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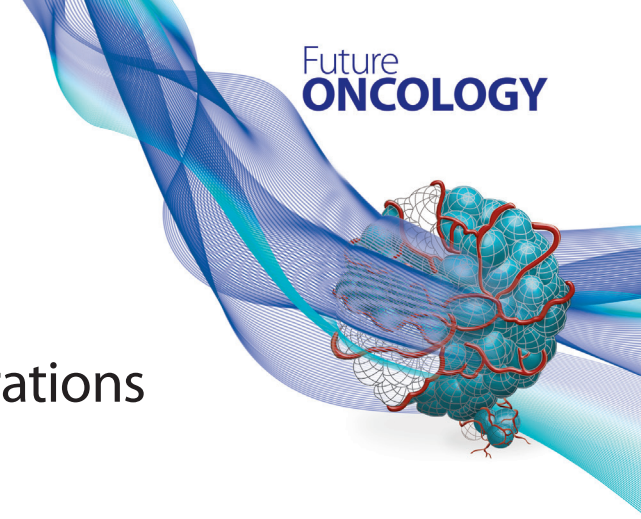

Early salvage radiation therapy post-prostatectomy: key considerations

Alessandro Morlacco[1] & R Jeffrey Karnes*[,1]

Post-prostatectomy radiotherapy (RT) is commonly employed to maximize oncologic outcomes in patients with pathologic adverse features (adjuvant RT) or to treat men with prostate-specific antigen or local recurrence after initial observation (salvage RT [SRT]). Randomized controlled trials have been unable to compare adjuvant RT versus SRT; however, there is growing retrospective evidence that observation and early SRT (eSRT) may be a suitable. The issue of patient selection is crucial; several clinical tools and some newer biomarker-based tools might help in this process. Moreover, the optimal prostate-specific antigen threshold for eSRT, the RT dose, the irradiation field and the use of hormonal therapy are still open questions. In this article, we review the current literature on eSRT and provide some insights on what's happening for the future.

First draft submitted: 22 April 2016; Accepted for publication: 20 June 2016; Published online: 8 July 2016

KEYWORDS
• adjuvant • biomarkers • early salvage • predictive models • prostate cancer • prostatectomy • radiation

Introduction: the clinical context

The optimal indication and timing for post-operative radiotherapy (RT) is still an unresolved issue to many. Post-radical prostatectomy (RP) radiation therapy is a commonly used adjunctive measure to maximize local control and long-term oncologic outcomes, but it may represent a source of added cost and morbidity.

The American Society for Radiation Oncology [1] and American Society of Clinical Oncology [2] guidelines suggest 'discussing' adjuvant RT (ART) with men who have adverse pathologic features at RP, including seminal vesicle invasion, positive surgical margins or extraprostatic extension. As the guidelines emphasize, patients should be informed of the potential reduction in the risk of biochemical recurrence (BCR), local recurrence and clinical progression, but also of the uncertain impact of ART on metastasis-free survival and overall survival (OS). The National Comprehensive Cancer Network (NCCN) guidelines [3] provide similar recommendations, but adding that observation may be appropriate after RP. Finally, EAU guidelines [4] are more explicit in listing two different options: immediate ART after recovery of urinary function or observation followed by salvage RT in the case of BCR, before the prostate-specific antigen (PSA) exceeds 0.5 ng/ml.

Adjuvant and salvage are currently the main modalities for RT administration after RP. Besides dose and field, which often overlap, the key differences between these two are the timing and oncological intent. In a modern definition, ART is commonly given with a post-operative undetectable PSA (or <0.2 ng/ml). However, the true timing of ART is more variable: some consider ART within the first three months after surgery (a definition frequently used in research); while many others wait until urinary function has stabilized, provided that PSA is still undetectable. Salvage

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RT (SRT) is the administration of RT in the setting of BCR or local recurrence in the absence of distant metastatic disease.

The definition of BCR has been matter of debate: while the 0.2 ng/ml threshold is currently accepted by most physicians, some studies have proposed the use of higher cut-off values, as they might be more accurate in predicting the risk of long-term clinical progression. Stephenson *et al.* [5] have proposed a 0.4 threshold for general use, but the author themselves acknowledge that the value might not be sufficiently sensitive when salvage local treatments are under consideration. On the other side, the use of ultrasensitive PSA essays (LOQs of 0.01 ng/ml or less) may lead to different definitions of BCR. Sokoll *et al.* [6] suggested that in men with a 'conventional' PSA value less than 0.1 ng/ml after RP, a threshold tenfold lower (0.01 ng/ml) might be helpful in stratifying men more or less likely to future BCR, predicting long-term BCR-free survival rates. Since these works focused on prediction of future BCR and not in redefining BCR itself, the impact of these findings on the administration of early SRT (eSRT) is still unclear. Regardless, today eSRT definition applies to SRT when administered at very low PSAs (from 0.1–0.2 to 0.5 ng/ml), although the exact meaning and the biological significance of 'very low PSA' is far from being universally shared, as will be discussed further.

