COUNTERPOINT: Early Salvage vs Adjuvant Radiotherapy for High-Risk Prostate Cancer

By Wayland J. Wu, MD and Louis Potters, MD, FACR, FASTRO

Sunday, October 15, 2017

Volume: 31 Issue: 10

Oncology Journal, Prostate Cancer, Radiation Oncology

The Data for Adjuvant Radiotherapy Remain Strong

Radical prostatectomy and radiotherapy remain the most popular treatments for localized prostate cancer.[1] In the most recent updated iteration of the Partin Tables, approximately 24% of patients undergoing prostatectomy for clinically localized prostate cancer are predicted to have adverse pathologic findings such as extraprostatic extension (EPE) or seminal vesicle invasion (SVI), and as many as 25% of patients will experience biochemical recurrence within 5 years of surgery.[2,3] For patients whose initial presentation of prostate cancer includes high-risk features, the rate of adverse pathologic findings increases to as high as 75%.[4] Use of adjuvant radiotherapy in men with pathologic T3 or N1 disease has been tested in three randomized clinical trials: Southwest Oncology Group (SWOG) 8794, European Organisation for Research and Treatment of Cancer (EORTC) 22911, and ARO 96-02.[5-7] Here we present the clear evidence for adjuvant radiotherapy in patients with high-risk prostate cancer.

SWOG 8794 was a multi-institutional randomized study comparing adjuvant radiotherapy with observation in men who had undergone radical prostatectomy for organ-confined disease but who were found to have advanced pathologic features on final pathology.[5] The inclusion criteria were as follows: no prior radiotherapy; negative bone scan; negative lymph node dissection (dissection did not need to be
performed in patients with low-risk disease); good performance status; and no evidence of urinary incontinence, infection of the pelvis, urine extravasation, or rectal injury. In 2009, long-term results of the SWOG 8794 trial demonstrated improved metastasis-free survival (hazard ratio [HR], 0.71; \( P = .016 \)) and overall survival (HR, 0.72; \( P = .023 \)) in subjects who received adjuvant therapy compared with those who were observed.[5] Subset analysis also demonstrated benefit regardless of the presence of a detectable postoperative prostate-specific antigen (PSA) level, EPE, positive surgical margins, SVI, or Gleason score of Grade Group ≥ 2. Survival in patients with detectable PSA postprostatectomy was worse than in patients with undetectable PSA. These findings suggest that early radiation therapy as opposed to salvage therapy is beneficial to survival.

EORTC 22911 similarly examined a cohort of men with adverse pathologic features following radical prostatectomy, randomizing them to either postoperative radiotherapy or a “wait-and-see” approach. Eligible patients had disease up to clinical stage T3, were node-negative, had no distant metastasis, were pathologic stage T2 to T3 with at least one adverse feature on final pathology, had good performance status, and were younger than 76 years of age. This trial found an improvement in biochemical-free survival but not in overall survival in subjects who received adjuvant radiotherapy.[6] Of patients in the control arm, 56.4% had salvage radiation; however, the authors did not provide a survival analysis in this subgroup. Toxicity was more frequent in the immediate radiation group; however, there were no grade 4 toxicities, and differences in the rate of severe toxicities between the immediate and salvage radiation groups were not statistically significant (5.3% vs 2.5%; \( P = .052 \)).

The SWOG 8794 and EORTC 22911 trials randomized patients with detectable postoperative PSA levels; thus, some would argue that these trials mixed both patients who received early salvage radiation and those who received adjuvant radiation into the same treatment group. ARO 96-02 examined patients who had undetectable PSA levels postprostatectomy as their primary treatment arm, and in this way differed from the two other trials.[7] A wait-and-see approach was used in the control arm. The investigators demonstrated an improved progression-free survival rate in the adjuvant radiotherapy arm after 10 years of follow-up (56% vs 35%; \( P < .001 \)).[7] Severe toxicity was infrequent: only 1 patient in the treatment arm experienced a grade 3 bladder toxicity, and 3 patients out of a total of 148 who received radiotherapy developed a stricture. Together, these trials represent level 1 evidence supporting the use of adjuvant radiotherapy to improve long-term outcomes in patients with adverse pathologic features postprostatectomy.

In addition to these randomized controlled trials, there have been several large retrospective studies that have looked at early vs delayed radiotherapy in patients with adverse pathologic features. Hsu et al published a retrospective study examining the effects of postoperative (ie, adjuvant) radiotherapy, early salvage radiotherapy (more than 6 months postprostatectomy, PSA level < 0.1 ng/mL), and late salvage radiotherapy (PSA level > 0.1 ng/mL).[8] With a median follow-up of 6.2 years in 305 patients, there was increased prostate cancer–specific mortality and/or metastases in the salvage cohort (HR, 4.0; \( P = .015 \)). Another study arrived at the same outcome in a large Surveillance, Epidemiology, and End Results cohort, in which delayed radiation therapy resulted in inferior prostate cancer–specific mortality (HR, 2.3; \( P = .020 \)).[9] Phase III clinical trials are underway examining adjuvant vs salvage
therapy, but until prospective data showing otherwise are available, immediate adjuvant therapy appears to be more efficacious.

Despite the accumulated evidence, adjuvant radiotherapy is underutilized in the setting of adverse pathologic features. The exact reason for this practice pattern remains unclear, but there are a range of excuses for not referring patients to radiotherapy.[10] One excuse is concern about the toxicity of radiotherapy. Nevertheless, studies examining salvage and adjuvant radiotherapy have reported no difference in overall long-term quality of life—and with modern radiation delivery techniques, the incidence of toxicity has declined further.[11-14] Another argument used to forgo adjuvant radiotherapy is that, given the natural history of prostate cancer and the availability of the ultimate salvage approach of hormone therapy, why not just wait for the PSA level to rise before using radiotherapy? However, such lines of thinking fly in the face of current data from randomized prospective trials and multiple retrospective series that clearly demonstrate an advantage for early radiotherapy, as reviewed previously. Furthermore, the paradigm for adjuvant therapy has been demonstrated in breast and other cancers.[15,16] Another concern that has been expressed is that not all studies have identified an overall or disease-specific survival advantage for adjuvant radiotherapy—only improved biochemical freedom from failure. However, it is important to keep in mind that biochemical failure leads to lifelong use of androgen deprivation therapy. The long-term quality-of-life impact of hormone therapy is significant, and experts are realizing that it is more detrimental than previously appreciated.[17] Therefore, adjuvant therapy, for which there is level 1 evidence that it improves biochemical freedom from recurrence, has a tremendous positive impact on quality of life in patients with adverse pathologic features. Regardless of one’s reservations, the data for adjuvant radiotherapy remain strong, and patients should be referred for immediate postprostatectomy radiation when adverse pathologic features are present.

Financial Disclosure: The authors have no significant financial interest in or other relationship with the manufacturer of any product or provider of any service mentioned in this article.

References:


