Can early salvage radiotherapy replace adjuvant radiotherapy as the new standard of care for high-risk postradical prostatectomy patients?

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SUMMARY

Patients with clinically localized prostate cancer often receive radiotherapy (RT) after radical prostatectomy (RP). The RADICALS-RT trial[1] was an international, multicentric, open-label, randomized controlled trial (RCT) to evaluate the efficacy and safety of adjuvant RT (ART) versus salvage RT (SRT) in high-risk post-RP patients with postoperative prostate-specific antigen (PSA) <0.2 ng/mL and one or more high-risk factors (pathological T-stage 3 or 4 (pT3–4), Gleason score 7–10, positive margins, or preoperative PSA of ≥10 ng/mL).

Patients were randomized to either receive ART or close observation with SRT in the case of PSA progression, defined as either two consecutive increasing PSA values with PSA >0.1 ng/mL or three consecutive increasing PSA values. Patients received RT to the prostate bed with or without the pelvis, within 2 months of randomization and 6 months of surgery in the ART arm, and within 2 months of PSA progression in the SRT arm. The primary outcome measure (freedom from distant metastases) is yet to mature, and biochemical progression-free survival (bPFS) was reported, defined as freedom from the following factors: PSA ≥0.4 ng/mL after RT, PSA >2.0 ng/mL at any time, clinical progression, initiation of nonprotocol hormone therapy, or all-cause death.

A total of 1396 patients were recruited and allocated to the ART (n = 697) and SRT (n = 699) treatment arms. In the ART arm, 93% (n = 647) of the patients received RT within 6 months. At the time of evaluation, 33% (n = 228) of the patients in the SRT arm had started RT following PSA progression. At a median follow-up of 4.9 years, there was no significant bPFS advantage between the two groups (hazard ratio for ART = 1.10; 95% confidence interval = 0.81–1.49; P = 0.56). The 5-year bPFS for ART and SRT groups was 85% and 88%, respectively. The initiation of nonprotocol hormone therapy reported in the ART and SRT groups was 7% and 8%, respectively, at 5 years.

Treatment toxicities, including diarrhea, proctitis, cystitis, hematuria, and urethral strictures, were reported significantly more in the ART arm. Patient-reported urinary incontinence was worse in the ART group at 1 year. The authors concluded that in the post-RP setting, observation with SRT in PSA progression should be the standard management.

COMMENTS

The appropriate timing of RT in the post-RP setting has been a matter of debate, having to choose between overtreatment with ART and risk of progression with SRT. The European Association of Urology guidelines[2] recommend ART to high-risk post-RP patients with an undetectable PSA after regaining acceptable continence 4 to 6 months post-RP. The guidelines recommend SRT in post-RP patients with biochemical recurrence (PSA >0.2 ng/mL) but no evidence of metastases before PSA exceeds 0.5 ng/mL.

The previous trials on ART were fraught with inconsistencies such as the inclusion of patients with detectable post-RP PSA, comparison to observation alone (absence of SRT), or lack of timely initiation of SRT (at higher PSA levels). Three recently published RCTs have addressed these issues and directly compared ART to early SRT in post-RP patients. The RADICALS-RT trial[1] was the largest of these and drove the meta-analysis outcomes based on these trials.

The GETUG-AFU 17 trial[3] compared ART (n = 212) to early SRT (n = 212) in post-RP patients (n = 424) with pT3–4 disease and positive surgical margins. No significant 5-year event-free survival benefit was observed in the ART (92%) versus SRT arm (90%). The RAVES trial[4] evaluated the noninferiority of early SRT (n = 167) to ART (n = 166) in post-RP patients (n = 333) with positive surgical margins, extraprostatic extension, or seminal vesicle invasion. The 5-year bPFS was similar in the SRT (87%) and ART arm (86%). Both trials prematurely stopped enrollment...
due to the unexpectedly low event rates. The ARTISTIC meta-analysis[5] was prospectively designed to evaluate these three trials and included 2153 patients. The 5-year event-free survival was PSA driven and did not improve with ART (89%) than SRT (88%). All trials reported significantly lower genitourinary toxicities in the SRT treatment arm [Table 1].

However, these trial populations may not represent the patient population receiving post-RP RT in actual clinical practice. The RADICALS-RT trial included any patient with a Gleason score of 7 or preoperative PSA of ≥10 ng/mL, leading to the trial population’s risk attenuation with only 17% (n = 235) of patients having a Gleason score ≥8 and 5% (n = 66) having lymphnode involvement. Moreover, only 33% of the patients (n = 228) in the SRT arm received RT, not consistent with a high-risk profile. Likewise, among the ARTISTIC meta-analysis population, only 15% had Gleason score ≥8 and 3% had lymphnode positivity [Table 1]. Moreover, the addition of hormone therapy to RT was not uniform across these trials. Hence, caution is advisable while extrapolating these results into clinical practice.

Regardless, these trials are the foremost evidence supporting the policy of observation with early SRT in most post-RP patients with lower treatment-related toxicity and comparable event-free survival. They also underscore the importance of close PSA monitoring and timely initiation of SRT. The follow-up data from RADICALS-RT trial reporting on long-term outcomes will further shed light on this matter.

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