Platinum Priority – Editorial  
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When Should We Pull the Trigger for Post–Radical Prostatectomy Radiotherapy?

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Short of a randomized controlled trial (RCT), the paper by Briganti and esteemed colleagues in this issue of *European Urology* provides the best current data to suggest that early salvage radiotherapy (eSRT) is comparable to adjuvant external radiotherapy (aRT) for men with pT3 prostate cancer after radical prostatectomy [1]. The authors are to be congratulated for putting together a large cohort of patients (N = 890) and a robust propensity-matched analysis to show that 2- and 5-yr biochemical controls are equivalent between these two treatment options. Briefly, they show 2- and 5-yr biochemical recurrence-free survival rates of 91.4% and 78.4%, respectively, in aRT versus 92.8% and 81.8%, respectively, in patients who had initial observation and eSRT at the time of relapse.

The strength of this work is in its multicenter cohort and tracking the observed plus eSRT group in comparison to the men who received aRT. In addition, the inclusion criteria were tight. In other words, the aRT group received radiation within 6 mo of when their prostate-specific antigen (PSA) level was <0.1 ng/ml and the eSRT group received the radiation when their PSA level was >0.2 ng/ml but <0.5 ng/ml. While this paper is not an RCT and some will be critical of this work, citing possible flaws and biases in the propensity-matching strategy and the lack of long-term follow-up, the results make sense and are plausible. This paper will help clinicians, like me, in the trenches to help patients with this difficult and important decision.

As I write this editorial, I just learned that the US Preventive Services Task Force will finalize its anti-PSA screening recommendations with a D rating [2]. I wonder how this may change things and how this will affect radical prostatectomy (RP), positive margins, and the issue of adjuvant versus salvage RT. If the D rating for PSA causes most medical insurers and governments to stop covering PSA testing, it will have a sobering impact. It may reverse the stage migration we have seen in the PSA era. We may be operating on more high-risk men and planning more aRT due to more unfavorable pathology, as but one consequence. Times remain very interesting in the prostate field!

Despite the possible future changes, currently we see a large population of younger, sexually active men with localized prostate cancer who are keen for a nerve-sparing RP. We have also seen a resurgence in popularity of RP as a result of the robotic technique and an overall increased dialogue about surgical technique and surgical experience [3,4]. Being enthusiastic for the nerve-sparing technique and sexual function rehabilitation postoperatively [5], many of these contemporary men are less likely to give blanket acceptance for aRT due to their concern for delayed or diminished sexual recovery. The data presented by Briganti et al are reassuring for these men and suggest that we can follow patients closely and pull the trigger for RT when their PSA levels are higher than the American Urological Association consensus definition of 0.2 ng/ml [6] and we are able to safely intervene before the PSA is >0.5 ng/ml.

One confounding variable that Briganti et al did not address is the troubling issue of benign increase in PSA level due to residual benign prostatic hyperplasia tissue remaining in situ after RP. In our zealous attempt to preserve neurovascular bundles, bladder neck tissue, and the distal urethral stump, surgeons sometimes leave some residual prostate tissue that can, over time, produce some PSA. In 2001, Amling et al classically showed that some men having a PSA level even at 0.4 ng/ml do not experience further

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progression [7]. Some patients have this smoldering PSA level that stays detectable but never seems to go high enough to definitively recommend SRT. In the case of the patients in this series, both groups (aRT and eSRT) were likely contaminated, with some patients with benign increasing PSA levels. Of the 225 men who received eSRT when their PSA level was >0.2 ng/ml but ≤0.5 ng/ml, some were radiated unnecessarily. However, it is still much less than up to one-half of the aRT group who received radiation but would never have experienced recurrence with observation. Because of my concern for radiating these patients with benign or smoldering PSA levels, I tend to wait a little longer for the PSA level to increase before radiating, especially if the postoperative pathology is equivocal. For a patient with a unifocal or small positive margin and/or the surgical Gleason sum is 7 and with an equivocal PSA rise of 0.2–0.4 ng/ml, I many times wait until the PSA level is >0.5 ng/ml before radiating, especially if the patient is keen on maintaining potency or regaining potency. With regard to aRT, sometimes complete continence is delayed >6 mo, so we cannot always follow the criteria of aRT used in this study. Longer follow-up in this series will be necessary to determine whether eSRT delivers the overall survival benefit that was seen by Thompson et al in the Southwest Oncology Group trial for aRT [8].

