Editorial

# Who benefits most from early salvage radiation therapy after prostatectomy?

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We are grateful for the opportunity to provide commentary on the recent work by Fossati *et al.*, entitled "Impact of Early Salvage Radiation Therapy in Patients with Persistently Elevated or Rising Prostate-specific Antigen After Radical Prostatectomy" (1). The optimal post-operative management of patients with prostate cancer who undergo radical prostatectomy (RP) is unclear. In general, there are two strategies for approaching radiotherapy. Adjuvant radiation therapy (ART) typically refers to post-operative radiation in the setting of high risk pathologic features but with an undetectable post-prostatectomy PSA, where the presence of residual prostate cancer is suspected but unknown. In this setting, radiation is typically delivered within a few months of surgery once there has been adequate recovery of urinary function. In contrast, salvage radiation therapy (SRT) refers to post-operative radiation in the setting of a rising or persistently detectable PSA, indicative of active prostate cancer and may be delivered several years after the initial RP (2). However, it is important to note that these definitions lack consensus.

At least three randomized trials have demonstrated a benefit of ART for select men with high risk pathologic features following RP (3-5). SWOG 8794 was a trial of 431 men with either positive margins, extracapsular extension or seminal vesicle invasion after RP who were randomized to immediate post-operative radiation versus observation. At a median follow-up of 12 years, patients who underwent immediate post-operative radiation had a reduced rate of biochemical recurrence (BCR) and improved metastasis-free survival (HR 0.71) as well as overall survival (HR 0.72) (4). A confounding factor of this study is that approximately one-third of the patients had a detectable PSA following surgery. In the subgroup of patients with a detectable PSA, a metastasis-free survival benefit from radiotherapy was still observed, however the risk of metastasis or death was higher in men who received radiation with a detectable PSA compared to men who received radiation with an undetectable PSA. Finally, two similar randomized trials, EORTC 22911 and ARO 96-02, showed a biochemical progression-free survival benefit from ART but no differences in overall survival (3,5). Thus, despite level I evidence supporting at least a BCR benefit of adjuvant radiation, widespread adoption has not occurred.

Although several randomized trials have evaluated the role of ART, a similar level of evidence does not exist for SRT (although trials are currently underway). The natural history of a BCR after RP is well known to be heterogeneous, reflective of a broad range of underlying tumor biology. While some patients will develop metastatic disease, this is not inevitable (6). Many patients may have a more indolent course and never develop clinical progression or prostate cancer related death. This is particularly

**Table 1** Risk grouping system with corresponding 8-year MFS based on 925 patients who underwent SRT following RP (1)

| Risk group | Criteria | 8-year MFS |
|---|---|---|
| Very low risk | Undetectable PSA after RP, Gleason score ≤7, and tumor stage ≤pT3a | 98% |
| Low risk | Undetectable PSA after RP, Gleason score ≤7, and tumor stage ≥pT3b | 87% |
| Intermediate risk | Undetectable PSA after RP with Gleason score ≥8 | 81% |
| High risk | PSA persistence after RP with Gleason score ≥7 | 74% |
| Very high risk | PSA persistence after RP with Gleason score ≥8 | 62% |

MFS, metastasis-free survival; PSA, prostatic specific antigen; RP, radical prostatectomy; SRT, salvage radiation therapy.

important in older men where competing risks for mortality exist. On the other hand, some men with rising or persistently elevated PSA may have residual disease outside of the prostate bed despite negative imaging, making pelvic radiotherapy ineffective at controlling what was presumed to be a local recurrence. Despite these challenges, a variety of retrospective studies demonstrate a role for SRT as a potentially curative therapy in patients with BCR following RP (7-9). There is consistent data indicating a benefit of initiating salvage radiation with a lower PSA at the earliest sign of recurrence, preferably with a PSA <0.2 ng/mL (10,11). At present, even in the era of ultra-sensitive PSA assessments, it cannot be concluded that initiation of SRT at the earliest sign of PSA progression is equivalent to ART in those patients at high-risk for post-surgical BCR. Furthermore, aside from initiating SRT with as low a PSA as possible, exactly which subgroups of patients benefit most from early SRT is controversial.

The work by Fossati *et al.* contributes substantially to this ongoing debate by generating a risk stratification system based on additional clinical and pathologic features in an effort to determine who may benefit most from early SRT. In their study, they retrospectively analyzed 925 patients treated with SRT at multiple institutions between 1996 and 2009. All patients had pT2-pT4N0 disease at the time of prostatectomy and were subsequently found to have either a rising PSA (following a previously undetectable PSA) or PSA persistence (>0.1 ng/mL at 1 month following surgery). The median PSA at the time of SRT was 0.3 ng/mL, and the median time from RP to PSA recurrence was 20 months. Salvage radiation consisted of local radiation to the prostate/seminal vesicle bed to a median dose of 68 Gy in 1.8/2.0 Gy daily fractions. Three-dimensional conformal radiotherapy (3DCRT) was used until 2002, after which intensity-modulated radiation therapy (IMRT) was gradually phased in. The use of androgen deprivation therapy (ADT) with SRT was non-standardized and in all 30% of patients received ADT with SRT for a median of 18 months. Patients in this study were also followed for a median of 8 years.

