Salvage or Adjuvant Radiation Therapy: Counseling Patients on the Benefits

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Key Words
Prostate cancer, adjuvant radiotherapy, salvage radiotherapy, risk stratification, generalizability

Abstract
Recent developments in the urologic oncology literature suggest that residual local disease—as opposed to the presence of occult metastases at surgery—may characterize a more substantial component of the natural history of the recurrence and progression of initially clinically localized prostate cancer than previously appreciated. These important studies have illuminated the extent to which postoperative radiotherapy (RT) may provide benefit to patients with adverse pathologic features (extraprostatic extension, seminal vesicle invasion, or positive surgical margins) or biochemical recurrence after radical prostatectomy. Nevertheless, the question of whether all patients with the aforementioned adverse features should undergo immediate adjuvant RT versus initial observation with more selective—but early—salvage RT in the event of biochemical failure remains the subject of heated controversy. This article reviews salient recent studies in this field to address important questions relevant to counseling patients on the use of postprostatectomy RT. Discussion points include data supporting benefit (efficacy), questions of generalizability of benefit (effectiveness) and risks, and important questions for further study. (JNCCN 2010;8:228–237)

Despite the stage migration and concomitant improvements in prostate cancer–specific survival (PCSS) associated with widespread prostate-specific antigen (PSA) screening, approximately 1 in 3 men with clinically localized disease will develop a detectable PSA after radical prostatectomy (RP) in contemporary series.1 The natural history of prostate cancer with biochemical failure after RP can be variable; however, approximately two thirds of these men will develop metastatic disease if left untreated and most will die of prostate cancer.2 The argument for postoperative radiotherapy (RT) is predicated on the assumption that some patients may have residual local disease of a potentially lethal phenotype after surgery and that the delivery of secondary local therapy may interrupt the natural history of disease and prevent progression to systemic disease. A basic question in this context is the extent to which this sequence of events—versus the presence of occult metastases at surgery—characterizes the natural history of recurrent and progressive disease.

An emerging body of literature showing efficacy for secondary RT suggests that residual local disease after surgery may represent a much more important avenue of prostate cancer progression than previously appreciated. For patients with high-risk features at RP or who experience biochemical recurrence after RP, solid evidence now shows that secondary RT provides benefit. Reflecting this, the most recent update of the NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer states “new evidence supports offering adjuvant/salvage RT in all men with adverse pathologic features or detectable PSA”3 (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org). In 2010, the dilemma is not in the question of whether postprostatectomy adjuvant or salvage RT are effective among high-risk patients as a group, but rather which

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individual patients ought to receive it and when.

Against this backdrop, this article attempts to synthesize salient recent studies in this field to address several important questions relevant to counseling patients regarding the use of postoperative RT. The first section reviews the evidence base showing benefit for postoperative RT in the adjuvant and salvage settings. The next section discusses insights from the data underscoring the heterogeneity of disease recurrence and response to RT among subgroups of patients in different treatment settings. The final section reviews the risks of postoperative RT and highlights important ongoing clinical trials addressing gaps in current understanding.

The Evidence Base Supporting Efficacy of Postprostatectomy RT

Immediate Adjuvant Postprostatectomy Radiation: Results of 3 Clinical Trials

The 3 prospective randomized trials examining adjuvant RT versus observation in high-risk patients after RP are among the most significant contributions to the urologic oncology literature in recent years. These trials are remarkable for several reasons. First, the overall consistency of benefit shown for secondary RT across multiple patient populations in different eras confirms the fundamental usefulness of this principle. Furthermore, given the demonstration of benefit for patients randomized to adjuvant RT with detectable PSA postoperatively, these data also indirectly support its benefit in the salvage setting. Finally, the various trials’ subgroup analyses help determine the marginal utility of this approach in terms of identifying factors that begin to characterize the somewhat differential relative benefits of secondary RT among specific subgroups of patients. This section highlights the similarities in the designs and positive overall results of the trials, and discusses insights from the subgroup analyses.

