Salvage therapy of intraprostatic failure after radical external-beam radiotherapy for prostate cancer: A review

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Abstract

Radical external-beam radiotherapy (EBRT) is a standard treatment for prostate cancer (PC) patients. Despite this, the rate of intraprostatic relapses after primary EBRT is still not negligible. There is no consensus on the most appropriate management of these patients after EBRT failure. Treatment strategies after PC relapse are strongly influenced by the effective site of the tumor recurrence, and thus the instrumental evaluation with different imaging techniques becomes crucial. In cases of demonstrated intraprostatic failure, several systemic (androgen deprivation therapy) or local (salvage prostatectomy, cryotherapy, high-intensity focused ultrasound, brachytherapy, stereotactic EBRT)
1. Introduction

For more than two decades external-beam radiation therapy (EBRT) has been considered standard practice for the radical treatment of patients with localized prostate cancer (PC). Consequently, this technique has evolved significantly. Technological advances have been progressively introduced, and treatments standards have evolved from two-dimensional (2D) to three-dimensional conformal radiation therapy (3D-CRT); more recently intensity-modulated radiation therapy (IMRT) and image-guided radiation therapy (IGRT) have also been introduced. In parallel with this technological evolution, a progressive increase in prescribed and delivered radiation doses to the prostate has been observed [1–3].

Modern EBRT as a primary treatment has been reported to be well tolerated with minimal late severe toxicity. Clear evidence of improved biochemical outcomes, using higher radiation doses, has also been confirmed in large series [1,2,4]. Despite these strategic efforts to optimize outcomes of EBRT, the rate of biochemical failure (BF) after primary EBRT in PC is still not negligible. In a large series of 3839 PC patients, treated with EBRT in the prostate-specific antigen (PSA) era, Kuban et al. [5] reported a biochemical failure rate of 33%. In the literature, published rates of biochemical recurrence are in the range 22–69% after curative RT ± androgen deprivation therapy (ADT) [6,7]. The management of PC relapse after EBRT is still undefined, and no consensus regarding the most appropriate treatment option has been established.

In this review, we analyze the correct definition of intraprostatic relapse after EBRT, focusing on the recent developments in imaging to detect prostatic recurrence. Results in terms of clinical outcome and toxicity of all the available salvage treatments for this type of local relapse are reviewed.

2. Definition of recurrence after EBRT

The introduction of routine PSA dosage radically changed clinical management of diagnosis and follow-up in PC patients and allowed clinicians to diagnose BF earlier [7,8]. As a transient PSA rise after radical EBRT could also be related to benign prostatic diseases, or could be associated with EBRT itself (the “PSA bounce phenomenon” [9]), various criteria to define a BF after primary prostate EBRT have been proposed. In 1996 the first Consensus Conference of the American Society of Therapeutic Radiology and Oncology (ASTRO), that was held in S. Antonio, stated that failure should be declared in the case of three consecutive rises in the PSA after a nadir, or when any salvage treatment because of a PSA rise is prescribed [10]. Nevertheless, these criteria presented some limits, such as the absence of a cut-off to consider as a BF a rise in PSA, and the poor performance in patients submitted to combined radiation – ADT therapy. Moreover, the duration of follow-up after EBRT can affect the interpretation of long-term control rates, and then these criteria could be related with some uncertainties to clinical progression or survival [11,12].

Given these limits, ASTRO criteria were revised during a second multidisciplinary Consensus Conference sponsored by ASTRO and the Radiation Therapy Oncology Group (RTOG) in Phoenix, Arizona [11]: a PSA rise of at least 2 ng/mL above the nadir was considered the standard definition for biochemical failure after EBRT ± ADT. The panel of experts recommended that the failure date should be assessed “at call” and not backdated, as in the previous consensus. An adequate follow-up was also suggested and considered crucial to avoid the artifacts resulting from short follow-up. Moreover, a BF should be declared also in the case of positive biopsies and/or prescription of salvage therapies (ADT, radical prostatectomy, brachytherapy, cryosurgery), even in the absence of these new PSA failure criteria [12]. Despite some limits (field of application strictly limited to EBRT ± ADT, potential bias in favor of EBRT series when compared with results of other treatment modalities), these new ASTRO Phoenix criteria have been definitely acquired as the new International standard.

To identify potential candidate patients for local retreatments, important information is the PSA doubling time (PSA-DT) [12]. Local failure occurs more frequently with a PSA-DT ≥ 6 months, while metastatic disease occurs more frequently with a rapid rise in PSA (PSA-DT <6 months).

It should be strongly highlighted that the value of the PSA-DT is not the only feature that could help clinicians identify patients that are potentially candidates for a second local treatment. Even if the identification of the correct selection criteria is still a subject for debate, it is crucial to correctly identify patients who would really benefit from a second local curative procedure, as only patients who do not have ‘infraclinic’ distant failure could potentially be cured.

3. Imaging of intraprostatic relapse after EBRT

The availability of accurate diagnostic tools would be very important because treatment strategies after PC
relapse are strongly influenced by the actual site of tumor recurrence.

However, diagnosis of local recurrence after EBRT can be rather challenging for conventional imaging modalities, also because of the radiation-induced changes to the prostate gland (parenchyma atrophy and fibrosis, and the reduction of the vascular supply and of the glandular secretions). Trans-rectal ultrasound (TRUS) is the most broadly available instrument for the assessment of local relapse. Its sensitivity is low, circa 50%, which is similar to the sensitivity of the digital rectal examination (DRE) [13,14]. Color Doppler, or contrast-enhanced ultrasound (CEUS) with microbubble contrast media, can that differentiate neovascularity-related changes in the prostate structures, can potentially be exploited for improving the sensitivity of TRUS [14]. Magnetic resonance imaging (MRI) is often used in the detection of the primary tumor and extra-capsular extent [15]. However, the influence of radiation-induced changes can also significantly affect MRI, because the contrast between recurrent carcinoma and benign tissue is not always evident after radiotherapy [13,15]. Despite this limitation, the MRI technique remains superior to DRE and TRUS. The introduction of functional imaging techniques – such as dynamic contrast-enhanced MRI (DCE-MRI), diffusion-weighted imaging (DWI) and proton MR spectroscopy imaging (MRSI) – improved accuracy in identifying locally recurrent carcinoma from 68% to 90%, according to some clinical experiences [13–17]. Table 1 summarizes indication of the European Society of Urogenital Radiology (ESUR) about the different MRI sequences [18].