Adjuvant versus salvage therapy: what's the evidence?

The greatest advantage of SRT is the potential avoidance of overtreatment, and its cost and morbidity in a relevant number of men. Indeed, a substantial proportion of patients with adverse pathologic features will not recur after surgery: in the main randomized clinical trials comparing ART versus initial observation [7,8], half of observed men were free of BCR at 5 years (i.e., potentially 50% overtreatment rate) and around a third were free of BCR at 10 years [7]. As mentioned, three landmark randomized trials (EORTC 22911 [7], SWOG 8794 [8] and ARO 96-02/AUO AP 09/05 [9]) provide the highest level of evidence for ART benefit with regard to BCR, but the cause specific and OS benefit shown in the SWOG trial was not confirmed in the EORTC/ARO trials. Despite the valuable insights provided by these trials, none of them was aimed at addressing the question of ART superiority over eSRT, due to some inherent problem in RT timing, aim definition and homogeneous treatment: in two of them (EORTC and SWOG) one third of the patients had a detectable PSA at the time of ART administration; while SRT was not administered to all of the patients with BCR (in the EORTC, only 56% of the patients with recurrence eventually underwent SRT). Even more importantly, a significant number of patients (40% in the EORTC and 41% in the SWOG) underwent SRT when a clinical or symptomatic loco-regional progression was already present: a more advanced stage in the long natural history of recurrent disease [10]. On the other hand, adjuvant radiation is not exempt from potential toxic effects: the SWOG trial reports a 23.8% of toxicities (including rectal and urinary-associated adverse events), compared with a 11.9% in the observation arm [11]. The potential impact of ART on functional outcomes is a particular concern: according to a single-center series by Suardi *et al.* [12], patients treated with ART had a 1.6-fold higher risk of incontinence. Finally, in a Cochrane review summarizing the results of the three trials, better outcomes were seen in the observation arms of all the studies [13].

Current evidence for eSRT

Most of the evidence regarding eSRT comes from retrospective studies. Moreover, a common limitation of these studies is the use of subsequent BCR as an outcome for sRT efficacy: longer follow-up and analysis of 'hard' clinical outcomes (clinical progression, cancer-specific survival and OS) are needed to confirm these results.

A recent review by Pfister *et al.* [14], which included ten retrospectives studies (1212 patients), examined eSRT. Although the authors did not directly compare SRT to ART, they reported good long-term outcomes for SRT, with an overall 5-year biochemical relapse-free survival (BRFS) of 71% (range: 48–81.8%). Only 6.7% of the patients underwent concomitant androgen deprivation therapy. Of interest, these data show an almost linear association of lower PSA values at SRT and better BRFS outcomes. A 0.5 ng/ml PSA cut-off may be established, even if an association between lower PSA and better outcome can be seen in some studies [15,16]. As far as toxicities are concerned, a low rate of grade 3 and 4 events was observed (0.3–1.6% for gastroenteric toxicities and 1–6% of genitourinary toxicities).

Briganti *et al.* [17] examined a multi-institutional cohort of 890 pT3pN0, R0/1 prostate

cancer men who underwent ART or observation ± eSRT (PSA <0.5 ng/ml), compared using a propensity-score matched analysis. No differences in 2- and 5-year BCRFS were observed. Of note, no patients received neoadjuvant or adjuvant hormonal therapy in the series. This study, despite its obvious limitations linked to the possible presence of unknown confounders and not accounted for in the matching model, suggests a substantial comparability between ART and timely administration of SRT.

Patient selection & RT timing: conventional tools

Refining patient selection for post-RP treatments is an important goal, and multiple tools have been developed to predict the risk of recurrence after RP. Unfortunately, such tools do not have specific validity in choosing who is going to benefit from post-operative therapy such as ART compared with observation ± eSRT. As such, they must be applied indirectly in this context. Nevertheless, clinically based scores, like the CAPRA-S score [18] and the Stephenson post-operative nomogram [19], are widely used in post-prostatectomy decision-making.

Choosing the right patients for adjuvant therapy or observation ± eSRT is crucial. Abdollah *et al.* [20] conducted a retrospective analysis of a single-center cohort of 1049 patients with adverse pathologic features (positive margins, extracapsular extension, seminal vesicle invasion, pT4 stage, nodal invasion) after RP and extended lymph node dissection. The authors reported that ART did not improve OS and CSS in patients with only one adverse risk factor, but did significantly improve survival in patients with two or more of the following risk factors: pGS ≥8, stage pT3b/4, and positive lymph node count >1. The authors also provide a nomogram that could be used in clinical practice. The results of this investigation suggest an explanation for the overall lack of benefit observed in the ART trials, given that only a subset of patients with higher risk features seems to benefit significantly from ART. Additionally, this study shows that patients with pathologically positive nodes (not included in any of the previous ART randomized controlled trials [RCTs]) might indeed benefit from ART. Of note, the RT dose received by patients in this study was significantly higher than in the RCTs (70.2 vs 60 Gy). The inclusion of a large group (37.7%) of node positive patients and the unstandardized use of both ART and hormonal therapy (41.6% of the total patients, with a significant difference between the ART and non-ART groups) plus nonseparation of pT3b from T4 are the main sources of criticism to this study, but also a demonstration that no real 'standards' exist.

Besides the ART/SRT choice, the indication and correct timing of SRT are other open issues. In other words, should we administer SRT to all men with BCR? And what PSA value should we consider 'significant' in order to pull the trigger?

Currently, it is clear that not all men with BCR will ultimately develop a clinically evident recurrence (22.9–37%) [10,21], and even fewer will die from their disease (5.8% with a median follow-up of 6.6 years after BCR, in a cohort including >90% of pGS 6 and 7 patients) [21]. Nonetheless, timely SRT provides a chance of cure for patients with an increasing or persistent PSA after RP. However, patients with a high risk of progression need early and aggressive salvage treatment. Trock *et al.* [22] demonstrated that salvage RT administered within 2 years of BCR was associated with a significant threefold increase in prostate cancer-specific survival relative to those who received no salvage treatment. This benefit remained significant after adjustment for pathological stage and other prognostic factors. The decision for eSRT versus observation in a man with BCR should, again, come from a discussion examining the potential drawbacks of RT versus the risk of cancer progression. Most men with longer PSA doubling times (>12 months) and favorable features at RP can in fact be observed [4].

A specific nomogram based on pathological features at RP (pathological Gleason score, extraprostatic extension, seminal vesicle invasion), time to BCR, preoperative PSA, PSA level at BCR and PSA DT has been developed by Brockman *et al.* [23] and showed a good accuracy (AUC: 0.763) in predicting prostate cancer mortality in men with BCR. PSA DT, indeed, is not strictly necessary in this nomogram: an accuracy of 0.754 was seen without this information, thus simplifying its application in clinical practice.

As far as the SRT timing is concerned, the idea of a 0.5 ng/ml maximum PSA threshold is generally accepted [14]. Some studies, however, showed a small but increased benefit for even lower PSA levels [15,16]. Hopper *et al.* [24] suggested that, in the era of ultrasensitive PSA, a lower threshold for SRT administration would be advisable and linked with better outcomes. We believe that a

balanced perspective on this subject could be provided by a recent paper by Fossati *et al.* [25]: a multicenter collaboration of 716 pN0 patients with undetectable post-operative PSA who underwent eSRT for PSA recurrence (PSA detectable within two or more determination but ≤0.5 ng/ml). Overall, each 0.1 ng/ml increase of PSA was associated with a 3% more risk of BCR at 5 years, but there was a significant interaction between pre RT PSA levels and the other known prognostic factors: after stratification for pathologic prognostic features (pT, GS, margin status), patients with at least two risk factors (pT3b/pT4 disease, pathologic Gleason score ≥8, and negative surgical margins) had a 10% increase of 5-year BCR rates for each additional 0.1 ng/ml, while men at lower risk experienced only a 1.5% increase. In men with significant risk factors, eSRT conferred better cancer control when administered at the very first sign of PSA rise. A considerable number of patients included in this series, indeed, received SRT for PSA values in the detectable range (>0.1 ng/ml), without waiting for the 0.2 threshold conventional defining BCR. The use of ultrasensitive PSA might very well bring down this 'detectable range' definition and foster an even more timely administration of SRT in patients at high risk of progression. However, the true clinical benefit of SRT administration for PSA values in the ultrasensitive detectable range is still largely unknown, and future studies might clarify this issue.

