The management of adverse pathology following radical prostatectomy (RP) is a difficult treatment dilemma. The debate centers on three treatment paradigms: additional systemic therapy, additional local therapy, or close observation. For the individual patient, the decision focuses on risk of systemic disease and risk of local recurrence. The excellent review article by Stephenson et al.[1] concisely and completely outlines the literature surrounding adjuvant versus salvage radiation therapy (RT) for patients with adverse pathology. It is unfortunate that although we are blessed with three randomized trials addressing the utilization of adjuvant RT, a lack of consensus remains as to the optimal management of these patients.

The three randomized trials all demonstrated that adjuvant RT improves outcomes in patients with pathologic extracapsular disease or positive margins. Wiegel et al. (ARO 96–02, n = 385) demonstrated that adjuvant RT almost halved the risk of biochemical recurrence in patients with undetectable prostate-specific antigen (PSA) following surgery (hazard ratio [HR]: 0.53; 95% confidence interval [CI], 0.37–0.79) [2]. Bolla et al. (European Organization for Research and Treatment of Cancer [EORTC] 22911, n = 1005) demonstrated a similar decrease in biochemical recurrence [3]. In both studies, the group that appeared to benefit the most was those with positive margins [2,4]. Unfortunately, neither study demonstrated improvement in overall survival, prostate cancer (PCa)-specific survival, or metastasis-free survival. However, both trials had a median follow-up of only 5 yr; it is possible that with longer follow-up and more events, differences in survival will be identified. The third study, by Thompson et al. (Southwest Oncology Group [SWOG] 8794, n = 425), clearly demonstrated that adjuvant RT improved not only biochemical recurrence but also the harder end points of metastasis-free survival (HR: 0.71; 95% CI, 0.54–0.94) and overall survival (HR: 0.72; 95% CI, 0.55–0.96) [5].

Why then has adjuvant RT not been embraced? First, two of these trials did not incorporate undetectable PSA into the inclusion criteria [3,5]. As outlined nicely by Stephenson et al. [1], neither SWOG 8796 nor EORTC 22911 enrolled patients prior to the widespread use of PSA or required an undetectable PSA at the time of randomization. In both studies, roughly a third of patients had detectable PSA at the time of randomization. This patient subset is at extremely high risk for recurrence, metastasis, and death. At the current time, neither arm of the study (observation or adjuvant RT alone) would be considered acceptable treatment for a patient whose PSA never decreased to <0.2 ng/ml after surgery [5].

The ARO 96-02 trial most closely replicates current practice and treatment. These patients all had undetectable PSA at the time of randomization. Unfortunately, this trial reflects the second reason patients are not routinely given adjuvant RT: the vast majority of untreated patients do not progress. At median follow-up of 5 yr, the clinical progression rate was only 2% in cases and 3% in controls [2]. Although an increased event rate will occur with longer follow-up, it is clear that the definition of high risk did not identify a patient population at high risk for failing at 5 years.

Case series support lack of progression in many high-risk populations. Boorjian et al. [6] examined 7591 consecutive patients who underwent RP at the Mayo Clinic between 1987 and 2003 and found that 1513 men had high-risk disease according to the D’Amico classification. Although the risk of death from PCa was almost 12 times higher in the high-risk group, 10-yr biochemical-free survival, metastasis-free survival, and cancer-specific survival were 55%, 89%, and 95%, respectively. Again, with longer follow-up, more events may be identified. Stephenson et al. assessed...
biochemical failure can be subsequently cured [9,10]. Trock et al. have shown that upward of 50% of patients who have undetectable PSA 10 yr later. They found that salvage RT was most effective in the subset with the lowest PSA. Biochemical-free survival was significantly reduced in patients with PSA >1.5 ng/ml at the time of treatment, only 15% had undetectable PSA 10 yr later.

A third reason adjuvant RT is underutilized is concerns about the side effects. In SWOG 8796, the risk of complications was manageable but was clearly higher in the treated arm. Overall RT was associated with a 23.8% complication rate compared to 11.9% in the control arm (p = 0.002; rectal complications: 3.3% vs 0% [p = 0.02]; urethral strictures: 17.8% vs 9.5% [p = 0.02]; total urinary incontinence: 6.5% vs 2.8% [p = 0.11]) [5]. Although the reported complications in EORTC 22922 and ARO 96-02 are much lower, neither study appears to have specifically examined lower urinary complications; therefore, it is likely that urologic complications are underreported.

Because adjuvant RT does not appear to be necessary in all patients and has unintended side effects, an alternative strategy is to treat only patients most likely to benefit, maximizing cure and minimizing side effects. Subset analysis of EORTC 22911 [4] revealed that the patients most likely to benefit were those with positive margins. These patients are not only at higher risk of recurrence but, importantly, at higher risk of local recurrence and therefore will benefit from a local therapy. It may even be possible to further define groups that are at risk for residual local disease and, therefore, that would benefit. Cao et al. examined 294 patients with positive margins and measured the linear millimeters of tumor at the margin. They found that the longer the margin, the more likely the recurrence. At approximately 7.5 yr, 70% of patients with 3–6 mm of margin and 100% of the patients with >6 mm of margin had recurved [8]. These findings provide a strong rationale for utilizing adjuvant radiation in this patient population.

Although no randomized trials have demonstrated the efficacy of salvage RT, multiple retrospective studies have proven that upward of 50% of patients who have biochemical failure can be subsequently cured [9,10]. Trock et al. [9] examined 635 patients who failed surgery and received either RT or observation. They demonstrated a three-fold reduction in risk of death from PCa with salvage RT. This risk reduction was most pronounced in patients with rapid PSA doubling time and early recurrence, two factors that are known to predict risk of death from PCa in patients who fail surgery [11].

Early utilization of salvage RT is critical to response. Stephenson et al. performed a multi-institutional analysis of 1540 patients with PSA recurrence after RP [10]. They found that salvage RT was most effective in the subset with the lowest PSA. Biochemical-free survival was approximately 50% at 10 yr for patients treated with PSA <0.5 ng/ml. In contrast, of patients whose PSA was >1.5 ng/ml at the time of treatment, only 15% had undetectable PSA 10 yr later.

Three ongoing randomized trials are attempting to determine which is better: adjuvant or early salvage RT. The TROG RAVES 0803 trial will examine 470 men with undetectable PSA and either pT3N0M0 or pT2N0M0 with positive margins. The patients are being randomized to immediate RT versus RT for a rising PSA. The end point is biochemical recurrence. The GETUG-17 trial is enrolling 718 men with pT3–4N0M0 disease with positive margins and undetectable PSA to immediate RT with androgen-deprivation therapy (ADT) versus salvage RT with ADT. The composite end point includes clinical progression, biochemical progression, and death at 5 yr. The last and most ambitious trial is RADICALS. In this 2600-patient trial, men with PSA <0.2 ng/ml plus pT3/4, Gleason 7–10, preoperative PSA ≥10 ng/ml, or positive margins will be randomized to immediate versus delayed RT. The end point is PCa-specific survival. As outlined by Stephenson et al. [1], there is concern that the trials are vastly underpowered; some experts believe that a trial with upward of 8000 patients and 20-yr follow-up will be needed to demonstrate an improved outcome.

In summary, the decision to proceed with adjuvant RT for locally advanced PCa or to reserve treatment for only those who develop biochemical failure is a difficult one. Many advocate a tailored approach that identifies and treats the patients at risk for death from disease while sparing patients with less risk the morbidity of treatment. Ongoing randomized trials may eventually answer this question, but at least for the next few years, the recommendation of Stephenson and colleagues [1] seems sound: careful and thorough discussions between the patient and multiple health care professionals that lead to a tailored approach. The treatment chosen is based on the patient’s individual risk of local recurrence and his concern about both cancer recurrence and side effects of treatment.

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References