Additional modalities that are still rather controversial in their indication are represented by molecular imaging techniques: i.e., positron emission tomography (PET) and/or single photon emission computed tomography (SPECT). SPECT is performed using $^{111}$In-labeled capromab peptide (Prostascint, Cytogen Corporation, Princeton, NJ), the labeled antibody to the prostate specific membrane antigen (PSMA) [19]. The tracer, so far investigated in more than 2000 patients, has shown an interesting sensitivity (up to 92%) for the detection of local recurrence after radical prostatectomy [20]. However, the correlation between PSA value and Prostascint detection of cancer recurrence after radiation therapy is weak, although still superior to that of DRE and TRUS [20,21]. Also PET with radio-labeled choline ($^{11}$C- and $^{18}$F-choline) or acetate tracers ($^{11}$C-acetate) is increasingly being applied in PC restaging after biochemical relapse [21]. The tumor cell retention of radio-labeled acetate depends on fatty acid metabolism, which appears to be predominant in PC cells, and from its incorporation into phosphatidylcholine (because of up-regulation of choline kinase) and neutral lipids [22,23]. Both radio-labeled choline and acetate imaging demonstrated that the overall detection rate in restaging prostate carcinoma is variable and depends directly on PSA absolute value and PSA kinetics [24]. This mechanism is not directly related to cell proliferation, but can be influenced by tumor hypoxia [25,26]. In local recurrence, however, the dependence on PSA value is negligible, and PET can be considered more reliable since the biochemical relapse after EBRT is associated with PSA values >2 ng/mL [13], with a sensitivity ranging from 81% to 100% in identifying local relapses [27,28]. Potentially, PET could also be of interest for target definition in salvage EBRT [29,30], but it should still be considered as an experimental procedure.

Finally, despite the potential of MRI and of PET in these clinical situations, it should be highlighted that recent guidelines of the European Association of Urology (EAU) and of the National Institute for Health and Clinical Excellence (NICE) in Britain do not recommend their routine prescription, limiting their use to well-defined clinical situations, but do favor their further evaluation, possibly in the context of clinical trials [31,32].

4. Treatment options

4.1. Androgen deprivation therapy (ADT)

Despite the conflicting data from non-randomized trials addressing the issue of the role of ADT in this clinical scenario, it is considered the standard of care for patients presenting with BF [33,34].

It remains controversial whether early-salvage ADT (i.e., at the time of BF) has better outcomes than either late-salvage ADT (i.e., at the development of clinically evident distant metastases) or observation. Data from non-randomized studies comparing early- versus late-salvage ADT after RT are summarized in Table 2 [34–37]. These studies showed improved overall survival (OS) with ADT according to PSA level (<10 ng/mL, ≤15 ng/mL, or <20 ng/mL). This improvement is limited only to low PSA, M0 patients [34,35], and/or to patients with longer PSA-DT (>7 months and >12 months) [34,36]. Conversely, a retrospective cohort analysis of 248 men with BF after EBRT showed no advantage for ADT (versus “watchful waiting”) in the subgroup of men with a PSA-DT >12 months ($P = 0.74$), leading to the conclusions that patients with signs of local recurrence only (low-risk patients with late recurrence signs and a slow PSA rise) are best managed by observation alone [38].

A recent secondary analysis of patients enrolled in the ICORG 97-01 randomized trial (comparing 4 months versus 8 months of neoadjuvant ADT before RT for intermediate- to high-risk PC) showed that early salvage ADT, based on PSA ≤ 10 ng/mL and the absence of distant metastases, improved OS [39]. Besides the limitations of the retrospective analysis, these reports evidenced the positive impact on OS of starting ADT at the earliest sign of recurrence. These advantages must be weighed against potential impact on quality of life or on age-related health problems, especially for young men and for long-term schedules [40,41]. Therefore, the optimal management and prescription of ADT in patients with localized PC developing BF after a radical course of RT still remains controversial, and some alternative schedules have
Indications of the European Society of Urogenital Radiology (ESUR) for the different MRI sequences.

<table>
<thead>
<tr>
<th>MRI sequences</th>
<th>Radiological aspect of cancer</th>
<th>Notes</th>
</tr>
</thead>
</table>
| T2-weighted images (T2WI)                 | Cancer appears as a round or ill-defined, low-signal-intensity focus in the peripheral zone   | • It provides the best depiction of the prostate’s zonal anatomy and capsule. T2WI is used for prostate cancer detection, localization and staging  
• T2WI should always be performed with at least two functional MRI techniques in order to provide better characterization of the anatomy and of the pathological tissues  
• Prostate intra-epithelial neoplasia, prostatitis, hemorrhage, atrophy, scars and post-treatment changes can mimic cancer on T2WI  
• Biopsy-related hemorrhage can cause artifacts that mimic cancer and limit lesion localization and staging. The interval between the biopsy procedure and MRI should be at least 4–6 weeks  
• Tumors located in the transition zone are more challenging to detect (the signal intensity characteristics of this zone and cancer usually overlap) |
| Dynamic contrast-enhanced (DCE)           | Cancer appears as a round or ill-defined, low-signal-intensity focus in the peripheral zone, rapidly enhancing after the administration of gadolinium-based contrast medium | • It is the most common imaging method for evaluating tumor vascularity  
• Several studies have found that DCE-MRI is superior to T2WI for prostate cancer localization  
• If the prostate has high vascularity, then DCE-MR cannot be used alone and should always be combined with T2WI and DWI  
• Diffusion-weighted imaging is, however, affected by magnetic susceptibility effects resulting in spatial distortion and signal loss |
| Diffusion-weighted imaging (DWI) with apparent diffusion coefficient (ADC) | Cancer shows lower ADC values compared to normal prostate tissue                           |                                                                                                                                                                                                  |
| Magnetic resonance spectroscopic imaging (MRSI) | Cancer shows lower levels of citrate and higher levels of choline than benign tissues         | • Commercially available software packages allow overlaying spectral information on T2WIs  
• The relevant metabolites are citrate (marker of benign tissue), choline (insignificant for diagnosis, but difficult to resolve from choline), and choline (marker of malignant tissue) |

