Adjuvant versus salvage radiotherapy following radical prostatectomy: do the AUA/ASTRO guidelines have all the answers?

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Debate continues surrounding the indications for adjuvant and salvage radiotherapy as the published randomized trials have only addressed adjuvant treatment. Salvage radiotherapy has been advocated to limit significant toxicity to patients that would not have benefited from immediate adjuvant radiotherapy. The American Urological Association and American Society for Radiation Oncology guideline released in 2013 has since recommended offering adjuvant therapy to all patients with any adverse features and salvage to those with prostate-specific antigen or local recurrence. The suggested criteria is limited in its application as it potentially subjects patients with few adverse features to adjuvant therapy despite not qualifying as high risk according to established postoperative predictive tools such as the Kattan nomogram. This article reviews the indications for postoperative radiotherapy, limitations of the guideline and alternative prognostication tools for clinicians faced with biochemical or locally recurrent post-prostatectomy prostate cancer.

Keywords: adjuvant radiotherapy • oncological outcomes • postoperative radiotherapy • prostate cancer • radical prostatectomy • salvage radiotherapy

The efficacy of adjuvant postoperative radiotherapy (ART) after radical prostatectomy for patients with ‘high risk’ features has been demonstrated in three randomized controlled trials [1–3]. This has led the American Urological Association (AUA) and American Society for Radiation Oncology (ASTRO) to release in 2013 a joint guideline on post-prostatectomy radiotherapy to address the expanding body of evidence on this approach [4]. One of their recommendations was that ‘physicians should offer adjuvant radiotherapy to patients with adverse pathologic findings at prostatectomy, including seminal vesicle invasion, positive surgical margins or extraprostatic extension because of demonstrated reductions in biochemical recurrence (BCR), local recurrence and clinical progression.’ Salvage radiotherapy (SRT) was also recommended for patients with prostate-specific antigen (PSA) or local recurrence after radical prostatectomy in whom there is no evidence of distant metastatic disease with biochemical relapse defined as 0.2 ng/ml or higher.

However, despite these recommendations, debate continues over the timing and role of post-prostatectomy radiotherapy leading to the relatively low rate of utilization of adjuvant radiotherapy around the world [5–10]. Many argue that SRT should be regarded as the standard of care for high-risk patients due to the toxicity related to ART and the potential overtreatment of patients that may not develop biochemical disease recurrence [4]. The purpose of this article is to explore some of these controversies that have led to the poor adoption of guideline recommendations.

Is the consensus definition of biochemical failure (PSA > 0.2) clinically relevant?
The guidelines state that clinicians should define BCR as a detectable or rising PSA value after surgery that is ≥0.2 ng/ml with a second
confirmatory level ≥0.2 ng/ml. They also recommend that patients should be informed that the development of a PSA recurrence after surgery is associated with a higher risk of development of metastatic prostate cancer or death from the disease.

The three randomized trials of adjuvant RT have essentially shown a halving in the risk of biochemical failure with adjuvant radiotherapy but only one has shown a benefit in reducing the rate of distant metastases and survival (Southwest Oncology Group study) [11]. Ten-year follow-up of the European Organization for Research and Treatment of Cancer and arbeitsgemeinschaft radiologische onkologie trials, however, have both failed to show a difference in progression-free survival (PFS) or overall survival leading some to question the validity of biochemical failure-free survival as an endpoint influencing treatment recommendations [3,12]. It is possible that due to the very long natural history of prostate cancer that more than 10-year median follow-up is necessary. In both studies, death due to prostate cancer is relatively uncommon (<5% of cohort) though there is the suggestion that in the subgroup of positive margins patients (aged <70 in the Bolla trial), there may indeed be a PFS benefit from adjuvant radiotherapy treatment [3]. Alternatively, some argue that perhaps adjuvant radiotherapy is eradicating ‘harmless BCRs’ which is why no clinical PFS benefit is shown.

The natural history of PSA progression after radical prostatectomy has been well documented in multiple studies [13–15]. While it is true that almost all patients developing metastatic disease will have exhibited a biochemical failure, PSA level after BCR was not shown to be predictive of metastatic disease progression in many of these studies. Instead pathological Gleason score 8 or greater, time from surgery to BCR, rapid PSA doubling time, advanced tumor stage and elderly age were found to be predictive of progression to distant metastases and prostate cancer-related death [13–15]. Therefore, these factors need to be considered when making decisions about the significance of any BCR.

