Adjuvant Versus Salvage Post-Prostatectomy Radiation Therapy: A Critical Review of the Evidence

The American Urological Association and American Society for Therapeutic Radiology and Oncology joint guideline on the use of adjuvant external beam radiation therapy (ART) following radical prostatectomy for prostate cancer is provided based primarily on the results of 3 prospective randomized controlled trials (RCTs).\textsuperscript{1–3} Regarding men with evidence of extra-capsular extension (pT3a), seminal vesicle invasion (pT3b) or positive surgical margins (R1), the consensus panel states that “whether ART is likely to benefit a particular patient and should be administered is a decision best made by the multidisciplinary treatment team and the patient with full and thoughtful consideration of the patient’s history, current functional status, values and preferences, and his tolerance for the potential toxicities and quality of life effects of radiotherapy.”

While I agree this is a reasonable conclusion based on the discordant results of the 3 RCTs with respect to overall survival,\textsuperscript{1–3} careful evaluation of the 3 trials including updated data on the German ARO (adjuvant radiation therapy vs observation) study\textsuperscript{3} recently presented at the Genitourinary American Society of Clinical Oncology meeting is worthwhile. Specifically, while all 3 studies\textsuperscript{1–3} show improved prostate specific antigen (PSA) failure-free survival, only the SWOG (South West Oncology Group) study\textsuperscript{1} confirmed a reduction in time to distant metastasis and prolongation in overall survival. The reason for this discordance is unknown but may be explained by several considerations.

First, when looking at the followup schedule and what was required to be performed at each visit, it is clear that followup was less frequent in the SWOG\textsuperscript{1} compared to the EORTC (European Organization for Research in the Treatment of Cancer)\textsuperscript{2} study. Specifically, men in the EORTC study were followed every 3 months during the first year, then every 4 months out to 5 years and then annually thereafter, whereas in the SWOG study followup was every 3 months during the first year but then every 6 months for 2 years and annually thereafter. In addition, radiographic studies consisting of a bone scan and imaging of the pelvis were required annually for all men in the EORTC study but only for clinical symptoms for men in the SWOG study. Both of these factors introduce the possibility of ascertainment bias in that men in the EORTC study are more likely to be diagnosed with recurrence sooner (ie when asymptomatic) compared to men in the SWOG study, meaning later use of salvage therapy including radiotherapy (RT) for men randomized to the observation arm of the SWOG vs the EORTC\textsuperscript{2} study. This difference could increase the impact that ART use had on the reduction in the risk of metastasis and death from prostate cancer for men in the SWOG compared to the EORTC study.

Second, while the proportion of men receiving salvage RT for any progression (ie symptomatic or asymptomatic) was nearly the same in the SWOG (70 of 211, 33%) and EORTC (158 of 503, 33%) studies, the actual observed rates of salvage RT use for asymptomatic progression among men randomized to observation in the SWOG (43 of 211, 20%) and EORTC (158 of 503, 33%) trials were significantly different (p = 0.003). If we consider that 13% of 211 men randomized to observation in the SWOG trial had salvage RT delayed until clinical symptomatic progression, this could have led to 27 (13%) men being treated at the time of symptomatic compared to asymptomatic progression, ie PSA failure. Considering that the absolute difference in the number of men in the SWOG study who had distant metastasis or died was 21 (114–93) and 22 (110–88), respectively, in the observation vs adjuvant RT arm, the benefit in these end points may be explained by later use of salvage RT in those randomized to observation in the SWOG compared to the EORTC trial.

RADICALS (Radiotherapy and Androgen Deprivation In Combination After Local Surgery, NCT # 00541047) and RAVES (Radiotherapy Adjuvant vs Early Salvage, NCT # 00860652) are ongoing RCTs evaluating whether progression-free and/or prostate cancer specific and overall survival are significantly prolonged by the use ART compared to early salvage RT at the time of PSA failure. Should these studies find no significant difference in these end points,
then it is likely that the survival benefit in the SWOG study was driven by later use of salvage RT in men randomized to the observation arm compared to the EORTC trial.

For now, to minimize the potential for overtreatment, some evidence exists to consider offering PSA surveillance and delaying RT until PSA failure in men with Gleason score 7 or less and pT3aR0 or pT2R1 prostate cancer because the vast majority who were followed with PSA monitoring and experienced PSA failure did so with a PSA doubling time (DT) of at least 10 months. It was then found, using a time dependent covariate analysis, that when salvage RT was delivered to men with a PSA DT of at least 10 months, they did not experience an increased risk of death compared to men treated with ART. Conversely, men with Gleason score 8 to 10 and pT3a, pT3b or R1 disease, or Gleason score 7 or less and pT3a and R1 or pT3b disease who experienced PSA failure did so most often with a PSA DT of less than 10 months. For men with a PSA DT of less than 10 months, salvage radiotherapy compared to ART was associated with an increased risk of death.

Therefore, while awaiting the results of the RADICALS and RAVES trials, discussing PSA surveillance and delaying RT until PSA failure (confirmed PSA level of more than 0.2 ng/ml) for men with Gleason score 7 or less and pT3aR0 or pT2R1 disease warrants consideration.

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REFERENCES