Postoperative Radiation Therapy for Pathologically Advanced Prostate Cancer After Radical Prostatectomy

Andrew J. Stephenson, Michel Bolla, Alberto Briganti, Cesare Cozzarini, Judd W. Moul, Mack Roach III, Hein van Poppel, Anthony Zietman

Glickman Urological & Kidney Institute, Cleveland Clinic, Cleveland, OH, USA; Centre Hospitalier Régional Universitaire de Grenoble, Grenoble, France; Department of Urology, Università Vita-Salute San Raffaele, Milan, Italy; Department of Radiotherapy, San Raffaele Scientific Institute, Milan, Italy; Division of Urology, Duke University, Durham, NC, USA; Department of Radiation Oncology, University of California-San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA; Department of Urology, University Hospital Gasthuisberg, Katholieke Universiteit Leuven, Leuven, Belgium; Department of Radiation Oncology, Massachusetts General Hospital, Boston, MA, USA

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Abstract

Context: Approximately 15–25% of men who undergo radical prostatectomy for localized prostate cancer (PCa) will experience recurrence of their cancer; men with poorly differentiated cancer, non–organ-confined disease, and positive surgical margins are at the highest risk.

Objective: Review accumulating evidence indicating that postoperative radiotherapy (RT) to the prostate bed favorably influences the course of disease in men with adverse pathologic features.

Evidence acquisition: Three phase 3 randomized trials of adjuvant RT versus observation have reported improved freedom from biochemical recurrence (BCR) and local control: Southwest Oncology Group (SWOG) 8794, European Organization for Research and Treatment of Cancer (EORTC) 22911, and the German Cancer Society (ARO 96-02).

Evidence synthesis: Conflicting evidence from these trials suggests that adjuvant RT can have a favorable impact on systemic progression, PCa-specific mortality, or overall survival. Observational studies have reported durable responses to salvage RT in a substantial proportion of high-risk patients (provided that it is administered at the earliest evidence of BCR) and reduced PCa-specific mortality. There is consensus that the outcome of patients receiving postoperative RT is best when the prostate-specific antigen (PSA) level is the lowest. However, it is unclear if better outcomes will be achieved administering adjuvant RT to all patients at increased risk for recurrent PCa who have an undetectable postoperative PSA level compared to close observation and timely salvage RT at the earliest indications of BCR.

Conclusions: Given the absence of data from randomized trials demonstrating superiority of one approach over the other in terms of quantity and quality of life, we advocate multidisciplinary input and shared and informed decision making among patients, urologists, and radiation oncologists based on the relative advantages and disadvantages of each approach.

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* Corresponding author. Glickman Urological & Kidney Institute, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195, USA. Tel. +1 216-445-1062; Fax: +1 216-636-4492. E-mail address: stephea2@ccf.org (A. J. Stephenson).
1. Introduction

Approximately 15–25% of contemporary men who undergo radical prostatectomy (RP) for the treatment of localized prostate cancer (PCa) will suffer cancer recurrence, manifested initially as an increasing serum prostate-specific antigen (PSA) level known as biochemical recurrence (BCR) [1–3]. Although BCR universally antedates the development of distant metastases and PCa-specific mortality (PCSM), not all men with BCR are destined to experience clinical disease progression due to the condition’s variable natural history. Risk factors for progression to distant metastases and PCSM include short postprostatectomy PSA doubling time (PSA DT), pathologic Gleason score 8–10, and short disease-free interval from RP to BCR [4–6]. Emerging evidence indicates that postoperative radiotherapy (RT; given as adjuvant therapy to men with high-risk pathologic features or as salvage therapy for those with BCR) significantly reduces the risks of PSA progression and local recurrence and may reduce the risk of distant metastases and PCSM.

Within the framework of a multidisciplinary approach, the aim of this article is to review the data concerning the pros and cons of immediate or adjuvant RT or of an approach involving delayed or salvage RT once BCR occurs, taking into account survival data and morbidity, to tailor the therapeutic decision with patients.