Adapted from Barentsz et al. [18].

been proposed [42]. In a recent non-inferiority study published by Crook et al., [43] continuous ADT was compared with ADT provided in 8-month cycles, with non-treatment periods determined according to the PSA level: the intermittent ADT was not inferior to the continuous schedule in terms of overall survival, and it also showed better results in terms of quality of life. Two randomized trials are currently ongoing, addressing the relevant issue of early ADT in patients who relapse after initial curative RT.

In conclusion, according to the NICE Clinical Guideline 58 that is regulating the National Health Service in Britain, ADT “…is not routinely recommended for men with prostate cancer…a higher long-term survival benefit could be accompanied by a shorter period of ADT at the cost of increased morbidity.”

Studies comparing early- versus late-salvage androgen deprivation therapy (ADT) after radical radiotherapy (RT) with or without ADT for prostate cancer.

<table>
<thead>
<tr>
<th>Ref</th>
<th>Study design</th>
<th>Population</th>
<th>Number of patients</th>
<th>Median follow-up (years)</th>
<th>Outcomes after salvage AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>34</td>
<td>Retrospective analysis</td>
<td>Clinically localized prostate cancer (all risk) treated with RT alone</td>
<td>381</td>
<td>3.8–4.2</td>
<td>PCSS and OS improved with early-salvage ADT (PSA &lt; 10 ng/mL BS-negative versus PSA &gt; 10 ng/mL BS-negative versus BS-positive)</td>
</tr>
<tr>
<td>35</td>
<td>Secondary analysis of RTOG 8610</td>
<td>Bulky stage T2–T4 prostate cancer, N0/N1, randomized to RT + 4 mo ADT versus RT alone</td>
<td>247</td>
<td>9</td>
<td>OS improved with early-salvage ADT (M0 versus M1, and PSA level &lt; 20 versus &gt; 20 ng/mL)</td>
</tr>
<tr>
<td>36</td>
<td>Retrospective analysis</td>
<td>Clinically localized prostate cancer (all risk) treated with RT± ADT, includes post-prostatectomy RT for rising PSA</td>
<td>124</td>
<td>6.2</td>
<td>OS improved with early-salvage ADT (PSA &lt; 15 ng/mL versus &gt; 15 ng/mL [HR 2.15] and PSA &gt; 7 versus &lt; 7 mo [HR 2.63])</td>
</tr>
<tr>
<td>37</td>
<td>Secondary analysis of RTOG 8531</td>
<td>Unfavorable-prognosis prostate cancer (i.e., T3 or N1), includes post-prostatectomy pT3, randomized to RT+ adjuvant life-long ADT versus RT alone</td>
<td>243 (RT-alone arm)</td>
<td>8.5</td>
<td>OS improved with early-salvage ADT (PSA &lt; 10 ng/mL versus ≥ 10 ng/mL [HR 1.5])</td>
</tr>
</tbody>
</table>

Ref, reference: ADT, androgen deprivation therapy; BS, bone scan; DSS, disease-specific survival; HR, hazard ratio; LF, local failure; M0, distant metastasis absent; M1, distant metastasis present; N0, pelvic node negative; N1, pelvic node positive; OS, overall survival; PCSS, prostate cancer-specific survival; RTOG, Radiation Therapy Oncology Group; PSADT, PSA doubling time.
cancer who have a biochemical relapse unless they have:
symptomatic local disease progression, any proven metastases,
or a PSA doubling time of <3 months” [32]. The recent
update of the EAU Guidelines supports the use of ADT in
the treatment of post-EBRT biochemical failures in patients
with a “…presumed systemic relapse…” [31].

Therefore, a comparison with other local salvage ther-
api es, also in terms of health technology assessment, is needed
and would be an important challenge in the era of tailored
treatments.

Actually, NICE and EAU guidelines suggest the use of
radiotherapy for localized failure after prostatectomy and to
evaluate (in the context of clinical trials) local treatments after
radical radiotherapy failure [31,32].

4.2. Salvage prostatectomy

The improvements in surgical experience and the technical
advances, including robotic surgery, have ameliorated surgical
performances for salvage radical prostatectomy (SRP) over the last decade [31,44]. Even if SRP is not the only
survival salvage approach (considering also pelvic exen-
teration, radical cystoprostatectomy or prostatectomy with
permanent umbilical cystostomy procedures) [45], laparo-
scoptic and robotic approaches could potentially be favored
by a lower rate of serious side effects [46-48]. Correct
selection of patients reduces the need for more aggressive
surgical approaches, improves outcomes, and reduces tox-
icity rates. It relies upon three main elements: (a) positive
biopsy, (b) metastases exclusion, (c) the presence of favor-
able prognostic factors. The most appropriate candidate for
SRP is a non-metastatic patient with the disease, suitable
also for surgery when radiation therapy was planned, and
having a life expectancy which could allow him to benefit
from intervention, with a PSA as low as possible (not
exceeding 10 ng/mL) and a Gleason score <7 (if a tumor
specimen is available and if it can be scored) [31]. Even with
the limits of the retrospective studies, recent series of SRP
suggest its superiority over other salvage treatment modal-
ities such as cryotherapy, HIFU or brachytherapy in terms
of biochemical control. However, data are scarce and no
conclusive statements can be made. Table 3 shows results of
the SRP series with at least 80 patients and/or 4 years of follow-
up [44,49–59]; the 5-years BF free probability rates after SRP
ranged between 28% and 71%. Several BF definitions after
SRP have been applied – PSA >0.1 ng/mL and rising [59],
PSA >0.2 ng/mL [48,50,52–54], PSA >0.4 ng/mL [60] – and
the median follow-up ranged from 45 to 120 months; this
might explain the wide variation in results, and it is limiting
a critical and comparative analysis. As the biochemical control
clearly worsens when the follow-up is longer (see results of
Pontes et al. [44] and Amling et al. [52], Table 3), early diag-
nosis of BF and aggressive treatment could produce better
and more durable results than the other salvage approaches [59].
Studies in Table 3 needed a biopsy to confirm the diagnosis
of relapse before SRP. Thus, the timing of biopsies became
a crucial point: if earlier diagnosis seems to be an important
prognostic factor, it could be also a potential but important
limit of the studies with shorter follow-up times and/or earlier
biopsies, as tumor clearance after radiotherapy may take up
to 30 months, with an overestimation of the post-EBRT local
relapse rates [61].