Together, these findings confirm an intuitive principle: it's important to contextualize the pre SRT PSA with the tumor features and administer SRT in a truly 'early' fashion in higher risk patients.

PSA doubling time (PSA DT) has been identified as another important prognostic parameter for systemic progression [26,27] and cancer-specific mortality [23,28] in patient with BCR. Even if there's agreement not to rush the administration of SRT in men with a PSA DT longer than 12 months [4,21,29–30], a cohort analysis of 635 men [22] showed more benefit for salvage RT when the PSA DT is less than 6 months, while another study of 519 men [31] reported a mortality reduction for both men with PSA DT <6 months and PSA DT ≥6 months. None of these studies, anyhow, addressed this issue in the setting of eSRT, and more data are clearly needed to provide a reliable answer to this question.

The role of PSA DT for ultrasensitive PSA essays is still uncertain. According to Seikkula *et al.* [32], who tried to correlate conventional PSA and ultrasensitive PSA, there was a poor to fair agreement between conventional PSA DT and ultrasensitive PSA DT, and there is no evidence that the benefit of ultrasensitive PSA DT provides benefit supporting decision making in the setting of post-RP patients. The average number of readings for determining ultrasensitive PSA DT was 4, but no 'optimal' number was determined. The accuracy of uDT improves when it approaches the traditional PSA threshold of 0.1 ng/ml.

As a common limitation, these newer studies on optimal PSA thresholds for eSRT focus on BCR as their only outcome rather than more reliable survival end points. Due to the relative novelty of this approach, indeed, it's quite difficult to find homogeneous and large cohorts of eSRT treated patients with long follow-up. As a consequence, the true association between PSA levels at eSRT and long-term 'hard' outcomes (systemic progression, CSS, OS) is still uncertain.

Patient selection for eSRT: newer tools

• Imaging

The role of imaging in eSRT is somewhat controversial. The current EAU guidelines state that imaging before SRT be done only in cases it can significantly change management. Consequently, in the setting of eSRT imaging is generally not recommended in all patients, unless there are specific concerns about possible systemic spread. Most current eSRT studies did not univocally require imaging studies before treatment. However, research has been focusing on two main imaging techniques in this setting: MRI and PET/TC.

MRI

Endorectal-coil MRI with contrast enhancement + TRUS have been evaluated in a population with median PSA 0.59 ng/ml (range: <0.1–13.1) after RP. Local recurrence was identified in 132 patients, with 124 (94%) detected on e-coil MRI, for an overall sensitivity of 91% and a specificity of 45%, while or patients with a PSA <0.4 ng/ml the sensitivity of MRI was 86%. On the other hand, Liauw *et al.* [33] reported a sensitivity of only 13% in men with PSA level <0.3 ng/ml. A recent review exploring the use of MRI in the setting of BCR does not provide a definitive answer as to whether MRI can be useful in clinical practice within

PSAs considered in the eSRT [34] ranges. More research is clearly needed in order to define the possible use of endorectal coil multiparametric MRI (with at least dynamic contrast-enhanced and T2-weighted MRI, and possibly diffusion-weighted imaging) in the definition of local targets for RT.

PET/CT

PET/CT is intensely studied in the setting of recurrent disease. ^{18}F-choline and ^{11}C-acetate PET/CT have been compared in detecting local residual disease in men with BCR (<1 ng/ml, median: 0.3) after RP [35]. Overall, 55% of studies were positive, but they still cannot yet be recommended as a standard diagnostic tool in for this subset of patients. More recently, the use of ^{68}Ga-PSMA PET/CT has been proven efficacious in evaluation of men with BCR (PSA ≥0.05 and <1.0 ng/ml) after RP [36]. Overall, the scan detected and localized a lesion in 54% of the patients, with a diagnostic yield directly correlated with PSA values. Interestingly, the exam identified lesions even in patients with PSAs <0.5. This ability of detecting lesion at low PSA levels and to localize them in the prostatic fossa, in the pelvic lymph node area and outside has potential implication in defining eSRT targets and deserves further evaluation. Similar results (PET/CT positivity in 44% of men with PSA <1) have been observed by Verburg *et al.* [37], who also identified higher PSA levels and shorter PSADT as independently associated with scan positivity, and extrapelvic metastases, a potential step towards a more tailored application of the ^{68}Ga-PSMA PET/CT itself. Finally, in a population of ^{18}F-choline negative patients, ^{68}Ga-PSMA-PET/CT in revealed a detection rate of 28.6% for PSA levels of 0.2–1 ng/ml [38]. Further studies will define the precise clinical indication of this promising technique and its value in eSRT candidates.