2. Rationale for postoperative radiotherapy

For men at risk for BCR or those with a rising PSA level, the initial critical management issue is determining whether recurrent disease (if it occurs) arises from the prostatic bed, from pelvic lymph nodes, or at a distant site, as postoperative RT may potentially cure men with the former two. Emerging evidence suggests that the initial pattern of treatment failure for men with recurrent disease after RP is predominantly local [7]. In a randomized trial of RP versus watchful waiting for clinically localized PCa, the 8-yr cumulative incidence of biopsy-proven local recurrence compared to distant metastasis after RP was 19% versus 13%, respectively [8]. Studies of pelvic imaging modalities in men with postprostatectomy BCR have reported evidence of local recurrence in 42–81% [9–12]. Salvage RT series have reported complete responses (post-RT PSA decline to undetectable levels) in ≥60% of men [13–16]. Thus, postoperative treatment strategies that target local persistence or recurrence may reduce the risk of systemic progression.

This concept is supported by data from randomized trials of adjuvant RT versus observation showing that the former is associated with significant reductions in PSA and clinical progression [17–19]. Several observational studies of salvage RT have shown durable complete responses in a substantial proportion of patients with adverse features [13,14,20]. A recent study also reported a reduction in PCSM among men with BCR and a short PSA DT who received salvage RT compared to those who did not [21].

3. Postoperative radiotherapy: adjuvant versus salvage

Although the benefits of adjuvant and salvage RT are apparent, the superiority of each approach remains to be determined because no randomized trials directly compare adjuvant and salvage RT. The paradigm of adjuvant RT is established for cancers of the breast and colon, for which randomized trials have demonstrated improvements in local control and overall survival (OS) [22,23]. However, unlike breast and rectal cancers, it is widely believed that serum PSA is an exquisitely sensitive marker of recurrent disease. The use of PSA may enable effective RT to be delivered in the salvage setting at an early stage, at a time when recurrent disease may remain localized to the prostatic bed. Observational studies suggest that BCR antedates the appearance of distant metastases by an average of 5–8 yr [24]. The development of ultrasensitive PSA assays (which can detect serum levels as low as 0.008 ng/ml) has enhanced the ability to detect recurrent PCa at an earlier stage and may lead to improved outcomes with salvage RT. Although the optimal PSA level to administer treatment is not defined, there is consensus that it should be given once a rising PSA trend indicative of recurrent cancer is confirmed.

We review the evidence in support of adjuvant and salvage RT and the relative advantages associated with each approach. We define adjuvant RT as that administered to the prostate bed in men with an undetectable postoperative PSA level. There is no specific time course for administering adjuvant RT, although common practice is to wait until postprostatectomy stress urinary incontinence has resolved, due to concerns that it may adversely affect recovery. Adjuvant RT is usually given within 4 mo after surgery; it was given within 3–6 mo of surgery in the three randomized trials. We consider postoperative RT given in the presence of a detectable and rising PSA (regardless of the absolute level) to be salvage therapy (provided that the detectable PSA level is measured at least 4–6 wk after RP to account for the half-life of PSA). However, it is important to bear in mind that most retrospective studies and none of the randomized trials testing adjuvant RT used an ultrasensitive assay.

3.1. Adjuvant radiotherapy

The rationale for adjuvant RT is based on several factors. First, the pattern of treatment failure suggests local failure is the most common site of recurrence in men without lymph node metastasis. Second, adjuvant RT is likely to be more effective than salvage RT because initially isolated local recurrence may disseminate outside the pelvis if one waits until evidence of recurrent disease. Third, adjuvant RT is likely to be more effective and less toxic than salvage RT because the former is given for unmeasurable persistent disease (as opposed to measurable persistent or recurrent disease) and may require a lower radiation dose [25–27]. The latter point is controversial for contemporary patients because these studies analyzed the outcomes of patients...
receiving salvage RT for “objective” recurrence (palpable mass on rectal examination and/or biopsy-proven local recurrence) and the most common indication now is a rising PSA level without clinical evidence of local failure. However, a retrospective series in contemporary patients showed improved disease control among patients receiving salvage RT at doses ≥70.2 Gy [28].

Adjuvant RT has been administered to men with adverse pathologic features after RP for decades. Observational, nonrandomized, comparative studies of adjuvant and salvage RT consistently reported improved BCR with the adjuvant approach [29–35]. The validity of these results is questionable due to the lack of randomization and the methodological limitation of comparing disease-free rates between a group of men with a theoretical risk of BCR (adjuvant group) and one with established BCR (salvage group). None of these studies was able to account for the true denominator in the salvage group: the proportion of patients with similar features who were initially observed after RP and who never manifested BCR. Many men in these studies received adjuvant RT for isolated extraprostatic extension and/or positive surgical margins (PSMs), and an estimated 60–70% of patients with these features will be cured by RP alone [36–38].