Are all patients with extraprostatic extension, surgical margin involvement or seminal vesicle involvement at high risk of recurrence?

Based on the adjuvant therapy trials, the AUA/ASTRO guidelines state that patients with pathologic T3 disease including seminal vesicle invasion or positive margins are at ‘high risk’ of recurrence with the randomized trials demonstrating a 5-year biochemical progression rate of between 40 and 56% in the surgery control arms. However, both the Southwest Oncology Group and European Organization for Research and Treatment of Cancer trial did not necessitate an undetectable postoperative PSA as an eligibility criteria and indeed, in the Southwest Oncology Group trial, a third of patients had a postoperative PSA of >0.2 indicating that many of these patients were receiving early SRT rather than true adjuvant treatment. In the era of ultrasensitive assays, is it fair to say that a patient with extraprostatic extension but clear margins and a postoperative PSA <0.01 is at ‘high risk’?

A much better approach is to use the Kattan nomogram which is the most widely utilized tool to risk stratify patients for disease recurrence post-prostatectomy [16]. It incorporates variables including surgical margin status, extracapsular extension, seminal vesicle invasion, lymph node invasion, primary and secondary Gleason score and preoperative PSA level to predict the 10-year biochemical-free progression rate [17]. The nomogram was validated in 5020 patients from three large high-volume referral centers with high concordance-index values up to 0.88. It has since been validated against other population groups in subsequent studies [18,19].

This nomogram is a reminder that high-risk prostate cancer is a complex, heterogeneous condition. A 64-year-old patient with a preoperative PSA of 5 and a pathologic T3a, Gleason 7 cancer with clear margins has a 10% risk of BCR. This can be compared to an 89% risk of recurrence in a 62-year-old patient with a preoperative PSA of 14 and found to have a Gleason 8 disease, a positive surgical margin and seminal vesicle invasion [20]. Therefore, some patients who fit the AUA/ASTRO guideline criteria for ART may receive relatively small benefit from radiation treatment and be unnecessarily exposed to potential side-effects from this modality. The guidelines provide clinicians with an overly simplistic approach to selecting patients for ART. We recommend referring to the validated nomograms that provide more comprehensive modeling to guide our risk stratification and patient selection, especially in those patients with an undetectable postoperative PSA.

Firas Abdollah and colleagues have highlighted that certain subgroups benefit more than others from adjuvant radiotherapy in two recent studies. The first was a single center study of 1049 patients receiving surgery alone or in combination with adjuvant therapy. A cancer-specific mortality benefit was seen only in patients with Gleason score ≥8, pT3b/4 disease or positive lymph node disease. A follow-up Surveillance Epidemiology and End-Results Medicare-linked database review of 7616 patients with adverse pathological features confirmed the findings from the earlier study [21]. These findings suggest that we reconsider the indications suggested by the AUA/ASTRO guidelines and reassess how we select patients who will receive the most benefit from postoperative radiotherapy.

Who & when to offer early SRT?

The guidelines state that patients should be informed that the effectiveness of radiotherapy for PSA recurrence is greatest when given at lower levels of PSA. What the guideline recommendations do not specify is what threshold of PSA should trigger the initiation of SRT; though in the body of the text they state that radiotherapy should ideally be started before the PSA exceeds 1 ng/ml. The guideline recommendation stems from research including the Christopher King systematic review of 41 papers looking at the timing of SRT after radical prostatectomy [22]. His recommendation is similar to the AUA guidelines stating that SRT should be given at the ‘lowest possible PSA’ and made the observation that there was an average 2.6% loss in biochemical relapse free survival seen for a 0.1 ng/ml increment of PSA level at the time of SRT. However, in his review, the average median pre-SRT PSA across all series was 1.1 ± 0.67 ng/ml with a range
of 0.25–3.7 ng/ml. As Dr King states in the discussion, the conclusion that SRT should be initiated at the lowest PSA level raises the practical question of what that PSA level is. Dr King conceded that this question was well beyond the scope of this study.

Recommendations that SRT be given at the lowest possible level can generate significant anxiety in patients exhibiting small rises in PSA using ultrasensitive assays following surgery (e.g., from 0.01 to 0.04 ng/ml). Patients should be counseled that at these very low levels, there is no proven benefit for starting SRT immediately and indeed there can be a strong rationale to wait to confirm a BCR and also to get a better feeling of the doubling time and hence aggressiveness of the disease. Obviously, each case needs to be individualized according to the original histopathological features, timing of any rise, individual function and patient wishes/anxiety. However, it is recognized that the AUA/ASTRO guideline recommended 1 ng/ml threshold is now routinely <0.5 ng/ml [23-25].