Overview of Trial Designs

The first publication of trials came in 2005, with the report of EORTC 22911, the largest of the 3. After undergoing RP between 1992 and 2001, 502 European patients were randomly assigned to immediate postoperative RT (60 Gy conventional irradiation delivered over 6 weeks) and 503 patients were assigned to a wait-and-see policy, or observation (OBS). Eligible patients were pathologically N0 and radiographically M0 and had 1 or more of the following features: extraprostatic extension, positive surgical margins, or seminal vesicle invasion. An undetectable PSA post-RP was not required (and not present in 11% of patients), and patients assigned to adjuvant RT initiated irradiation at a median of 90 days after surgery. The original primary end point of palpable local recurrence was revised to clinical progression-free survival in 1995 and biochemical recurrence-free survival (defined as an increase of 0.2 ng/mL over the lowest postoperative PSA value) in 2003.

SWOG 8794 evaluated 425 North American patients treated with RP between 1988 and 1997 found to have extraprostatic extension, positive surgical margins, or seminal vesicle invasion and no evidence of lymph node metastases or abnormalities on bone scan, with initial results published in 2006. After 1995, patients with specified lower-risk preoperative features were not required to have undergone lymphadenectomy. Central pathologic review was available for 73% of cases, with 95% concordance between central and institutional pathology reviews where available. An undetectable PSA after surgery was not required for study entry, and approximately one third of enrolled patients had a persistently elevated PSA. Patients were randomized within 16 weeks after RP, and those assigned to adjuvant RT received a dose of 60 to 64 Gy in 30 to 32 fractions, with treatment beginning within 10 working days of randomization. Distant metastasis-free survival was the prespecified primary end point of this trial, and biochemical recurrence was assessed with a PSA cutoff of 0.4 ng/mL.

The results of ARO 96-02/AUO AP 09/95, a multicenter study of 388 German patients who underwent RP between 1997 and 2004, were published earlier this year. Eligible patients were pT3N0 with negative bone scan, randomized within 2 weeks of RP, and those receiving adjuvant RT underwent 3-dimensional treatment planning before receiving a dose of 60 Gy in 30 fractions, which started 6 to 12 weeks after surgery. The primary end point of biochemical recurrence (defined by the local undetectable thresholds, all < 0.1 ng/mL) was evaluated in prespecified analysis subsets, including intent-to-treat for all eligible patients (n = 388, ITT1), intent-to-treat among patients achieving an undetectable PSA (n = 307, ITT2—the prespecified primary analysis subset), and a per-protocol approach (n = 268, PP).
among patients with an undetectable PSA.

**Overall Results of Adjuvant RT Trials**

The overall results of these 3 similarly designed studies are remarkably consistent, showing an approximate halving of the risk for biochemical relapse with adjuvant RT (Table 1). At a median follow-up of 10.9 years, the biochemical recurrence–free survival (BRFS) rates in SWOG 8794 were 64% for adjuvant RT versus 35% for OBS, respectively (hazard ratio [HR], 0.43; 95% CI, 0.31–0.58; P < .001). In EORTC 22911, the 5-year BRFS rates were 74.0% for adjuvant RT versus 52.6% for OBS (HR, 0.48; 95% CI, 0.37–0.62; P < .0001) and 72% versus 54%, respectively, in the primary analysis subset of ARO 96-02, which consisted of patients with an undetectable PSA after RP (HR, 0.53; 95% CI, 0.37–0.79; P = .0015). A recent update of SWOG 8794, with median follow-up of 12.6 years, reported statistically significant benefits for adjuvant RT in terms of metastasis-free (HR, 0.71; 95% CI, 0.54–0.94; P = .016) and overall (HR, 0.72; 95% CI, 0.55–0.96; P = .023) survival. Further follow-up is needed to assess these end points in the 2 European studies.

Taken together, these data clearly show benefit for adjuvant RT in patients with pT3N0 prostate cancer or positive surgical margins. The subgroup analyses of the trials provide a more granular view of the complexity of counseling patients regarding their specific expectation of benefit.