Definitive evidence that adjuvant RT improves the outcome of men with pathologically advanced PCs is available from three phase 3 randomized trials: Southwest Oncology Group (SWOG) 8794, European Organization for Research and Treatment of Cancer (EORTC) 22911, and the German Cancer Society (ARO 96-02) (Table 1) [17–19,39]. All three trials reported significant improvements in local control and freedom from BCR with adjuvant RT, and SWOG 8794 reported improved metastasis-free survival and OS and decreased the need for androgen deprivation therapy (ADT).

Between 1988 and 1997, SWOG 8794 randomized 425 men with non–organ-confined cancer or PSMs (pT2 + N0M0 or pT3N0M0) to immediate adjuvant RT using 60–64 Gy by conventional technique versus observation [17]. Because the study did not require men to have an undetectable PSA prior to study entry, 33% of men in both arms had PSA > 0.2 ng/ml at the time of randomization. The use of salvage RT was not mandated by protocol in the observation arm, and a total of 70 men (33%) ultimately received postoperative RT (most for a rising PSA). The median PSA at the time of salvage RT in these men was 1.0 ng/ml, which would be considered “late” salvage therapy by current standards.

Over a median follow-up of almost 13 yr, adjuvant RT was associated with a significant improvement in the metastasis-free survival (hazard ratio [HR]: 0.7; p < 0.016) and OS (HR: 0.7; p = 0.023) [17]. Metastasis-free survival considers the development of distant metastasis and death from any cause as events. The rate of observed distant metastasis was low (37 [17%] in the observation arm and 20 [9%] in the RT arm), and the majority of events in the analysis of metastasis-free survival and OS were deaths without evidence of metastatic PCs (77 of 114 [68%] in the observation arm and 73 of 93 [78%] in the RT arm). Adjuvant RT was also associated with reductions in the need for salvage ADT (HR: 0.4; p < 0.001) and PSA progression (HR: 0.4; p < 0.001) in the 374 patients with available data on postoperative PSA. In exploratory analyses, all subgroups (Gleason 2–6 vs 7–10, pT3a or PSM vs seminal vesicle invasion [SVI], undetectable vs detectable PSA) appeared to benefit from adjuvant RT with respect to metastasis-free survival. Rectal and urinary toxicity and urethral stricture rates were higher with adjuvant RT, but the overall rates were low.

EORTC 22911 randomized 1005 men with pN0M0 PCs with non–organ-confined disease (84%) or isolated PSMs (16%) to 60-Gy conventional adjuvant RT within 16 wk of RP or observation between 1992 and 2001 [18]. Overall, 301 men (30%) had PSA > 0.2 ng/ml at the time of randomization (157 in the observation arm, 144 in the RT arm). In the observation arm, men with treatment failure were recommended to receive salvage RT. However, only 113 men (51%) with treatment failure received salvage RT, 45% of whom received late RT on the basis of clinically evident locoregional failure. Over a median follow-up of 5 yr, adjuvant RT was associated with a significant improvement in PSA progression-free survival (PPS; the primary end point) (HR: 0.5; p < 0.001) and clinical PFS (HR: 0.6; p < 0.001). Regarding the latter end point, the majority of events were due to locoregional failures (51%) or deaths.

### Table 1 – Major phase 3 randomized trials evaluating adjuvant radiotherapy versus observation after radical prostatectomy

<table>
<thead>
<tr>
<th>First author (yr)</th>
<th>Study design; median follow-up: PSA requirement</th>
<th>Conclusions</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thompson (2009) [17]</td>
<td>pT3 and/or positive margins with or without adjuvant RT; 152 mo; not specified (33% PSA &gt; 0.2 ng/ml)</td>
<td>Improved PSA control, metastasis-free survival, and overall survival</td>
<td>Longest follow-up with one-third receiving salvage therapy with a similar magnitude of benefit</td>
</tr>
<tr>
<td>Bolla (2005) [18,42]</td>
<td>pT3 and/or positive margins with or without adjuvant RT; 127 mo; not specified (30% PSA &gt; 0.2 ng/ml)</td>
<td>Improved PSA control and local failure; no difference in overall survival, metastasis-free survival, or clinical progression-free survival</td>
<td>Benefit restricted to those with positive surgical margins; inadequate follow-up and/or study size to address survival</td>
</tr>
<tr>
<td>Wiegel (2009) [19]</td>
<td>pT3 and/or positive margins with or without adjuvant RT; 54 mo; undetectable PSA (20% PSA &gt; 0.1 ng/ml in intention-to-treat analysis)</td>
<td>Improved PSA control; too few events to assess metastasis and survival end points</td>
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PSA = prostate-specific antigen; RT = radiotherapy.
without evidence of clinical failure (29%). The rate of grade 3 or 4 toxicity was low (<5%) in both arms and was not significantly different. A separate analysis in a subset of 100 patients in this trial did not find an increased risk of urinary incontinence among those randomized to adjuvant RT versus observation [40].