The past 2 years have seen the emergence of multiple predictive tools that aid the clinician in counseling patients on the likelihood of success with SRT following a BCR. Stephenson et al. published the first nomogram addressing SRT post-radical prostatectomy (RP) in an internally validated 1540 patient multi-institutional cohort [26]. SRT was initiated at a PSA level 0.2 ng/ml or higher at least 6 weeks postoperatively followed by a subsequent higher PSA level or a single PSA level 0.5 ng/ml or higher resulting in a median PSA level of 1.1 ng/ml (IQR: 0.6–2.2). A proportion of patients included in the validation model received pre-radiotherapy (pre-RT) androgen deprivation therapy (14%). They included multiple variables including pre-surgery PSA, pathological Gleason score, seminal vesicle invasion, extracapsular extension, surgical margin status, lymph node status, neoadjuvant androgen deprivation therapy, a persistently elevated postoperative PSA, PSA doubling time, pre-RT PSA level and radiation dose (cGy) to predict the 6-year biochemical progression-free probability. This model had a high concordance index of 0.69 and provided a long-awaited systematically developed tool to guide clinicians on selecting patients for SRT. However, the high median PSA level for this population meant that these findings were not necessarily applicable to patients receiving early SRT.

Briganti et al. released the first nomogram predicting the 5-year BCR probability in node negative patients receiving early SRT (defined as SRT commenced prior to pre-RT PSA levels rising above 0.5 ng/ml) that incorporated variables including surgical margins, pathological Gleason score, pathological T2–3 stage and pre-RT PSA level [20,27]. Validated in a multi-center 472 men cohort over a median follow-up of 48 months, they found that all these variables were significantly associated with BCR on multivariate analysis. This nomogram emphasized more weight on pathological T3b stage, Gleason 8–10 score and positive margin status. Pre-RT PSA level was included as a range from 0.05 to 0.5 ng/ml with a 0.4 ng/ml equivalent to pT3a status.

It is important that nomograms such as these are incorporated into patient discussions so that patients are counseled about the likelihood of being rendered biochemically disease free with SRT. This obviously needs to be balanced against the potential toxicity of the radiotherapy treatment. However, many patients exhibiting a biochemical failure following surgery are never offered SRT which was the case for nearly half of patients in the surgery arm of the European Organization for Research and Treatment of Cancer trial. According to the post-prostatectomy nomograms, it is rare to find a subgroup of patients receiving early SRT that do not have at least a 20% chance of being rendered biochemically disease free. Hence, we agree with the guideline recommendations that all patients exhibiting a biochemical failure should be offered SRT.

**What is the evidence addressing adjuvant versus early salvage treatment?**

Although there are currently no randomized trials to address this issue, several retrospective observational studies have provided evidence showing that salvage techniques can achieve a durable oncological response. Trock et al. at Johns Hopkins performed a retrospective analysis of 635 men with clinically localized T1–2 after radical prostatectomy and staging pelvic lymphadenectomy including 160 that received SRT alone and 78 with SRT and hormonal therapy with a median follow-up from diagnosis of recurrence of 6 years [28]. SRT was offered to patients found to have a single post-operative PSA measurement of 0.2 ng/ml or higher. They found a clinically significant reduction in cancer-specific mortality compared to those who did not receive salvage therapy (hazard ratio [HR]: 0.34; 95% CI: 0.17–0.69; p = 0.03) regardless of hormonal therapy.

Duke University published a 519 men study with a median follow-up of 11.3 years after PSA recurrence similar findings [29]. SRT, also initiated for post-RP PSA level of 0.2 ng/ml or higher, was found to improve all-cause mortality among patients with rapid PSA doubling time less than 6 months (adjusted HR: 0.35; 95% CI: 0.17–0.72; p = 0.004) or protracted PSA doubling time of 6 months or longer (adjusted HR: 0.60; 95% CI: 0.37–0.98; p = 0.04).

The Mayo Clinic presented findings from their larger 2:1 matched cohort study in a group of 2657 men post-RP that developed PSA failure [30]. SRT was defined as treatment initiated greater than 90 days post-RP. PSA recurrence was defined as 0.4 ng/ml and higher post-RP. SRT was delivered to 865 men and on multivariate analysis was found to lower the risk of local recurrence, defined as biopsy proven disease in the prostatic bed (HR: 0.13; 95% CI: 0.06–0.28; p < 0.0001) and metastatic progression (HR: 0.24; 95% CI: 0.13–0.45; p < 0.0001). All-cause mortality was not affected by SRT in this study (p = 0.48).