ADT (before and/or during primary EBRT or before SRP)
seems to offer no further oncological advantages, but disease
progression during ADT is a very unfavorable prognostic
factor. As no data exist on the efficacy in terms of cancer-specific
survival [60,62] of pelvic lymph-node dissection (LND) asso-
ciated with SRP, despite the possible role of LND to delay
further progression of clinically recurrent PC, no firm conclu-
sion could be drawn and the procedure should be considered
only in highly selected patients.

Table 3
Outcomes and complication rates of surgical radical prostatectomy (SRP) series.

<table>
<thead>
<tr>
<th>Ref.</th>
<th>No. pts</th>
<th>Median interval between RT and SRP</th>
<th>Median follow-up after SRP</th>
<th>OCD (%)</th>
<th>BRFS (%)</th>
<th>CSS (%)</th>
<th>PSM (%)</th>
<th>+LN (%)</th>
<th>Rectal injury (%)</th>
<th>Anast. stenosis (%)</th>
<th>Urinary incont. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>44</td>
<td>35</td>
<td>–</td>
<td>12–120 months</td>
<td>30</td>
<td>28</td>
<td>79</td>
<td>70</td>
<td>12</td>
<td>9</td>
<td>11</td>
<td>46</td>
</tr>
<tr>
<td>49</td>
<td>11</td>
<td>–</td>
<td>53.5 months</td>
<td>71</td>
<td>71</td>
<td></td>
<td></td>
<td></td>
<td>0</td>
<td>0</td>
<td>64</td>
</tr>
<tr>
<td>50</td>
<td>79</td>
<td>–</td>
<td>50 months</td>
<td>53</td>
<td>53</td>
<td>72</td>
<td></td>
<td></td>
<td>6</td>
<td>12</td>
<td>39</td>
</tr>
<tr>
<td>51</td>
<td>29</td>
<td>4.9 years</td>
<td>5.1 months</td>
<td>28</td>
<td>69</td>
<td>31</td>
<td></td>
<td></td>
<td>6.9</td>
<td>22</td>
<td>67</td>
</tr>
<tr>
<td>52</td>
<td>108</td>
<td>36 months (Minimum &gt;10 years)</td>
<td>39  (Period: 1966–1996)</td>
<td>39</td>
<td>43</td>
<td>70</td>
<td>36</td>
<td>18</td>
<td>6</td>
<td>21</td>
<td>51</td>
</tr>
<tr>
<td>53</td>
<td>100</td>
<td>47 months</td>
<td>58 months</td>
<td>50</td>
<td>66</td>
<td>10</td>
<td>7</td>
<td>1</td>
<td>30</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>54</td>
<td>100</td>
<td>10 Years</td>
<td>35</td>
<td>55</td>
<td>73</td>
<td>21</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>55</td>
<td>138</td>
<td>–</td>
<td>39</td>
<td>84</td>
<td>39</td>
<td>77</td>
<td></td>
<td></td>
<td>10</td>
<td>22</td>
<td>44</td>
</tr>
<tr>
<td>56</td>
<td>11</td>
<td>36.9 months</td>
<td>83</td>
<td>81</td>
<td>55</td>
<td>91</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>57</td>
<td>51</td>
<td>–</td>
<td>7.2 years</td>
<td>25</td>
<td>47</td>
<td>36</td>
<td>28</td>
<td></td>
<td></td>
<td></td>
<td>30</td>
</tr>
<tr>
<td>58</td>
<td>146</td>
<td>4.6 years</td>
<td>3.8 years</td>
<td>44</td>
<td>54</td>
<td>16</td>
<td>13</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>59</td>
<td>404</td>
<td>41 months</td>
<td>55</td>
<td>55</td>
<td>37</td>
<td>83</td>
<td>25</td>
<td>16</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

OCD, organ-confined disease; BRFS, biochemical recurrence-free survival; CSS, cancer-specific survival; PSM, positive surgical margins; LN, lymph nodes; pts, patients.
Table 4
Outcomes and complication rates of the larger salvage cryotherapy series.