**Salvage Radiation is Associated With a Survival Benefit When Compared With No Salvage**

The authors recently reported on a retrospective cohort study of 635 men who underwent RP from 1982 to 2004 and experienced biochemical or local recurrence. Within the cohort, 397 received no salvage treatment, 160 received salvage RT alone, and 78 received salvage RT combined with hormonal therapy. With a median follow-up of 9 years (6 years after recurrence), salvage RT alone was associated with a significant 3-fold increase in PCSS versus no salvage therapy (HR, 0.32; 95% CI, 0.19–0.54; P < .001). Among men who underwent salvage RT, the median radiation dose was 66.6 Gy and the median time from recurrence to initiating salvage RT was 1 year. The addition of hormonal therapy to salvage RT was not associated with a significant increase in PCSS, and the survival benefit of salvage RT was limited to men with a PSA doubling time (PSADT) of less than 6 months who underwent salvage RT within 2 years of biochemical recurrence. Additionally, consistent with other studies examining biochemical outcome after salvage RT, the survival benefit in this study cohort was seen only among men whose PSA became undetectable after salvage RT.

Subgroups based on standard prognostic factors, including PSADT, Gleason score, surgical margin status, and pathologic stage, were evaluated for interactions with salvage RT (Figure 1). PSADT was the only factor associated with a statistically significant interaction, and a PSADT cutpoint of either more than 6 months or less than 6 months was associated with the greatest improvement in model fit. Salvage RT in patients with PSADT of less than 6 months was associated with a greater than 75% reduction in cancer-specific mortality. For men with PSADT of less than 6 months, PCSS was higher for those who received salvage RT, regardless of margin status or Gleason score. In contrast, among men with

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**Table 1 Biochemical Recurrence-Free Survival Rates in Adjuvant Radiotherapy Trials**

<table>
<thead>
<tr>
<th>Trial (Arm)</th>
<th>BRFS</th>
<th>Median Follow-Up (y)</th>
<th>Hazard Ratio (95% CI)</th>
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<tbody>
<tr>
<td><strong>SWOG 8794</strong></td>
<td></td>
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<tr>
<td>Immediate ART</td>
<td>64%</td>
<td>10.9</td>
<td>0.43 (0.31–0.58); P &lt; .001</td>
</tr>
<tr>
<td>“Wait and see”</td>
<td>35%</td>
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<tr>
<td><strong>EORTC 22911</strong></td>
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<tr>
<td>Immediate ART</td>
<td>74.0%</td>
<td>5</td>
<td>0.48 (0.37–0.62); P &lt; .0001</td>
</tr>
<tr>
<td>“Wait and see”</td>
<td>52.6%</td>
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<tr>
<td><strong>ARO 96-02</strong></td>
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<tr>
<td>Immediate ART</td>
<td>72%</td>
<td>5</td>
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<td>“Wait and see”</td>
<td>54%</td>
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Abbreviations: ART, adjuvant radiotherapy; BRFS, biochemical recurrence–free survival.
Salvage or Adjuvant Radiation Therapy

PSADT of greater than 6 months, salvage RT was associated with improved PCSS only in the subgroup with positive surgical margins and Gleason score of 8 to 10. Finally, to facilitate comparison of survival experiences between the cohort is this trial and the one in the adjuvant RT trials, an analysis restricted to patients with stage pT3 showed that those treated with salvage RT had an 89% 10-year overall survival rate. This compares favorably with the 10-year overall survival estimates in SWOG 8794: 74% for patients randomized to adjuvant RT versus 66% for those randomized to initial observation.6

This study is significant for several reasons. Although the data are retrospective and nonrandomized, it is the first study of salvage RT to include a comparator group not receiving salvage treatment. In this context, it is the first to show both overall and cancer-specific survival benefits for salvage RT after RP, and the magnitude of the survival benefit is comparable to that observed in adjuvant RT trials. These results are also important because they underscore the concept that a short PSADT after RP is not simply a poor prognostic factor, but also a factor predictive of potential survival benefit for secondary RT. This somewhat surprising finding has clear implications for clinical practice. Furthermore, with a 1-year median interval between recurrence and initiating salvage RT—substantially longer than current best practice,
outlined in a later section—these results may in fact underestimate the survival benefit that can be expected from contemporary salvage RT. These data support the strong consideration of salvage RT for men with biochemical recurrence after RP, even among, and particularly in, men with rapid PSADTs.