In exploratory analyses, all subgroups of men appeared to derive significant benefit from adjuvant RT in terms of PSA progression (HR: 0.46–0.66; \( p \leq 0.02 \) for all comparisons). However, in a subsequent publication based on retrospective, blinded central pathology review of 552 RP specimens (55%), only surgical margin status caused a statistically significant interaction with the treatment effect \( (p < 0.01) \) to such an extent that the treatment benefit in patients with negative margins (regardless of other risk factors) was not significant [41]. Among patients with PSMs, a beneficial effect for PSA progression was obtained with adjuvant RT in men with high–Gleason score cancers and those with SVI.

In a recent unpublished update of EORTC 22911 after a median follow-up of 10.6 yr, patients receiving adjuvant RT had a significantly improved 10-yr biochemical progression–free probability (HR: 0.5; 95% confidence interval [CI], 0.4–0.6; \( p < 0.001) \), but no significant differences were observed in 10-yr clinical PFS (HR: 0.8; 95% CI, 0.7–1.01; \( p = 0.054) \), 10-yr systemic progression (10% vs 11%, \( p > 0.1) \), or 10-yr OS (81% vs 77%, \( p > 0.1) \) [42]. The authors concluded that conventional adjuvant RT improves biochemical PFS and local control without significantly affecting distant metastases or OS.

ARO 96-02 randomized 388 men with non–organ-confined PCa (pathologic stage pT3abcN0) to adjuvant RT within 12 wk of RP versus observation [19]. Seventy-eight men with a persistently elevated PSA after RP were excluded from the intention-to-treat analysis by protocol design, leaving 307 patients (148 in the adjuvant RT arm, 159 in the observation arm) for analysis of the primary end point, PFS. Over a median follow-up of 54 mo, 67 progression events were observed in the observation arm and 38 in the RT arm (most of which were due to BCR), and the 5-yr PFS was 54% and 72%, respectively (HR: 0.53; 95% CI, 0.4–0.8; \( p = 0.002) \). The benefit in favor of adjuvant RT was also observed when the 78 patients with persistent PSA elevation after RP were included in the analysis \( (p = 0.05) \). There appeared to be a benefit to adjuvant RT across all subgroups, with the exception of those with negative surgical margins. In both groups, the number of metastases \( (n = 9) \) and mortality events \( (n = 13) \) precluded a meaningful analysis of these end points. The rate of grade 3 or 4 late adverse events was low (0.3%).

In summary, these trials have demonstrated convincingly that adjuvant RT compared to observation significantly diminishes the risk of PSA progression and local failure. Despite variations in patient selection and treatment received, all three trials consistently show a 50–60% reduction in the risk of PSA progression. However, SWOG 8794 and EORTC 22911 report conflicting results for the impact of adjuvant RT on distant metastasis and OS. What is consistent between these two trials is a low rate of distant metastases in the observation arm (18% in SWOG 8794 and 11% in EORTC 22911) over a median follow-up of 11–13 yr. The major event driving the improvement in metastasis-free survival and OS with adjuvant RT in SWOG 8794 is a reduction in deaths from competing causes without evidence of distant metastasis. Thus it is uncertain whether adjuvant RT reduces the risk of metastasis and death from PCa compared to observation. Lastly, given that 20–33% of men in these trials had detectable PSA at the time of randomization, an argument could be that they are comparing adjuvant or “early” salvage RT with late salvage RT or no local salvage therapy. Although some may interpret this as evidence supporting early salvage RT, it is possible that greater improvements in all end points would have been observed with adjuvant RT had these trials required an undetectable PSA at the time of randomization in the eligibility criteria.