A variety of clinical and pathologic data was then collected for the development of a prognostic tool to predict for the development of distant metastases following SRT. Regression tree analysis was performed first and identified three variables to stratify patients on. This was used to generate five distinct risk groups, which exhibited differing 8-year metastasis-free survival (MFS) rates (*Table 1*). Since the entire cohort received SRT, it was not possible to create a comparison with an observation group to determine a benefit of SRT. Instead, the authors tested for an association between pre-SRT PSA level and MFS in each of the 5 risk groups, as a surrogate to demonstrate a measurable benefit of SRT. On multivariable Cox regression analysis of the entire group, pre-treatment PSA level was associated with MFS as expected from prior studies. However, they found that the association between pre-SRT PSA and MFS varied among each risk group. In particular, patients in the low, intermediate and high risk groups were found to have a statistically significant improvement in MFS when the pre-SRT PSA was lower. This suggested that for patients in these risk groups, early administration of SRT was associated with improved cancer control. In contrast, for patients in the very low and very high risk groups, the risk of developing distant metastases did not significantly change based on the pre-treatment PSA level. Thus, in these two groups, a therapeutic benefit of SRT was felt to be unlikely. Finally, the authors note that the risk of late grade 2 or higher GI as well as GU toxicities in the very low and very high risk groups was approximately 10–20%, although this was not scored prospectively. There were no grade 4 or higher side effects reported.

Is this risk stratification system believable? Overall, the

 

3 identified risk factors (PSA persistence after RP, Gleason score and tumor stage) are logical and have been associated with recurrence risks in prior studies (8,12,13). The risk grouping system is able to account for the heterogeneous clinical behavior of BCRs, i.e., some BCRs are likely too indolent to benefit from SRT and some are at such a high risk for metastatic disease that SRT to the pelvis may not be beneficial. Therefore, there is likely truth in the proposed risk stratification system in terms of prognosis. However, as all patients received radiotherapy, it is unclear whether or not delivery of radiotherapy to the very low or very high risk groups did not impact outcomes, despite a lack of association between pre-SRT PSA and MFS. Would outcomes have been worse without SRT?

In particular, for very low risk patients, perhaps the need to initiate SRT at a lower PSA is less critical due to the indolent nature of growth of these tumors but with SRT nonetheless providing an equal chance for permanent disease eradication across all PSA levels. Similar to active surveillance, is there a cost to the patient of knowing they have a slowly growing but untreated cancer? Alternatively, could a lower dose of radiotherapy be used for this subgroup, as opposed to no radiotherapy? The answers are not obvious. Furthermore, in the very high risk group, it is important to recognize that the small sample size (65 patients, 7% of the cohort) likely limits the power to detect a difference in MFS. These men were also generally treated shortly after surgery and with very low PSA levels (median PSA of patients with a persistent PSA was 0.2 ng/mL), decreasing the potential effect size and further limiting the ability to detect a difference in outcomes. As such, the analysis of the very high risk cohort may simply have been underpowered.

A few additional caveats are worth noting. The primary endpoint of distant metastases was defined to include pelvic nodal failures, and pelvic nodal failures represented 40% of the events in the distant metastases endpoint. It does not appear that the pelvic nodal beds were irradiated, therefore could nodal radiotherapy have improved outcomes, particularly in the very high risk group? Certainly, the role of pelvic nodal radiotherapy for intact prostate cancer is controversial, and it is unclear from the available data in the study whether or not these nodal failures would have been included in standard nodal fields. RTOG 0534 is a multi-arm ongoing randomized trial evaluating the benefit of pelvic nodal radiotherapy in addition to prostate fossa irradiation during SRT and will help shed light on this issue. Furthermore, recent data supports a survival benefit of the addition of ADT with SRT (14). Could the addition of short or long courses of ADT have improved the benefit of SRT in the very high risk group?

As the above data was retrospective in nature, additional ongoing prospective trials will hopefully provide more conclusive findings. In particular, the Radiotherapy Adjuvant Versus Early Salvage (RAVES) trial is an ongoing randomized trial testing the hypothesis that observation with early SRT is not inferior to ART for men with pT3 disease and/or positive surgical margins following RP (15). Radiotherapy and Androgen Deprivation in Combination after Local Surgery (RADICALS) is another large, ongoing trial in the UK, Canada, Denmark and Ireland examining the optimal timing of post-operative radiation as well as the role of ADT when RT is delivered. Although these trials may not address all the questions raised by this study, they should provide high quality data that will contribute to the discussion. Novel imaging modalities may improve patient selection by identifying where the source of BCR is arising from. For instance, fluciclovine ($^{18}$F) PET/CT has shown promise in localizing areas of BCR when PSA levels are <1.0, both within the prostate bed and at distant sites (16). Finally, there have been major advances in our understanding of the genetic drivers of prostate cancer and the development of metastases. In the future, incorporation of genomic information, through commercially available tests such as Prolaris, Oncotype DX Genomic Prostate Score, Decipher and others, may help guide patient selection and personalize radiotherapy recommendations (17). In the meantime, the work of Fossati *et al.* provides additional predictive factors to help determine which patients may benefit most from early SRT until future prospective trial data matures.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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