Taken together, these studies represent the somewhat radical change in the evidence base supporting the efficacy of postoperative RT for high-risk patients. The adjuvant trials provide the highest level of evidence, with consistent benefits seen in multiple study populations across different geographic and temporal settings. The salvage study, although retrospective in nature, shows for the first time a survival benefit for this approach, with the greatest benefit seen in patients with short PSADTs. These studies do not, however, answer the fundamental question of whether individual patients should be counseled for immediate adjuvant RT based on pathologic features, versus observation with selective early salvage RT. This question balances concern over inadequate therapy versus overtreatment, with its associated unnecessary cost, bother, and toxicity. Although level I evidence supports relatively widespread immediate adjuvant RT, some arguments for a more selective approach are described.

Where Does Postoperative Radiation Have the Greatest Marginal Utility?

The preceding section outlined the solid documentation of benefit attributable to postoperative RT. However, the uncertainty, and therefore the crux of the debate in 2010, is whether all patients with pT3 disease or positive surgical margins (approximately one third of patients in surgical series) should undergo immediate adjuvant RT. An alternative strategy might be to consider immediate adjuvant RT among the subgroup at highest risk for relapse, and recommend observation with selective salvage RT delivered shortly after documentation of biochemical failure among a broader subset of patients. This section discusses insights highlighting relative limitations to the broad generalizability of the adjuvant RT trial data and recent data outlining current understanding of how to optimize the delivery of salvage RT when the strategy of initial observation is selected.

Subgroup Analyses of Adjuvant RT Trials

Despite the strikingly consistent overall results, subgroup analyses of SWOG 8794, EORTC 22911, and ARO 96-02 are somewhat less consistent and suggest that the benefit of adjuvant RT may not be uniform across patients meeting the broad and consistent inclusion criteria. A benefit in metastasis-free survival was associated with adjuvant RT in men with or without detectable PSA post-RP in SWOG 8794. The point estimates for the metastasis-free survival HR were less than 1.0 for subgroups by extent of disease (extracapsular or + margins vs. seminal vesicle involvement), although the upper bounds of the 95% confidence interval were greater than 1.0 for both groups. Importantly, the results for patients with negative margins were not reported separately. An analysis of BRFS by post-RP PSA subgroups in the SWOG study found a 5-year BRFS of 38% for men with post-RP PSA of 0.2 ng/mL or less who received salvage RT at failure versus 34% for those with a PSA greater than 0.2 and 1.0 ng/mL or less who received immediate adjuvant RT, providing indirect evidence suggesting rough equivalency for the timing and indications used for salvage RT in this study population. As the authors commented, these data “suggest the control rate is not so much directly dependent on timing of RT as it is with the microscopic bulk of tumor (as represented by PSA level).”

The initial report of the results of EORTC 22911 found BRFS benefits for adjuvant RT in all subgroups (HR, 0.40–0.66; all P < .05), including patients with or without capsule perforation, seminal vesicle involvement, positive surgical margins, and undetectable PSA post-RP. Interestingly, an update of EORTC 22911 based on cases with complete central pathologic review found only positive surgical margin status (regardless of margin location) to have a significant interaction with adjuvant RT benefit in terms of BRFS, “to such an extent that the treatment benefit in patients with negative margins is not significant.”

The finding of a significant association between margin status and adjuvant RT benefit was also reported in the subgroup analyses of ARO 96-02. In light of the revised conclusions in the EORTC follow-up study, it is noteworthy that 85% of all cases in the German trial underwent complete central pathology review. They also found significant associations between pT stage (pT3a/b, which involved unilateral/bilateral extracapsular extension without seminal vesicle involvement had clear benefit, vs.
pT3c, involving seminal vesicle invasion [per the UICC staging system] and pre-RP PSA greater than 10 with BRFS after adjuvant RT.7

Limitations to the Generalizability of Adjuvant RT Trial Data

The rigorous design and execution of these 3 trials is laudable and provides the highest level of clinical evidence to support the use of adjuvant RT among patients meeting inclusion criteria. However, despite the inherent limitations of subgroup analyses, when taken together, the subgroup analyses of the 2 trials reporting data on patients with negative surgical margins are consistent in suggesting no significant benefit of immediate adjuvant RT in these patients. These findings highlight one relative limitation to the internal validity of the trial data: the uniformity of the overall conclusions within specific subsets of patients meeting the inclusion criteria.

