior to suggesting salvage electroporation after failed RT as
an alternative to the existing salvage therapies described
above [117].

Other directions for future PCa treatment options include
advancement in immunotherapy targeting checkpoint inhibi-
tors, such as sipuleucel-T, particularly for castrate-resistant
PCa [118]. Indeed, with expansion of treatment technology,
developments in focal therapy options and refinement of phy-
sician technique with increased usage, salvage treatment mo-
dalities will continue to advance and provide effective surviv-
al outcomes with minimal complication for patients with re-
current PCa after radiation failure.

Conclusion

There is currently no one standard of care for PCa after
failed RT. However, patients with confirmed biochemical
recurrence (using the Phoenix definition) should all be
evaluated with systemic imaging to rule out distant metas-
tases followed by local imaging and biopsy (Fig. 1). Presently,
the large majority of patients who present with
localized recurrence after RT are treated with systemic hor-
monal therapy or observation [6, 7]. While ADT can be an
important component of management, especially for pa-
tients at high risk for micrometastasis undetectable by im-
ageing, local salvage therapies such as SRP, SCT, salvage
HIFU, and salvage RT should be considered as treatment
options for patients with local disease.

As described, recent investigations into the efficacy and
toxicity of each aforementioned therapy are encouraging,
demonstrating reasonable biochemical control and accept-
able complication rates. However, as these studies com-
prise disparate sample sizes, varied time of follow-up, di-
verse definitions of salvage failure, heterogeneous mea-
sures of toxicity, discrepant outcome reporting, and are
mostly retrospective in nature, they are difficult to directly
compare. Therefore, management of recurrent PCa after
failed radiation requires prudent consideration of a pa-
tient’s unique oncologic characteristics, tolerance to treat-
ment toxicity profile, and individual condition and prefer-
ence. The principal physician should also take into account
the factors identified in the series above that predict re-
sponse to salvage treatments such as PSA level prior to
primary treatment, pre-salvage PSA level, Gleason score
at time of recurrence, and location of cancer recurrence.

Compliance with Ethical Standards

Conflict of Interest  Nicole M. Golbari and Aaron E. Katz each declare
no potential conflicts of interest.

Human and Animal Rights and Informed Consent  This article does
not contain any studies with human or animal subjects performed by any
of the authors.
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- Of importance
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