• Biomarkers

More recently, several genomic tests have been developed with the aim of improving post-RP outcome predictions and personalizing the indications for adjuvant therapies.

The use of a 22-RNA biomarker panel genomic classifier (GC) known as Decipher®, (GenomeDx) has been reported to better prognosticate or risk-stratify men in the post-RP setting. In a work by Den *et al.* [39], the GC was tested in a population of 188 post-RP irradiated patients (ART or SRT) with regard to the risk of metastatic progression. The GC outperformed the CAPRA-S score in outcome prediction and, more importantly, identified patients who may benefit from ART versus observation with eSRT. In a two-group analysis, patients with low-level GC expression (<0.4) treated with either ART or SRT have a comparable five-year risk of metastasis, while men with higher levels of GC (>0.6) have a significantly lower risk of metastasis if treated with ART (80% hazard reduction in Cox models). This study has some limitations, linked with the retrospective analysis, the variations in selection criteria for ART versus SRT among patients and physicians and the nonstandardized use of ADT. The median PSA pre-SRT was 0.2, although the study was not strictly limited to eSRT patients. In spite of that, these results suggest the possible usefulness of a GC in personalizing the management of men with adverse pathology (pT3 and/or R1) after RP.

Focusing only on SRT treated patients, Freedland *et al.* [40] tested the ability of Genomic Classifier to once again predict development of metastatic disease. This report included 170 RP patients who received RT for BCR with a median follow-up of 5.7 years post-radiation, this study demonstrated a better performance of GC over clinical models for the outcome of metastatic progression (AUC: 0.85 vs 0.65 and 0.63 for the Briganti nomogram and CAPRA-S score, respectively). Risk reclassification, particularly in terms of 'downgrading' was also observed with GC: 39% of patients in the upper two tertiles of risk by Briganti were in the first tertile according to GC, and 97% of them remained metastasis free at follow-up. When CAPRA-S was compared with GC, the reclassification of intermediate–high-risk patients was as high as 49%. Of note, this study was not designed to address eSRT patients only (median PSA at RT 0.6 ng/ml), although in a subset analysis restricted to patients receiving SRT at PSA ≤0.5 ng/ml GC had an AUC of 0.79 vs 0.44 and 0.68 with Briganti nomogram and CAPRA-S score. Prediction of outcome post-SRT is crucial to define the need for further treatment, such as early chemotherapy or newer hormonal agents, which obviously should be reserved to patients at the highest risk of progression. A short follow-up and a relatively limited number of events are other important drawbacks of this study. These findings need to be validated in larger cohorts with longer follow-up, with survival as the

primary outcome or retrospectively applied to the prospective studies.

Ongoing research

The results of several ongoing randomized clinical trials comparing ART and SRT and addressing some specific aspects of SRT are eagerly awaited, in the hope they can provide more definitive answers to these important clinical questions: the RT timing, the role of concurrent use of ADT and the impact of these treatments on quality of life, sexual function, urinary and bowel function [41]. Some recently published results are already providing insights on some clinical questions about SRT.

• Concomitant hormonal deprivation

RTOG 9601 (NCT00002874), a Phase III RCT compared RT + placebo (64.8 Gy in 36 fractions of 1.8 Gy) vs RT + AAT (24 months bicalutamide, 150 mg daily) during and after salvage RT for elevated PSA (range: 0.2–4.0 ng/ml) after RP. Actuarial OS at 10 years was 82% for RT plus AAT and 78% for RT + placebo and a hazard ratio of 0.75 (95% CI: 0.58–0.98; p = 0.036), showing also a reduction in metastatic prostate cancer and in prostate cancer-specific death [42]. Of note, this trial recruited patients from 3/98 to 3/03 and is not specifically aimed at eSRT.

• SRT dose & toxicity

SAKK 09/10 (NCT01272050) compared the toxicities of 64Gy versus 70 Gy SRT (without hormonal treatment) in men with BCR (PSA ≤2 ng/ml) and without macroscopically identifiable recurrence after RP. The results did not show statistically significant differences in rates of gastrointestinal and genitourinary grade 2 and 3 adverse events, while the urinary symptoms scores were significantly worse in the 70 Gy arm. Besides these effects, data on efficacy will clarify the optimal RT schedule in this setting.