Although patients with positive surgical margins had more consistent benefit from adjuvant RT in the trials, clinical experience shows that biochemical failure is not a certainty in this circumstance, reflected in the updated NCCN guideline recommendation for observation or RT in this context.3 To illustrate one aspect of this heterogeneity, Table 2 presents the 10-year probability of an undetectable PSA in patients at Johns Hopkins who underwent RP and have capsular penetration (pT3a) according to Gleason score and margin status. As shown in the table, immediate adjuvant radiation would result in unnecessary treatment and morbidity in 75% of men who have positive margins and Gleason 6 disease in this setting, supporting observation and early salvage when necessary. Conversely, among patients with Gleason 7 disease under the same circumstances, only 35% would be subjected to unnecessary treatment; the authors believe adjuvant RT should be more strongly considered for these patients.

In light of regional and temporal variation in practice patterns and the well-described stage migration associated with widespread PSA screening, a somewhat broader set of limitations relate to the external validity of these data (i.e., their generalizability to the overall population). In a recently published retrospective matched case-control study, Porter et al.12 found no significant improvement in outcome associated with adjuvant RT. One specific potential limitation to generalizability is the extent to which the trial cohorts represent the population of patients who underwent RP when the studies were enrolling.

The authors evaluated the results of their practice of initial observation and selective delayed intervention (analogous to the “wait-and-see” arms of the adjuvant RT studies) for patients who met eligibility criteria for SWOG 8794 and underwent surgery in the same years as patients in the study. None of the 648 era-matched patients in their cohort underwent neoadjuvant or adjuvant RT or hormonal therapy, and a median follow-up of 12 years was comparable to that reported for SWOG 8794 (12.6 years). As shown in Table 3, the 5- and 10-year BRFS rates with surgery alone in this contemporaneous cohort were substantially higher than those observed in patients randomized to immediate adjuvant radiation in SWOG 8794. These results are with a PSA definition of 0.2 ng/mL, versus that of greater than 0.4 ng/mL used in the SWOG trial. The table also shows that the 5- and 10-year rates of freedom from hormonal therapy, which are another reported advantage of immediate adjuvant RT in the SWOG study, were comparable if not slightly higher in the authors’ era-matched cohort. Data such as these are obviously sensitive to differences in case mix and other factors, and clearly do not override the validity of the prospective clinical trial data; they simply raise questions regarding the generalizability of the published trial results to contemporaneous patients outside the study who met inclusion criteria. More detailed analyses in this vein, beyond the scope of this review, could provide additional insight and opportunities for further descriptive and hypothesis-generating study.

Broadly speaking, generalizing the experience in the 2 European populations to patients in the United States may have limitations. Nevertheless, they

<table>
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<th>Table 2 10-Year Probability of an Undetectable PSA after Radical Prostatectomy Alone</th>
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<tr>
<td>Prostatectomy Gleason Score 6</td>
</tr>
<tr>
<td>Capsular penetration, negative margin</td>
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<tr>
<td>Capsular penetration, positive margin</td>
</tr>
<tr>
<td>Prostatectomy Gleason Score 7</td>
</tr>
<tr>
<td>Capsular penetration, negative margin</td>
</tr>
<tr>
<td>Capsular penetration, positive margin</td>
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</tbody>
</table>
represent more than 70% of the adjuvant RT trial participants, and also include patients from more recent surgical series with tumor burdens potentially more comparable to those seen today than the pre-PSA–era SWOG cohort. Given the well-described stage migration associated with PSA screening, for the SWOG trial in particular, patients undergoing RP from these earlier years (1988–1997) may have greater volume of disease than contemporary patients. This may create a bias exaggerating the attributable benefit of adjuvant RT versus what might be experienced currently. In any event, the clinical stage distribution of these trials are not typical of contemporary surgical series, in which T1c is most common, and the rates and—potentially more importantly—pathologic extent of positive margins may also be lower in current experiences. Clearly, longer follow-up of the 2 European studies will continue to provide information. In addition, the similar inclusion criteria of the 3 trials suggests the possibility of eventual meta-analyses to further clarify some of the unresolved questions in terms of differential efficacy among specific subgroups.