Dose escalation has been shown in randomized trials to improve the outcome of patients receiving external beam RT as primary therapy for localized PCa [43]. The optimal dose to be given in the postoperative setting to maximize efficacy without increased toxicity is less clear. No current trials are investigating dose escalation in the postoperative setting. The practice at most institutions is to deliver 65–70.2 Gy. Recent studies indicate that doses >70.2 Gy can be given safely using modern conformal therapy with or without image-guided techniques, with some reporting improved outcomes in terms of biochemical progression [28,44,45].

### 3.2. Salvage radiotherapy

The rationale for salvage RT is based on several factors. First, it restricts therapy- and treatment-related complications to those patients who have evidence of BCR. Second, the risk of competing causes of mortality far exceeds the risk of PCSM for the majority of men who are candidates for postoperative RT. Third, the ability of RT to cure patients with residual pelvic disease after RP may not be compromised if it is deferred until the earliest evidence of BCR (ie, early salvage RT when the serum PSA first reaches detectable levels). Fourth, the majority of candidates for adjuvant RT (PSMs and/or extraprostatic extension without evidence of SVI) are cured by RP alone and their long-term risk of PCSM is low.

Unlike adjuvant RT, no evidence from prospective randomized trials currently shows that salvage RT improves freedom from BCR, local failure, distant metastasis, cancer-specific survival, or OS. In addition, no level 1 evidence shows that initial observation and “timely” salvage RT at the earliest evidence of BCR is inferior to adjuvant RT. Existing clinical trials are either ongoing or insufficient to determine whether observation with deferred salvage RT is an inferior treatment strategy compared to immediate adjuvant RT. The trials of adjuvant RT cannot be used as proof that adjuvant RT is superior to salvage RT, as the use of the latter in the observation arm was not dictated by protocol and RT was administered relatively late in the course of recurrent disease among those who received it. In SWOG
PSA level sensitive PSA assay to monitor patients and recommends administered at PSA levels between 0.1 and 0.2 ng/ml. Three or more rising PSA levels, and RT is usually anticy are referred for salvage RT based on a pattern of two or author's practice, high-risk patients with long life expectancy are referred for salvage RT based on a pattern of two or three or more rising PSA levels, and RT is usually administered at PSA levels between 0.1 and 0.2 ng/ml. Similarly, one radiation oncologist (M.R.) uses an ultrasonic PSA assay to monitor patients and recommends salvage RT at the first consistent evidence of a rising PSA level >0.02 ng/ml. However, stable or slowly rising PSA levels <0.5 ng/ml should be interpreted cautiously, as the source of PSA may be residual benign prostate epithelial glands. One of the urologists (J.W.M.) does not administer salvage RT until the PSA is >0.3 ng/ml, due to this concern.

A recent multi-institutional observational study of 1540 patients who received salvage RT between 1987 and 2005 (14% of whom received neoadjuvant ADT for a median of 4 mo) for BCR after RP reported an overall 6-yr progression-free probability of 32% over a median follow-up of 53 mo [14]. However, an estimated 48% who received salvage RT alone without ADT when the PSA was ≤0.50 ng/ml were disease-free at 6 yr compared with 40%, 28%, and 18% when treated at PSA levels of 0.51–1.00, 1.01–1.50, and >1.50 ng/ml, respectively. The ability to control recurrent disease in 50% of men with recurrent PCa with early salvage RT is very similar to the 50% relative reduction in PSA progression seen in SWOG 8794, EORTC 22911, and ARO 96-02.

Retrospective studies have also reported that a substantial proportion of patients with risk factors for metastasis progression and PCSM may achieve a durable response to early salvage RT alone, suggesting that it may lead to a similar improvement in survival as adjuvant RT. In an earlier retrospective study of 501 patients treated with salvage RT for BCR, 15%, 38%, and 70% of patients who were free of PSA progression at 4 yr had Gleason score 8–10, PSA DT <10 mo, and BCR within 12 mo of RP, respectively [13]. Considering men with these risk factors who received salvage RT when the PSA level was ≤1.0 ng/ml, 18–77% were disease-free at 4 yr, depending on their Gleason score, PSA DT, and surgical margin status. In the follow-up study by these investigators in >1500 patients, those with high-risk features such as Gleason score 8–10 and/or PSA DT <10 mo had a 41% chance of being disease free at 6 yr if they received salvage RT when the PSA level was <0.5 ng/ml, and this result was 48% if they also had PSMs [14]. This is clinically significant because this same group of patients has a 60–70% chance of developing metastasis at 6 yr in the absence of salvage treatment [24].