<table>
<thead>
<tr>
<th>Ref.</th>
<th>No. pts</th>
<th>Median follow-up (months)</th>
<th>BRFS (%)</th>
<th>Definition of failure</th>
<th>Incontinence</th>
<th>Rectal toxicity (fistulas)</th>
</tr>
</thead>
<tbody>
<tr>
<td>68</td>
<td>279</td>
<td>5 years</td>
<td>58.9</td>
<td>Three consecutive rises</td>
<td>4.4%</td>
<td>3.2%</td>
</tr>
<tr>
<td>69</td>
<td>118</td>
<td>18.6 months</td>
<td>34</td>
<td>PSA ≥ 0.5 ng/mL</td>
<td>6.7%</td>
<td>3.3%</td>
</tr>
<tr>
<td>70</td>
<td>59</td>
<td>7 years</td>
<td>59</td>
<td>PSA ≥ 0.5 ng/mL</td>
<td>8%</td>
<td>3.4%</td>
</tr>
<tr>
<td>71</td>
<td>176</td>
<td>7.5 years</td>
<td>39% (at 8 and 10 years)</td>
<td>PSA nadir + 2</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>72</td>
<td>51</td>
<td>10.1 years</td>
<td>61</td>
<td>PSA ≥ 0.5 ng/mL</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>73</td>
<td>58</td>
<td>2 years</td>
<td>70</td>
<td>PSA ≥ 0.5 ng/mL</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>74</td>
<td>797</td>
<td>3.4 years</td>
<td>66</td>
<td>PSA ≥ 0.5 ng/mL</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>75</td>
<td>100</td>
<td>33.5 months</td>
<td>59 (at 3 years)</td>
<td>Three consecutive rises</td>
<td>13%</td>
<td>1%</td>
</tr>
</tbody>
</table>

Ref, reference; pts, patients; BRFS, biochemical recurrence-free survival; PSA, prostate-specific antigen.

Table 5
Outcomes and complication rates of larger salvage high-intensity focused ultrasound (HIFU).

<table>
<thead>
<tr>
<th>Ref.</th>
<th>No. pts</th>
<th>Median follow-up (months)</th>
<th>BRFS (%)</th>
<th>Definition of failure</th>
<th>Incontinence</th>
<th>Bladder-neck stenosis/Urethral stricture</th>
<th>Rectal toxicity (fistulas)</th>
</tr>
</thead>
<tbody>
<tr>
<td>82</td>
<td>31</td>
<td>7.5</td>
<td>50</td>
<td>PSA &lt; 0.2 ng/mL</td>
<td>7%</td>
<td>36%</td>
<td>6%</td>
</tr>
<tr>
<td>83</td>
<td>167</td>
<td>18.1</td>
<td>17 (at 5 years)</td>
<td>PSA ≥ 1 ng/mL</td>
<td>49.5%</td>
<td>7.8%</td>
<td>3%</td>
</tr>
<tr>
<td>84</td>
<td>71</td>
<td>14.8</td>
<td>61</td>
<td>PSA ≥ 0.5 ng/mL</td>
<td>7%</td>
<td>17%</td>
<td>6%</td>
</tr>
<tr>
<td>85</td>
<td>290</td>
<td>48</td>
<td>Not reported</td>
<td>Phoenix ASTRO consensus definition and/or prescription of hormonal therapy</td>
<td>19.5%</td>
<td>16%</td>
<td>2%</td>
</tr>
</tbody>
</table>

Abbreviations: Ref, reference; pts, patients; FUP, follow-up; BRFS, Biochemical Recurrence Free Survival; PSA Failure, Cut off to assess PSA failure; GU, genito-urinary

Looking at toxicities, erectile dysfunction and urinary incontinence ranged respectively between 80% and 100% [47,48,63] and 32% and 67%, respectively (Table 3). Some studies reported rates of 100% of urinary incontinence [64].

Erectile dysfunction seems frequently not to be a major problem in this setting, as it is often present before SRP [63,65]. As shown by the Cancer of the Prostate Strategic Urologic Research Endeavor (CAPSURE) Study, the 93.5% of patients presenting a post-RT failure (including a relevant number of them presenting a local relapse) received hormonal therapy, despite the resulting erectile dysfunction [8]. It should be noticed that, when compared to those initially treated with surgery, these patients are older (27% aged >75 years), with more advanced disease, and that almost 40% of them had already had hormonal treatments at presentation. In this context, only 0.9% of them have been submitted to SRP, and erectile dysfunction related to surgery does not seem to be the most relevant issue. Looking at the bladder toxicity after SRP, in particular urinary incontinence, it remains high (despite the introduction of mini-invasive techniques), ranging between 20 and 100% [47,48,64]. Structures of the anastomosis are not rare and, even if the studies did not always report data about this possible side effect, rates ranging between 11% and 30% have been published in the literature (Table 3). Rectal injuries are less frequent, but not negligible, with rates ranging between 1% and 10% (Table 3).

In conclusion, SRP could be considered as an option in selected patients with local relapse. Its results should be carefully evaluated, taking into account the potentially severe side effects, and compared with the results of other available treatments options (Tables 4–6).

4.3. Cryotherapy

Cryotherapy consists in the localized ablation of prostatic tissue by low temperature and thawing, which causes direct injury to cells as well as secondary injury from the inflammatory response of the body. Modern cryotherapy uses liquid nitrogen or argon gas circulating through hollow needles to freeze the prostate and helium gas to warm the urethra via the Joule–Thompson effect. Patients who are presenting a prostate gland volume ≥60 mL and/or have undergone a transurethral resection of prostate (TURP) should be excluded because of the potential high risk of urinary morbidity (incontinence and urethral strictures) [66].

The results obtained in 1600 patients treated with salvage cryosurgery using various-generation cryotherapy devices have been published (median follow-up: 18 months to 10 years), with biochemical control rates ranging between 34% and 70% [67–74] (Table 4). However, the heterogeneity in the criteria used to establish efficacy (PSA ≥ 0.3 ng/mL, nadir plus 2 ng/mL, PSA ≥ 0.4 ng/mL, and PSA ≥ 0.5 ng/mL) reflects the lack of agreement between cryosurgeons [67–74]. By assuming that the prostate gland is completely ablated and no other metastatic foci are present in the body, undetectable PSA could reasonably be considered the optimal endpoint for cryotherapy and, obviously, some of the reported biochemical response could be re-sized where properly redefined.