Several large matched-group analysis studies presented findings that questioned the oncological efficacy of SRT compared to ART. Ost et al. retrospectively compared adjuvant intensity-modulated radiotherapy to salvage intensity-modulated radiotherapy (offered after a PSA recurrence >0.2 g/ml) in matching 89 patients in each group according to preoperative PSA level, Gleason score and pathological T stage [31]. The ART group...
had significantly better biochemical PFS (bPFS) compared to SRT (3-year biochemical relapse free survival: 91 vs 79%; p < 0.05). Trabulsi et al. had similar results in their retrospective multi-center study of 192 patients with 6.1 years follow-up after radiotherapy for pathological T3–4 patients. They found a 5-year bPFS of 73% for ART and 50% for SRT (p = 0.0007) with both SRT and Gleason score of 8 or greater significant predictors of BCR on multivariate analysis [32].

Optimizing timing of ART has also provided further stimulus for the adjuvant and salvage debate. A SEER database analysis by Kowalczyk et al. of 963 pT3N0 patients receiving ART compared groups according to early (less than 4 months post-RT) to delayed (4–12 months post-RT) across outcomes of overall mortality, prostate cancer-specific mortality, bone-related morbidity, salvage hormonal therapy and intervention for urethral stricture [33]. Although delaying ART beyond 9 months reduced urethral stricture burden, therapy started less than 5 months postoperatively improved prostate cancer-specific mortality, while even earlier ART improved bone-related morbidity and salvage hormonal therapy rates. However, the lack of postoperative PSA levels for this study is a significant limitation given the possibility of that many of the delayed patients may indeed have been having salvage treatment.

Timing has been similarly investigated in SRT studies, with other groups reporting findings from SRT studies suggesting that survival outcomes may be improved by selecting patients at earlier points of recurrence. Maurizi et al. found in a retrospective unmatched study of 302 ART and 126 SRT patients who were treated for rising PSA after undetectable levels or persistently elevated levels post-prostatectomy that SRT patients had poorer bPFS than the ART group (5-year bPFS: 71 vs 49%; p < 0.0001) [34]. Importantly, pre-RT PSA level was the only predictor with a significant effect on BCR for the SRT group. Patients with a pre-RT PSA level of 1 ng/ml or less had significantly better bPFS than those with higher PSA levels (5-year bPFS: 61.8 vs 38.2%; p = 0.02).

Briganti et al. reported a large multi-centre retrospective cohort study of pathological T3 patients and/or positive surgical margins comparing adjuvant to early SRT for a detectable PSA less than or equal to 0.5 ng/ml (n = 890) [25]. The 5-year bPFS for ART (78.4%) and SRT (81.8%) did not reach statistical significance between the two groups on post-propensity matching (p = 0.9). Pazona et al. reported further compelling evidence that lower pre-RT PSA levels was associated with improved oncological outcomes with non-responders having a significantly higher pre-RT PSA level compared with responders (1.2 ng/ml vs 0.7 ng/ml) [35]. These results highlight the conflicting data around combined ART and SRT studies. Comparisons in these studies may have reflected patient selection with many men in the ART arm unlikely to have progressed to BCR given the large proportions that did not have a detectable PSA pre-RT.

Several recent systematic reviews have refocused attention on the importance of pre-RT PSA levels on oncological control in this group of patients. Dr King in a review article concluded on adjuvant and salvage RT techniques from 2013 that early SRT was a favorable alternative strategy to ART. Pfister et al. reported findings from a systematic review of 10 retrospective studies assessing early SRT defined as pre-RT PSA levels 0.5 ng/ml or less among patients with lymph node negative disease [36]. A pooled analysis of 886 patients yielded a mean 5-year bPFS of 71% (range: 48–81.8%) which is comparable to results from ART therapy studies. Another systematic review of 41 SRT studies found that pre-RT PSA (p < 0.001) and RT dose (p = 0.0052) were significant independent predictors of BCR after RT [22]. SRT patients with a PSA level of 0.2 ng/ml or less prior to treatment had a 5-year bPFS of 64% with an average loss of 2.6% bPFS for each 0.1 ng/ml PSA at the time of SRT (95% CI: 2.2–3.1). Several studies published after this systematic review also noted improvements in bPFS with pre-RT PSA levels below 0.28–0.3 ng/ml [24,37]. These findings have highlighted that the optimal timing for early SRT may in fact be lower than the 0.2 ng/ml cut-off recommended by the AUA/ASTRO guideline. This has been recognized and already included in the new nomogram proposed by Briganti et al. [27].