Perhaps the most fundamental limitation of generalizing the adjuvant RT trials to contemporary practice—and a focus of controversy—is the variation in the indications for and timing of salvage RT among patients randomized to initial observation. Since these trials were designed, experts have come to understand that the results of salvage RT are very sensitive to the timing of therapy, with the greatest benefit seen in patients initiating salvage RT at early PSA rise after surgery. In the context of this evolving understanding of salvage RT, the trials do not show that adjuvant RT is superior when delivered in accordance with the best-available evidence.

### Insights Regarding Postprostatectomy Salvage RT

A detectable PSA after RP signals the missed opportunity for surgical cure and raises the question of whether and how to administer secondary treatment. Evidence indicates a perception among urologists that biochemical recurrence heralds occult metastatic disease. Patterns of care are consistent with this perception, with a minority of patients receiving salvage RT during secondary therapy—the only potentially curative maneuver—with most undergoing hormonal therapy. Against this backdrop, 2 pivotal publications in the past 5 years inform optimal salvage RT practice and provide a basis to support the broader use of salvage RT in this setting. Although retrospective in nature, these studies provide important insights into the potential benefits of salvage RT, which can clearly be used in patient counseling and treatment selection.

Stephenson et al. published a retrospective cohort study of 501 patients from 5 centers who had salvage RT with a median dose of 64 Gy for detectable and rising PSA after RP between 1987 and 2002. More than two thirds of patients experienced a complete response to salvage RT (defined as PSA nadir of ≤ 0.1 ng/mL) with or without neoadjuvant androgen deprivation therapy. Progression was defined as a serum PSA of 0.1 ng/mL above the post-salvage RT nadir and the actuarial progression-free probability (PFP) at 4 years was 45% (95% CI, 40%–50%). PSA progression was associated with a Gleason score of 8 to 10, pre-salvage RT PSA greater than 2.0 ng/mL, negative surgical margins, seminal vesicle invasion, and PSADT 10 months or less. Nevertheless,

### Table 3 Comparative Outcomes for Contemporaneous Patients

<table>
<thead>
<tr>
<th></th>
<th>5-Year</th>
<th>10-Year</th>
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<tr>
<td><strong>Biochemical Recurrence-Free Survival</strong></td>
<td></td>
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</tr>
<tr>
<td>SWOG XRT</td>
<td>71.5%</td>
<td>54.6%</td>
</tr>
<tr>
<td>SWOG OBS</td>
<td>44.6%</td>
<td>28.4%</td>
</tr>
<tr>
<td>Hopkins (SWOG era)</td>
<td>85.6%</td>
<td>75.1%</td>
</tr>
<tr>
<td><strong>Distant Metastasis-Free Survival</strong></td>
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<tr>
<td>SWOG XRT</td>
<td>87.7%</td>
<td>73.1%</td>
</tr>
<tr>
<td>SWOG OBS</td>
<td>83.1%</td>
<td>60.8%</td>
</tr>
<tr>
<td>Hopkins (SWOG era)</td>
<td>97.1%</td>
<td>94.5%</td>
</tr>
<tr>
<td><strong>Freedom From Hormonal Therapy</strong></td>
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</tr>
<tr>
<td>SWOG XRT</td>
<td>92.3%</td>
<td>84.6%</td>
</tr>
<tr>
<td>SWOG OBS</td>
<td>79.2%</td>
<td>64.6%</td>
</tr>
<tr>
<td>Hopkins (SWOG era)</td>
<td>95.4%</td>
<td>89.3%</td>
</tr>
</tbody>
</table>

Abbreviations: Hopkins (SWOG era), Johns Hopkins patients meeting inclusion criteria for SWOG 8794 who underwent surgery in the same years as those in SWOG 8794; SWOG OBS, patients in SWOG 8794 randomized to “wait and see”; SWOG XRT, patients in SWOG 8794 randomized to immediate adjuvant radiotherapy.

*Biochemical recurrence defined as PSA ≥ 0.2 ng/mL in Hopkins (SWOG era) versus PSA ≥ 0.4 ng/mL in SWOG 8794 patients
patients with Gleason scores of 8 to 10 and positive margins undergoing early salvage RT (PSA ≤ 2 ng/mL) had a 4-year PFP of 81% when PSADT was greater than 10 months and 37% when it was 10 months or less, suggesting benefit even for patients at highest risk. Consistent with previous reports, the investigators found an association between very low pre-salvage RT PSA (≤ 0.6 ng/mL) and response to salvage RT, with HRs of 1.6 (95% CI, 1.2–2.2) and 2.8 (95% CI, 2.0–4.0) for PSA of 0.61 to 2.0 ng/mL and greater than 2.0 ng/mL, respectively.

In a follow-up study with an expanded cohort of more than 1500 patients, Stephenson et al.17 validated the importance of pre-RT PSA levels as a predictor of response. These investigators showed that patients treated with salvage RT alone at PSA levels of 0.5 ng/mL or lower had a 6-year progression-free survival rate of 48% compared with 26% for those treated at higher PSA levels. Notably, the 6-year progression-free survival rate was 41% among the subgroup who had a pre-RT PSA level of 0.5 ng/mL or less with a PSADT of 10 months or less or Gleason scores of 8 to 10. The approximate halving of progression risk among patients undergoing early salvage RT is analogous to the consistent degree of biochemical response benefit reported in the 3 adjuvant RT trials described earlier. The Stephenson data and the Hopkins salvage RT data obviously have all the limitations of single- and multi-institutional retrospective series, with potential referral biases, bias in use of salvage RT, and other potential limitations to the generalizability of these data. Nevertheless, these data changed the understanding of the potential usefulness of salvage RT, and the improved responses associated with salvage RT initiated at low PSA levels. The optimum PSA threshold for early salvage RT is unknown, but the Stephenson data suggest that it is certainly less than 0.4 ng/mL. Although reliable ultrasensitive PSA testing may have a role in this setting, which may be illuminated in future study, the authors recommend considering the threshold to be a confirmed detectable PSA of at least 0.1 ng/mL.

**Downside Risks of Postprostatectomy Radiation**
The potential for toxicity necessarily factors into the consideration of postprostatectomy RT and provides support for more selective use. The results of SWOG 8794 report an approximate doubling of the urethral stricture rate (24% vs. 12%; relative risk 2.0; P = .02) and total incontinence (6.5% vs. 2.8%; RR 2.3; P = .11) among patients randomized to adjuvant RT.5 Rectal complications occurred in 3.3% of patients treated with adjuvant RT, with none reported in the subgroup randomized to initial observation.

The EORTC 22911 investigators reported significantly more frequent grade II or III toxicities among the patients who underwent adjuvant RT, but no grade IV toxicity and only marginal differences in the rates of grade III toxicities at 5 years, with 4.2% in the adjuvant RT group versus 2.6% in the “wait and see” group (P = .0726).6

The German investigators for ARO 96-02, in which 3-dimensional conformal treatment planning was performed for all irradiated patients, reported only 1 event of grade III bladder toxicity.7 Both EORTC 22911 and ARO 96-02 used the EORTC scoring system, which does not specifically assess urinary incontinence, although an interim analysis of the EORTC study did not show an increased risk for urinary incontinence among irradiated patients.8

Although patients undergoing salvage RT seem to have similar absolute risks for acute and late toxicity from pelvic radiation, the timing of radiation relative to the recovery of urinary function after prostatectomy may have important functional consequences. Sanda et al.9 documented the distinct pattern of change in quality-of-life domains related to urinary continence and sexual function observed in patients after prostatectomy, with deep nadirs at 2 months after treatment. Given that the patients randomized to adjuvant RT initiated treatment at a median of 81 days (ARO 96-02), 90 days (EORTC 22911), or 4 months (SWOG 8794) postoperatively, this timing may adversely impact or even “stall” functional convalescence at a suboptimal level in the recovery process. Furthermore, experience in the primary RT series indicates that postoperative RT may adversely impact erectile function. Finally, although rarely, pelvic irradiation has been associated with an increased risk for secondary malignancies.20,21 These considerations provide further context within which to weigh the risks and benefits when counseling patients on different strategies of postprostatectomy RT.