Thus, cryotherapy is a challenging option in patients showing a BF after RT, but the expected side effects on urethra, rectum, penile bulb and erectile nerves could be considered prohibitive in some experiences, and seems also to be related to the operator experience; Izawa et al. [75] showed rates of urinary incontinence, obstructive symptoms, sexual
<table>
<thead>
<tr>
<th>Ref.</th>
<th>No. pts</th>
<th>Type BRT</th>
<th>Dose BRT</th>
<th>Adjuvant ADT (%)</th>
<th>Median follow-up (months)</th>
<th>BRFS (years)</th>
<th>Definition of failure</th>
<th>Urinary incontinence</th>
<th>GU 3–4 toxicity</th>
<th>GI 3–4 toxicity</th>
<th>Erectile dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>104</td>
<td>13</td>
<td>LDR</td>
<td>¹²⁵I: 170 Gy (median)</td>
<td>NR</td>
<td>36</td>
<td>51% (5)</td>
<td>Metastases-free survival</td>
<td>31%</td>
<td>NR</td>
<td>15%</td>
<td>NR</td>
</tr>
<tr>
<td>105</td>
<td>31</td>
<td>LDR</td>
<td>¹⁹⁸Au: 100–200 Gy</td>
<td>NR</td>
<td>23</td>
<td>67% (5)</td>
<td>Overall survival</td>
<td>0</td>
<td>NR</td>
<td>16%</td>
<td>NR</td>
</tr>
<tr>
<td>106</td>
<td>25</td>
<td>LDR</td>
<td>¹²⁵I: 135 Gy</td>
<td>0</td>
<td>47</td>
<td>70% (4)</td>
<td>Phoenix criteria [11]</td>
<td>0</td>
<td>NR</td>
<td>24%</td>
<td>NR</td>
</tr>
<tr>
<td>107</td>
<td>31</td>
<td>LDR</td>
<td>¹⁰³Pd: 120 Gy ¹²⁵I: 144 Gy</td>
<td>97</td>
<td>30</td>
<td>87% (5)</td>
<td>ASTRO criteria [10]</td>
<td>0</td>
<td>NR</td>
<td>5%</td>
<td>NR</td>
</tr>
<tr>
<td>108</td>
<td>17</td>
<td>LDR</td>
<td>¹⁰³Pd: 90 Gy ¹²⁵I: 120 Gy</td>
<td>47</td>
<td>62</td>
<td>53% (5)</td>
<td>ASTRO criteria [10]</td>
<td>24%</td>
<td>24%</td>
<td>0</td>
<td>NR</td>
</tr>
<tr>
<td>109</td>
<td>17</td>
<td>LDR</td>
<td>¹⁰³Pd: 120–126 Gy ¹²⁵I: 103.5–112.5 Gy ¹²⁵I: 145 Gy</td>
<td>71</td>
<td>44</td>
<td>57% (4)</td>
<td>ASTRO criteria [10]</td>
<td>6%</td>
<td>47%</td>
<td>6%</td>
<td>NR</td>
</tr>
<tr>
<td>110</td>
<td>31</td>
<td>LDR</td>
<td>– ¹²⁵I: 11 Gy (median to 90% of the volume)</td>
<td>–</td>
<td>108</td>
<td>20% (5)</td>
<td>Phoenix criteria [11]</td>
<td>NR</td>
<td>19% (late)</td>
<td>6% (late)</td>
<td>NR</td>
</tr>
<tr>
<td>111</td>
<td>37</td>
<td>LDR</td>
<td>¹⁰³Pd or ¹²⁵I: 122 Gy (median to 90% of the volume)</td>
<td>84</td>
<td>86</td>
<td>54 (10)</td>
<td>Phoenix criteria [11]</td>
<td>NR</td>
<td>11%</td>
<td>NR</td>
<td>85%</td>
</tr>
<tr>
<td>112</td>
<td>49</td>
<td>LDR</td>
<td>¹⁰³Pd: 170 Gy ¹²⁵I: 160 Gy (median)</td>
<td>NR</td>
<td>64</td>
<td>34% (5)</td>
<td>Two rises above nadir</td>
<td>6%</td>
<td>14% (TURP)</td>
<td>2%</td>
<td>NR</td>
</tr>
<tr>
<td>113</td>
<td>15</td>
<td>LDR</td>
<td>¹⁰³Pd: 125 Gy ¹²⁵I: 144 Gy</td>
<td>0</td>
<td>23</td>
<td>71% (3)</td>
<td>Phoenix criteria [11]</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>13%</td>
</tr>
<tr>
<td>114</td>
<td>10</td>
<td>HDR</td>
<td>11 Gy × 2 fr.</td>
<td>0</td>
<td>NR</td>
<td>NR³</td>
<td>ASTRO criteria [10]</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>NR</td>
</tr>
<tr>
<td>115</td>
<td>21</td>
<td>HDR</td>
<td>6 Gy × 6 fractions</td>
<td>52</td>
<td>19</td>
<td>89% (2)</td>
<td>ASTRO criteria [10]</td>
<td>0</td>
<td>14%</td>
<td>0</td>
<td>100% (grade 2)</td>
</tr>
</tbody>
</table>

Ref, reference; GU, genitourinary; pts, patients; BRT, brachytherapy; ADT, androgen deprivation therapy; BRFS, biochemical recurrence-free survival; GI, gastrointestinal; ED, erectile dysfunction; LDR, low dose rate; HDR, high dose rate; NR, not reported.

³ In 7/11 cases: biochemical non-evidence of disease (bNED), in 3/11: PSA level continuously rose after salvage HDR-BT; 1/11: biochemical failure.
impotence and severe perineal pain in 73%, 67%, 72% and 8%, respectively. Rates of rectal injuries (fistulas) ranging between 1% and 3% have also been reported, especially in the salvage setting (Table 4). The technology of cryoablation devices has been improved, and the development of new-generation real-time ultrasound probes as a guide for freezing ablation allows safer and more precise treatments than in the first experiences [76]. Methods to reduce the unacceptably severe urinary toxicities (e.g., urethra-sparing techniques performed by urethral warming catheters and thermocouplers) carry a not negligible risk of excluding cancer foci in the prostate gland, particularly at the apex region, from ablative freezing doses. Moreover, a single course of cryotherapy is often not sufficient and multiple sessions are needed, causing a significant increase in morbidity, especially regarding sexual dysfunctions (>90% of treated patients [77–79]).

