Who, When, Where, and How: Salvage Prostate Cancer With Radiotherapy

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Despite the common use of postoperative radiotherapy (RT) in patients managed initially with radical prostatectomy (RP), a number of questions remain. Raldow and colleagues build their arguments around three randomized trials that indicated a significant benefit of immediate adjuvant radiotherapy in patients with high-risk features. They acknowledge that routine adjuvant radiotherapy might result in the treatment of patients who may never develop biochemical recurrence after RP and that early salvage radiotherapy has thus been suggested as an alternative. They provide an excellent review of the studies of, and arguments for, salvage radiotherapy, and they highlight many of the key issues involved with its delivery. There are, however, a number of issues that we believe are worthy of additional comment.

What Are Adjuvant and Salvage Radiotherapy?
Raldow and co-workers differentiate adjuvant and salvage radiotherapy and suggest that strong evidence exists for adjuvant but not for salvage radiotherapy. Although the findings of SWOG (Southwest Oncology Group) 8794, EORTC (European Organisation for Research and Treatment of Cancer) 22911, and ARO (Arbeitsgemeinschaft Radiologische Onkologie) 96-02/AUO (Arbeitsgemeinschaft Urologische Onkologie) AP 9/05 support adjuvant radiotherapy, both SWOG 8794 and EORTC 22911 included patients with persistently detectable or unknown postoperative prostate-specific antigen (PSA) levels (> 10%). Thus, these studies included patients who technically received salvage radiotherapy and in subset analyses were shown to have benefited from the treatment. We disagree, therefore, that there is a lack of evidence for salvage radiotherapy. Retrospective studies further support this and showed that early salvage radiotherapy confers a higher probability of progression-free survival.[12] Thus, there is already good evidence for the efficacy of salvage radiotherapy.

Where and How?
One recurring theme from studies of postoperative radiotherapy is that early radiotherapy confers better biochemical control. However, the optimal planned volume and target location for postoperative radiation are issues which are not yet clearly settled. Standard treatment volumes have traditionally included only the prostate bed, based on bony landmarks. However, the prostate bed has been shown to have daily variations in its location. Various image-guided techniques have been shown to be effective in minimizing daily set-up error; to account for inter-fraction variability of the prostate bed location, we favor employing gold fiducial markers as the simplest and most reliable of these approaches.[3] In addition to targeting the prostate bed, retrospective studies from Stanford and Italy suggest that pelvic nodal targets should be considered.[4,5] These investigators demonstrated that high-risk patients who have a pathologic Gleason score ≥ 8, a preoperative PSA level > 20 ng/mL, seminal vesicle or prostate capsule involvement, and/or pathologic lymph node involvement had better outcomes when pelvic nodes were treated.[4,5] For these subsets of patients, promising preliminary data suggest that novel imaging approaches such as lymphotropic nanoparticle-enhanced magnetic resonance imaging (MRI) and [11C]choline positron emission tomography/computed tomography (PET/CT) may be helpful in identifying sites of lymph node metastases in postoperative patients.[6,7] Such approaches may allow lymph node regions to be boosted to higher doses using intensity-modulated radiotherapy (IMRT). Alternatively, one could use standardized guidelines or additional radiographic imaging information by ensuring that the nodal volumes treated include the presumed positive nodes.[8] The optimal approach for integrating new imaging modalities remains to be determined.
The role of androgen deprivation therapy (ADT) in combination with postoperative radiotherapy needs to be fully clarified. However, there is some evidence supporting the use of ADT with RT in post-RP patients who have unfavorable factors, such as negative margin pre-RT PSA levels > 0.5 ng/mL.\[9\]

Although postoperative RT is usually well-tolerated, one side effect of particular concern for many men is sexual dysfunction. Patients who have had a history of a urologic procedure and receive external beam RT have been shown to have an increased risk of impotence.\[10\] The effects of radiation on erectile dysfunction are likely dose-dependent, and it is recommended that the mean dose to 95% of the penile bulb volume be kept < 50 Gy and D70 and D90 limited to 70 Gy and 50 Gy, respectively.\[11\] The penile bulb is not the critical component of the erectile apparatus, but it appears to be a surrogate for structure(s) critical for erectile function.\[11\] With accurate daily localization of the prostate bed and adherence to strict dose limits to the penile bulb, radiation-induced erectile dysfunction can be minimized.

**Randomized Trials of Salvage Radiotherapy**

The optimal timing of postoperative radiotherapy remains an unsettled subject of debate. Ongoing trials that aim to shed light on the benefits of adjuvant vs salvage radiotherapy include the RADICALS (Radiotherapy and Androgen Deprivation in Combination After Local Surgery), GETUG (Groupe d'étude des Tumeurs Uro-Genitales)-17, and RAVES (Radiotherapy Adjuvant Versus Early Salvage following radical prostatectomy) studies. The RADICALS trial will help to address both the issues of timing of postoperative radiotherapy (adjuvant vs salvage) and the use of androgen deprivation in conjunction with radiotherapy. GETUG-17 and the Tasman Radiation Oncology Group initiated RAVES phase III studies that will also evaluate the benefits of salvage radiotherapy. The main difference is that the GETUG-17 trial requires 6 months of ADT in conjunction with radiotherapy, whereas the RAVES trial involves salvage radiotherapy alone. With time, these studies can further clarify who, when, where, and how we optimally deliver postoperative radiotherapy for prostate cancer.

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**References:**


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