**Summary and Future Directions**
The data reviewed are important for several reasons,
not least because they challenge some previously prevailing assumptions. The growing body of literature on salvage and adjuvant RT represents an important evolution in the understanding of the natural history of high-risk prostate cancer. Interestingly, when SWOG 8794 was designed some doubt existed about the usefulness of this approach, because the primary risk for failure was believed to be systemic versus local. One somewhat surprising finding was that even at 10 years of follow-up, the risk for distant metastases was surprisingly low (16% in the group randomized to initial observation). Furthermore, the Hopkins salvage RT data showed that the association with survival benefit was strongest for patients with PSADT of less than 6 months—a subgroup associated with high rates of metastatic disease and cancer-specific mortality. This finding was contrary to the previous prevailing belief—including that of the investigators who described that finding—that a short PSADT was synonymous with occult metastatic disease.

In both the adjuvant and salvage settings, postprostatectomy RT may substantially reduce (approximately 50%) the rates of subsequent progression. Taken together, the literature now unequivocally supports the usefulness of secondary RT after RP, even for cases with very high-risk features, and underscores the importance of supporting accrual to the ongoing trials evaluating strategies to optimize local disease control. Nevertheless, the question of whether early salvage RT offers equivalent benefit to adjuvant RT—the main focus of one ongoing clinical trial—remains without a definite answer in 2010. Patterns of failure and response to secondary local treatment suggest that clinical trials focusing on optimizing local control, rather than on systemic therapy alone, may in fact be most important for improving the outlook for patients at high risk for treatment failure.

Ongoing Clinical Trials of Postprostatectomy RT

Currently, 3 prospective trials are ongoing that are hoped to add to the future understanding of some of the complex issues highlighted in this article. In the United Kingdom and Canada, the Radiotherapy and Androgen Deprivation in Combination After Local Surgery trial (RADICALS, MRC PR10) recently opened. Men who have undergone RP may be randomly assigned to either adjuvant or early salvage RT at PSA failure. This RT timing randomization trial aims to recruit approximately 2700 patients from the ambitious overall accrual goal of more than 4000. Additionally, men undergoing either adjuvant or salvage RT will be secondarily randomized to RT alone, RT plus 6 months of hormone therapy, or RT plus 24 months of hormone therapy. This important trial will hopefully identify the optimal timing of post-RP RT and the extent of benefit from the addition of hormonal therapy to secondary RT.

RTOG 96-01 has completed accrual and will be evaluating survival end points for patients who were pT3N0 and/or had positive surgical margins and PSA persistence or progression (0.2–4.0 ng/mL) as the only evidence of failure. Patients were randomized to 64 Gy salvage RT alone or in combination, with 2 years of bicalutamide, 150 mg, daily. The ongoing trial RTOG 05-34 (SPPORT) is evaluating salvage RT versus salvage RT to prostate bed plus 4 to 6 months of hormonal therapy, versus salvage RT to prostate bed and pelvic lymph nodes plus 4 to 6 months of hormonal therapy.

This trial addresses not only the question of the extent of benefit associated with the addition of hormonal therapy to salvage RT, but also whether inclusion of pelvic lymph node fields adds benefit—a question of increasing relevance given the more frequent omission of lymphadenectomy in cases deemed to be of relatively lower risk based on preoperative features.

As the results of these important contemporary trials are pending, an inevitable degree of uncertainty remains regarding the optimal approach for individual patients. As the 2009 update of the NCCN Prostate Cancer Guidelines state, “all men with biochemical progression or adverse features after prostatectomy should be offered salvage or adjuvant RT, respectively…. The reason that all men…should be offered RT is that response has been shown difficult to predict.” For patients with high-risk features at RP or biochemical recurrence after RP, solid evidence shows that secondary RT may provide benefit. Whether an individual patient should receive adjuvant RT on the basis of pathological features alone or initial observation with salvage RT in the event of biochemical recurrence remains a complex and controversial question that should be addressed with shared decision-making.
References