In conclusion, at present there is no robust evidence in favor of cryotherapy in the salvage setting after radiotherapy failure.

4.4. High-intensity focused ultrasound (HIFU)

HIFU is a local treatment causing tissue ablation by intense ultrasound waves with focused heating of the targeted region. The HIFU technique in different tumor sites has been the object of experimental studies for 50 years, principally involving the liver. In the prostate, HIFU was originally proposed for benign diseases, but was then rapidly introduced as a non-invasive option for PC patients with a definitive or salvage intent [80–84]. Different biochemical (decreasing PSA) and pathological (high rate of negative biopsies or negative specimen of SRP performed after HIFU) evidences of the efficacy of HIFU have already been published [85,86].

HIFU shares with other salvage local therapies the limits of the heterogeneity in the definition of PSA failure in the published studies; these limits are even more evident for salvage HIFU series. Globally, data on about 200 patients treated with HIFU as salvage treatment after EBRT are available (see Table 5). Crouzet et al. [84] in the largest published experience of 290 patients, with the longest follow-up of 48 months—obtained 7-year cancer-specific and metastasis-free survival rates of 80% and 79.6%, respectively.

In the salvage setting, HIFU led to local toxicities much more frequently than when used as primary treatment [82,87]. Urinary incontinence (7–50%), late urethral strictures (7.8–36%) and recto-urethral fistulas (2–6%) are the principal side effects of salvage HIFU (Table 5). The rate of recto-urethral fistula after salvage HIFU was shown to be more common when EBRT was combined with brachytherapy [88,89]. In the series of Murat et al. [82], 11% of patients required the implantation of an artificial urinary sphincter, confirming the high rate of urinary side effects with the risk of re-intervention already shown by Zacharakis et al. [87]. Some authors recommend a bladder-neck incision before salvage HIFU in order to minimize acute urinary retention and bladder outlet obstruction [82,89,90].

It is worth noting that the assessment of toxicity is not consistently reported in the HIFU series, and various criteria are applied, so the real rates of late injury might be under-evaluated.

In conclusion, the evidence for salvage HIFU (and cryotherapy) in treating BF after RT remains limited.

In fact, the NICE Guidelines statement is that “...High-intensity focused ultrasound and cryotherapy are not recommended for men with locally advanced prostate cancer other than in the context of controlled clinical trials comparing their use with established interventions”; however, the same Guidelines recommend “clinical trials into comparative clinical and cost effectiveness of local salvage treatments such as cryotherapy and HIFU” [32].

4.5. External-beam radiation therapy (EBRT)

Studies on re-irradiation have been published for various tumors sites [91–93], but they have rarely been reported for intraprostatic recurrent PC, with principal series concerning the role of BRT (see Section 4.6).

Apart from the availability of other salvage treatments, several clinical, technical and anatomical reasons could explain this lack of data. Among them: elderly age of the majority of patients, frequent metastatic evolution, clinically evident or subclinical normal tissue damage due to the high doses of EBRT already delivered (at least 70 Gy).

However, the use of EBRT in this context has been theoretically considered and documented in a very limited group of patients. High doses of EBRT are needed to treat PC, as the presence of a dose–response effect has been well established [94]. Theoretically, re-irradiation up to significant doses could be effective in at least some patients with late intraprostatic recurrences. “Small field” RT to limited volume relapsing PC could reduce the tumor clonogen number and, as a consequence, prolong the progression-free interval. The concept of spatial cooperation between radiation and systemic therapy might also be attractive in this kind of clinical scenario [91]. The indication for such a local approach should in principle be based on the interval between primary RT and diagnosis of recurrent disease (early recurrence indicating low radiosensitivity), absence of radiation injury from the primary treatment, patient’s preferences, comorbidities and general conditions. EBRT re-irradiation may be realized with different technical solutions, including IMRT (nowadays largely available) and stereotactic body irradiation (SBRT), that can be realized with different machines, such as CyberKnife© units, modern Linac-based systems (True Beam©, RapidArc©, V-MAT©, Axesse©), Helical Tomotherapy© or VERO© [91,95,96].

SBRT is particularly interesting, as it allows the reduction of the safety margins around the target (thus minimizing the exposure of the previously irradiated surrounding normal tissues) and hypofractionation, which is very often used when stereotactic techniques are employed, and that could be of
particular value for PC considering its low alpha/beta ratio [97].

Recently, a couple of reports on stereotactic prostate re-irradiation have been published [98,99]. Vavassori et al. [98] reported the preliminary results on six patients treated with CyberKnife SBRT (30 Gy in 5 fractions over 5 consecutive days). Jereczek-Fossa et al. [99] updated this study: nine more patients were considered, and overall 15 patients with biopsy-proven isolated intraprostatic recurrence were treated with the same CyberKnife SBRT schedule; 6/15 also received systemic therapy. Complete biochemical response was registered in six out of nine patients treated with SBRT only (no systemic therapy), confirming the potential radiosensitivity of intraprostatic recurrence. The pattern of failure was predominantly out-field (four out of five events). Actuarial 3-year progression-free survival was 22%. Interestingly, no acute or late rectal toxicity was registered. Urinary toxicity included five acute events (only one grade 3) and three late events (only one grade 3). The authors concluded that CyberKnife re-irradiation using 30 Gy/5 fractions is a feasible approach to isolated intraprostatic recurrence, offering excellent in-field tumor control and a low toxicity profile. Similarly, no late toxicity was registered in another study, after 9 months follow-up in two PC patients re-treated with helical tomotherapy, with a biochemical response observed in one of these patients [100].

Partial re-irradiation has also been proposed with the advance in molecular imaging and radiation treatment planning and delivery [101]. This concept, based on the limited multifocality of recurrent PC, could be of particular interest as it potentially allows better sparing of the surrounding healthy tissues [101,102].

Effective local therapy might reduce the burden of the systemic therapies usually given to patients with recurrent PC.

In conclusion, EBRT re-irradiation is not a standard and has rarely been used as salvage treatment for locally relapsing prostate cancer (1.9% of the 438 patients initially treated with radiotherapy considered by the CAPSURE study [8]). This option should be considered only in very selected cases. The prospective collection of data on these treatments is strongly advised, even if a formal perspective trial is difficult to imagine because of the small number of potential candidates.

### 4.6. Brachytherapy (BRT)

Even if BRT is a well-established treatment option for low-risk and, in selected cases, intermediate-risk PC patients [33], only a few experiences have been published about its use for the treatment of post-RT intraprostatic relapse. The first studies were published in the 1990s [103,104], but only recently has BRT been progressively and more extensively employed in this particular clinical setting. The dose delivered – either with $^{125}\text{I}$ or $^{103}\text{Pd}$ – varied between 108–170 Gy and 90–170 Gy, respectively, and the type of source did not appear to be related to the outcome, even though a direct comparison between the two sources in the salvage setting has never been performed. Table 6 shows clinical outcomes and toxicity of salvage BRT [103–114]. However, some biases could surely affect the results and the possibility of making conclusions about efficacy and safety of salvage BRT, also because of the different definitions of BF used in the published studies, and the use of neoadjuvant and/or adjuvant hormonal therapies that is not always clearly reported. In general, despite these limitations, published 5-year biochemical disease-free survival (bDFS) rates range from 20% to 87%. The number of patients enrolled in the studies is often limited (13–49), with only five studies presenting results from >30 patients, and only three of these five reports presenting mature results with a median follow-up >60 months [109–111]. In these three studies, a total of 117 patients were enrolled, accounting for 40% of the patients treated by salvage BRT. After a median follow-up of 64–108 months, the reported 5-year bDFS ranges from 20% to 64%. Burri et al. [110] also reported data about the 10-year bDFS, with an interesting rate of 53% (median follow-up: 86 months). It should be noted that in their study, 84% of patients also received ADT at the time of salvage BRT.

Usually, BRT has been delivered using LDR techniques, but two studies have been published (in 2007 and 2012) about the use of HDR–BRT [113,114]. Jo et al. [113] treated 11 patients with 2 fractions of 11 Gy: they reported 7/11 cases of biochemical non-evidence of disease (bNED), 3/11 patients presenting PSA level continuously rising, and 1/11 patients showing a biochemical failure. These authors reported no G3–G4 toxicities, but they did not give information about the length of the follow-up time. Lee et al. reported their experience with 21 patients treated with 6 fractions of 6 Gy: the bDFS rate was 89%, but the median follow-up was only 19 months and the data on the bDFS were calculated at 2 years. Moreover, 52% of patients received adjuvant ADT [114]. Toxicity was acceptable, with no rectal toxicity, 14% rate of G3–G4 urinary toxicity, and 100% rate of G2 erectile dysfunction.

Table 6 shows a summary of the complications reported in the studies. Even if the gastrointestinal or genitourinary complications were the most common types, not all the studies give information about safety. The incidence of G3–G4 genitourinary and gastrointestinal complications ranges from 0% to 47% and from 2.7% to 24%, respectively. Erectile dysfunction rates were high with salvage BRT in two studies at 85% [110] and 100% [115], but much lower in another recent study, at 13% only [114]. In general, data about sexual dysfunction is very rarely reported in the available studies, and it is impossible to reach a definitive conclusion about this issue.

### 5. Conclusions

The rate of BF after curative EBRT for PC is not negligible and should be defined following the consensus definition of nadir + 2 ng/mL (ASTRO “Phoenix” definition). The
prescription of several MRI sequences and of TC–PET with radiolabeled choline is increasingly frequent in these clinical situations, but no single diagnostic modality could be considered as a standard to detect early local recurrence after EBRT. Moreover, prospective data collection is needed to clarify their efficacy in distinguishing between local and distant relapse.

Furthermore, in most patients systemic progression occurs despite local salvage therapy, probably because of micrometastatic disease outside the prostate and pelvis that is missed by the available diagnostic tools. Thus, to date, androgen deprivation is the most common management option in the salvage setting after curative RT, but its deleterious side effects, especially for long-term schedules, should be carefully considered.

If successful, local therapy could minimize the burden of the systemic therapies usually prescribed to patients with recurrent PC. No data exist on the best schedule and timing for associating a systemic therapy with the local treatments.

Several reports on the results of local approaches for intraprostatic failure after EBRT (prostatectomy, HIFU, cryotherapy, re-irradiation) have been published. Considerable limitations can be found in these reports: retrospective nature, small number of cases, heterogeneous criteria for toxicity and tumor outcome reporting, and no information on follow-up and/or on some relevant endpoints (for some of these reports). Moreover, no standard doses or protocols are available, and only some patients receive combined therapies (e.g. local treatment and ADT). At present no firm recommendations can therefore be made. Meanwhile, perspective collection of outcome data on the few selected patients treated with local treatment modalities is strongly suggested.

Ideally, salvage therapy must be tailored to the initial tumor features, PSA kinetics and patient conditions and preferences.

Most probably, SRP can represent a viable option in the case of fit, motivated patients with biopsy-proven intraprostatic failure of low- to intermediate-risk cancer with no evidence of extraprostatic disease and acceptance of erectile dysfunction. However, most of the patients treated with primary EBRT have been previously excluded and/or are not suitable for surgery because of age or clinical reasons; previous irradiation could affect the feasibility and safety of SRP, which is often offered only by high-volume urology centers. Early diagnosis and appropriate selection of the patients remain the key factors to obtain better outcomes and lower intraoperative complications, bleeding or rectal injuries.

Alternative local salvage therapies are currently reserved for highly selected patients, but their efficacy and safety should be carefully evaluated and no conclusive statements may yet be made.

The distinction between isolated local and distant metastatic failure is crucial: future developments in imaging modalities, in conjunction with PSA kinetics, will possibly allow a better selection of patients based on the type and the behavior of the intraprostatic relapse.

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