Local salvage ablation therapy after radiation therapy for prostate cancer — are we there yet?

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The most common treatment for biochemical recurrence of prostate cancer after primary radiation therapy is androgen deprivation therapy (ADT).[1] Given that some patients may only have local relapse and given the adverse metabolic and bone effects of ADT,[2] local salvage options may warrant consideration in these patients.

In this issue of *CUAJ*, Nair and colleagues[3] report retrospective propensity score-matched analyses comparing salvage cryotherapy and high-intensity focused ultrasound (HIFU) against no local salvage therapy for recurrent prostate cancer post-radiotherapy. They found that salvage cryotherapy was associated with clinically and statistically significant improved survival outcomes compared to no local salvage therapy. With relatively shorter followup, differences in outcomes did not reach significance for the salvage-HIFU vs. no local salvage comparison.

This study is notable for its use of a control group receiving no local salvage therapy, for its use of propensity score-matching, and for its long followup (median followup of 25.1, 14.3, and 11.6 years in the salvage cryotherapy, salvage HIFU, and no-local therapy groups, respectively). However, there are limitations worth mentioning. The study groups originate from different source populations. These groups may have unmeasured systematic differences in patient selection, radiation treatment protocols and dosing, and followup protocols. Additionally, while the analysis was able to account for several key prognostic factors, even the propensity score match was not able to completely balance Gleason ≥8, baseline prostate-specific antigen (PSA), and pre-radiation ADT (all standardized differences >0.1). Further, the study was unable to account for post-radiation prognostic factors, such as PSA nadir, PSA at initiation of recurrence, time to recurrence, and PSA doubling time.[4]

Despite these limitations, this study adds to the literature in support for at least offering salvage cryotherapy to well-selected patients with sufficient life expectancy. Furthermore, this group has previously reported that salvage cryotherapy is associated with a 50% chance of avoiding ADT at 10 years of followup.[5] Risks of serious complications, such as recto-urethral fistula (3.3%) and severe incontinence (6.7%)[6] are acceptable and compare favorably against salvage radical prostatectomy, where the risk of incontinence is 20–78% and the risk of rectal injury is 0–9%.[7]

Some may desire a prospective, randomized trial prior to widespread clinical use of salvage ablative techniques for radio-recurrent prostate cancer. However, it is inherently challenging to randomize patients to procedural interventions,[8,9] and in this space, it will be unlikely to accrue enough patients for a sufficiently powered analysis.

Conversely, it is worth noting that the supporting evidence comparing salvage radiation vs. no salvage for biochemical recurrence after radical prostatectomy is also non-randomized.[10-12] Early salvage radiation is also indirectly supported by transitivity logic. The recent ARTISTIC meta-analysis of three contemporary randomized trials (RADICALS, RAVES, and GETUG-AFU-17) found that observation with early salvage radiation is non-inferior when compared to adjuvant radiation,[13] which in turn, offers improved biochemical and local control compared to observation.[14,15] Thus, a metastasis-free or overall survival benefit for post-prostatectomy salvage radiation remains to be prospectively confirmed, yet we still offer it to patients with the hope of providing an opportunity to achieve cure.

Based on most recent data, local salvage therapies remain underused for biochemical recurrence after radiation therapy, with only 2% of men <72 years old receiving local salvage therapy.[1] More work is needed to identify barriers to wider adoption of post-radiation local salvage treatments to the extent with which salvage radiation has been used after radical prostatectomy. Given that a prospective, randomized trial in this space is unlikely, we may need to decide on the role of salvage ablative techniques for radio-recurrent prostate cancer based on non-randomized data. Multidisciplinary discussions between radiation oncologists and urologists can be helpful, and shared decision-making with patients incorporating their individual values will likely be the way forward.

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