Three large, retrospective, single-institution series provide conflicting data on whether or not SRT as a single modality can prolong survival. In a series of 2657 RP patients with recurrence of increased PSA level who were treated at the Mayo Clinic, 856 (32%) received SRT [9]. On multivariate analysis, SRT significantly reduced the incidence of subsequent local recurrence (hazard ratio [HR] 0.13; 95% confidence interval, 0.06–0.28). However, SRT did not significantly decrease mortality compared to those not receiving SRT following biochemical recurrence (5- and 10-yr survival rates: 92% vs 91% and 70% vs 69%, respectively).

Conversely, a study from Johns Hopkins analyzed 635 patients who had either a biochemical or local recurrence following RP [10]. At recurrence, patients were managed with observation, SRT alone, or SRT in combination with hormonal therapy in 63%, 25%, and 12% of cases, respectively. Cancer-specific survival was significantly prolonged in patients who received RT, with or without hormonal therapy, compared to observation (96% and 96% vs 88% at 5 yr, and 82% and 86% vs 62% at 10 yr).

Finally, from my institution, RT appeared to prolong survival in a series of 4036 men who underwent RP at Duke between 1988 and 2008, regardless of whether the PSA doubling time was short or long [11]. This cohort included 519 men who had a biochemical recurrence and were fully evaluable. SRT was given, either alone or as part of a combined approach that included androgen-deprivation therapy (ADT), in 219 of these patients (37%). At a median follow-up of 11.3 yr, multivariate analysis demonstrated a significant decrease in all-cause mortality both in those with a PSA doubling time <6 mo and in those with a PSA doubling time ≥6 mo (adjusted HR: 0.53 and 0.52, respectively). Despite limitations inherent in these retrospective studies, the results provide reasonable evidence that SRT shortly after biochemical relapse may alter the natural history of prostate cancer.

Although not addressed by Briganti and associates, the addition of ADT to primary definitive RT benefits men with high-risk clinically localized prostate cancer as well as those with locally advanced disease. Two large randomized trials being conducted by the Radiation Therapy Oncology Group (RTOG) eventually should provide important information about the role of hormonal therapy in conjunction with SRT. RTOG 9601 (NCT00002874) and RTOG 0534 (NCT00567580) both include patients with persistent elevation of PSA after RP, as well as those with rising PSA. In RTOG 9601, there was a statistically significant improvement in freedom from PSA progression when adjuvant bicalutamide was added to RT compared with RT alone (57% vs 40%) and a statistically significant decrease in the incidence of metastatic disease (7% vs 13%). The actuarial overall survival rates at 7 yr were 91% and 86%, respectively, which did not reach statistical significance. However, there were too few deaths to permit a statistical comparison of overall survival. In addition, the trial used bicalutamide monotherapy, not a gonadotropin-releasing hormone agonist, an approach that is unconventional in the United States and in most of Europe. In RTOG 0534, patients are randomly assigned to RT alone to the prostate bed, RT to the prostate bed combined with neoadjuvant and concurrent ADT, or RT to the prostate bed and pelvic lymph nodes with neoadjuvant and concurrent ADT. The trial does not include an arm with RT to the pelvic lymph nodes without ADT. RTOG 0534 is currently enrolling patients.

Finally, a new recently approved biomarker may allow better decision making. A very accurate ultrasensitive PSA assay that measures PSA level down to 0.6 pg/ml was approved by the US Food and Drug Administration in 2011 [12]. In a large multicenter trial, it was shown that a low slope (<2.0 pg/ml per month) of rise during the first 3–20 mo post-RP (based on three values) predicted nonclinical recurrence. For RP patients with positive margins or high-risk features, this assay may help further inform our decision regarding postoperative RT.

**Conflicts of interest:** The author has nothing to disclose.

**References**