A notable concern of retrospective studies attempting this address this controversy is that men were often irradiated to the prostatic bed only and at low-to-moderate RT doses. A wider adoption of whole-pelvis radiotherapy to prophylactically treat the pelvic lymph-nodal area and/or a moderate dose-escalation may significantly modify the scenario in the near future.

**Expert commentary & five-year view**

Early SRT has emerged as an attractive alternative to adjuvant therapy, but we continue to rely on retrospective and level 2 cohort or case–control studies to guide our decision making. This is an exciting period in prostate cancer care and the opportunity is now open to further fine tuning the balance between cancer control and toxicity reduction. The greatest controversy is now improving individualization of patient care in those men who may need to consider post-operative radiation therapy, an issue which is inherently reliant on timing, careful monitoring of PSA levels in combination with the other recognized pathological risk factors. The current guidelines do not adequately support individualized care for post-prostatectomy men.

In response to the contradictory data on ART and SRT survival outcomes and lack of randomized trial data on the efficacy of early SRT, three randomized trials are aiming to provide improved guidance on the choice between ART and early SRT. The Trans-Tasman Radiation Oncology Group’s Radiotherapy – Adjuvant Versus Early Salvage is aiming to recruit 470 patients randomized to either ART (commenced less than 4 months post-prostatectomy) or early SRT (triggered by a PSA level of 0.2 ng/ml or greater) with at least one feature of positive surgical margins, extraprostactic extension or seminal vesicle involvement with an endpoint of BCR [38]. Post-operative PSA levels also need to be 0.1 ng/ml or less at recruitment. The UK Medical Research Council/National Cancer Institute of Canada Trials Group Radiotherapy and
Androgen Deprivation in Combination with Local Surgery trial is expanding on the focus to adjuvant hormonal therapy [39]. It is aiming to recruit 2600 patients to either immediate ART or early SRT after two consecutive rises in PSA level to a level above 0.1 ng/ml and then randomize to 6 or 2 months of hormone therapy or radiotherapy alone with an endpoint of cancer-specific survival. The third trial is GETUG-17, a multi-institutional European study investigating 718 patients randomizing patients with pT3–4, node negative disease with positive margins and undetectable PSA to ART with ADT or SRT with ADT. The end-point is a composite of clinical recurrence, BCR and death at 5 years. A promising meta-analysis is planned between the three trials upon completing follow-up that will hopefully provide the necessary insights to decide between these two therapies [40]. These randomized trials comparing adjuvant to early salvage radiation therapy will hopefully provide much awaited answers to this issue.

### Key issues

- Current guidelines define biochemical recurrence (BCR) as detectable or rising prostate-specific antigen value after surgery >0.2 ng/ml with a second confirmatory level >0.2 ng/ml.
- Long follow-up (median 10 or more years) is required to characterize metastatic and cancer-specific survival for prostate cancer recurrence.
- PSA level after BCR needs to be considered with Gleason score, time from surgery to BCR, rapid PSA doubling time, advanced tumor stage and elderly age when considering prognosis and postoperative radiotherapy.
- Risk factors including extraprostatic extension, positive surgical margin or seminal vesicle involvement need to be interpreted in combination with other variables, ideally using a validated predictive tool such as the Kattan nomogram.
- Studies comparing adjuvant to salvage radiotherapy (SRT) have shown biochemical survival benefit in commencing early SRT at lower pre-radiotherapy PSA levels, often lower than the figure recommended by the AUA/ASTRO guideline.
- Early SRT has been increasingly recommended at lowest possible PSA levels despite no proven benefit for starting SRT immediately on first PSA recurrence.
- New nomograms predicting survival after post-prostatectomy radiotherapy provided more tools to characterize patient prognosis and highlight the importance of offering SRT to all patients with biochemical failure.
- Shared-care decision making with the patient must include a discussion balancing the benefits of BCR control and potential treatment toxicity.
- Upcoming adjuvant versus early SRT randomized trials will provide new data to address the shortcomings of current evidence comparing these two modalities.

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