• Other ongoing trials

RADICALS RT (NCT00541047) [43], active in the UK, Canada, Denmark and Ireland is still recruiting patients (the target is 1250 patients for the mid-2016, with more than 1161 recruited as of 12/2015 [44]). The specific aim of this trial is to assess the timing of RT and the use of hormone therapy in conjunction with post-operative RT. Patients for whom the optimal RT timing is uncertain (one or more of: pT3/4, Gleason 7–10, pre-operative PSA ≥10 ng/ml, positive margins) are being randomized to Arm I (immediate RT) or arm II (early salvage RT in case of PSA failure). Moreover, patients requiring immediate RT and patients who eventually need early salvage RT undergo hormone therapy duration randomization before the administration of RT. Arm III patients will receive no hormone therapy, while Arm IV patients receive RT and short-term (6 months) hormone therapy with LHRH or bicalutamide and arm V receive RT and long-term (24 months) ADT with the same agents.

GETUG 17 (NCT00667069) is a French trial comparing ART + ADT (LHRH) and SRT + ADT in patients who have undergone surgery for pT3a, pT3b (or pT4 by reaching the bladder neck), or R1 disease, pN0 or pNx. The final results are expected for 2022. The preliminary results of GETUG 16 (NCT00423475), aimed at comparing the efficacy of SRT alone vs SRT + ADT (6 months course of goserelin) for patients with BCR after RP, showed a benefit in the SRT+ADT arm with regards to 5-year progression-free survival, but more mature survival data are needed [45].

The RAVES trial (NCT00860652) [46], active in Australia and New Zealand, includes R1 and/or pT3 patients has been closed to recruitment after inclusion of 333 subjects. However, due to the overall low event rate, it is considered unlikely that a clinically significant difference between the two arms will be seen. Conversely, the EORTC 22043-30041 trial was early terminated because of poor patient recruitment.

Conclusion

The optimal timing of post-operative RT does not have a clear-cut answer. ART seems to decrease the rate of subsequent BCR but this does not appear to be 'enough' for clinicians to endorse its universal use. Until higher level evidence is available, in an effort to balance cost, toxicity and oncologic control, initially observing a man with adverse pathology at RP is acceptable; retrospective evidence supports the use of eSRT in properly selected men. Risk-adapted strategies, using the available clinical models and, potentially, newer biomarker-based strategies, may improve patient selection and counseling.

Future perspective

Besides the indication and timing issue (ART vs observation with eSRT), there are still many unknowns in post-operative RT, such as dose, volume and use of hormonal therapy and

application to higher risk disease such as pN1. Many of these questions will probably receive a more precise answer from the ongoing trials. Unfortunately, as history repeats itself, several trials might be out-of-date since the very moment their results become available potential radiation and/or systemic therapies will also have advanced. For this reason, we believe that good quality retrospective evidence might have an important role in providing clinical answers. In the future, we certainly expect a continued role for surgery in the potential multimodal treatment of prostate cancer. There are certainly many treatments for advanced prostate cancer. A central issue moving forward is more concentration of personalized treatments. We will likely move away from a 'one-size-fits-all' strategy in prostate cancer management even in the post-operative settings mentioned in this article. Patients desire more precise answers to their clinical situation, rather than trusting 'generalized' statements, and a deeper knowledge of prostate cancer biology is expected to provide these answers.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

EXECUTIVE SUMMARY

- Adjuvant radiotherapy (ART) and salvage radiotherapy (SRT) are the two main modalities for radiotherapy. administration after radiotherapy.
- Randomized controlled trials have shown a benefit for ART versus initial observation in reducing biochemical recurrence (BCR) but unclear impact on survival, and did not address the issue of early SRT (eSRT).
- Retrospective evidence shows that eSRT is a feasible and safe option.
- Not all men with BCR need eSRT, and the decision requires a risk-adapted strategy.
- The prostate-specific antigen threshold for eSRT administration is debated, but patients at higher risk benefit from a timely approach (first BCR sign).
- Ongoing randomized controlled trials will provide more answers to key questions (ART vs eSRT, use of hormonal therapy).
- Clinical models and newer biomarker-based tools may help in:
  - Choosing between ART and observation ± eSRT;
  - Refine the indication and timing for eSRT.

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