As discussed, a recent, single-institution, retrospective series has reported evidence that salvage RT may reduce the risk of PCSM, and men with short PSA DT appear to derive the greatest benefit [21]. In this study of 635 men with BCR after RP, 238 men who received salvage RT (including 78 who also received ADT) had significantly improved PCSM compared to 397 who received ADT only for biochemical or clinical progression (adjusted HR: 0.32–0.35; p < 0.001) [21]. Although the men who received salvage RT had lower Gleason scores and proportionately fewer had SVI and lymph node metastasis compared to those who were observed, an analysis of outcomes between the groups by PSA DT showed the beneficial impact of salvage RT for PCSM was greatest for those with short PSA DT (<6 mo). Men with longer PSA DT also had reduced PCSM if they received salvage RT, although the low risk of PCSM in this subset limited the statistical power of the study to detect significant differences. In summary, these retrospective studies indicate that timely salvage RT is associated with a reduced risk of clinical progression and PCSM.

As discussed, the majority of men with isolated extraprostatic extension and/or PSMs are cured after RP alone [47]. A recent multi-institutional analysis failed to demonstrate that extensive versus focal PSMs, multiple versus solitary PSMs, or location of a PSM discriminates among men for BCR compared to simply modeling surgical margins as positive versus negative [36]. In addition, the risk of metastasis and PCSM among men with these features is also relatively low. A multi-institutional analysis of >23 000 men who were treated by RP at one of five US academic centers reported a 15-yr PCSM of 2–10% among men with extraprostatic extension or PSMs, and neither parameter was significantly associated with PCSM after adjusting for other parameters [48]. Thus a policy of adjuvant RT for patients with isolated extraprostatic extension and/or PSMs likely represents overtreatment for the majority of these patients who are cured after RP alone. Likewise, the number of men with these features needed to treat with adjuvant RT to affect PCSM is likely to be very high, given the low risk of PCSM. It must be emphasized that the results are derived from patients treated at high-volume hospitals by
Men with pathologic Gleason score 8–10 and/or SVI have a risk of BCR of ≥50% [47], and these men are also at a substantially increased risk of PCSM [48]. In the study by Eggener et al, these factors were the only parameters significantly associated with PCSM in multivariable analysis. The risk of PCSM at 15 yr among men with pathologic Gleason score 8–10 and SVI was 26–37% and 22–27%, respectively. Men with these pathologic features appear to be a cohort with a sufficiently increased risk of BCR and PCSM for whom adjuvant RT may be justified; in the adjuvant RT arm compared to the control arm in SWOG 8794 (23.8% vs 11.9%, \( p = 0.002 \)) [17]. Complications included proctitis or rectal bleeding in 3.3% of the treatment group versus no men in the observation group. Urethral stricture rate and total urinary incontinence were also higher in the adjuvant RT arm (17.8% vs 9.5% and 6.5% vs 2.8%, respectively). However, global assessment of quality of life became similar by year 2 and was increasingly superior in the adjuvant RT arm over the following 3 yr. In EORTC 22911, grade 3 toxicity at 5 yr was reported in 4.2% in the adjuvant RT arm versus 2.6% in the wait-and-see group [18]. Although the risk of urinary incontinence with postoperative RT appears to be low, it is anticipated to have a negative impact on recovery of sexual function for previously potent men who have undergone a bilateral nerve-sparing RP. Lastly, external beam RT as primary treatment for localized PCa is associated with a low but significantly increased risk of secondary malignant neoplasms [49,50]. Postoperative RT is likely to be associated with similar risks. In the current era, postoperative RT may be associated with improved toxicity profile and cancer control, given the development of modern conformal therapy with or without image-guided techniques, dose escalation, use of computed tomography–based delineation of the prostate bed, taking into account the operative and pathologic reports and incorporating guidelines for contouring the planning target volume and selecting adequate margins [51].

An unresolved issue is the role of ADT in combination with adjuvant or salvage RT. The benefit of ADT in the primary treatment setting for men with intermediate- to high-risk PCa is well established [52–55]. A rationale for using ADT in the postoperative setting can be found, given the limitations of dose escalation. Observational studies have reported reduced rates of PSA progression when patients received ADT in combination with postoperative RT [14]. The Radiation Therapy Oncology Group (RTOG) 0534 trial is investigating whether the addition of 4–6 mo of ADT improves freedom from clinical progression among men receiving salvage RT. Likewise, EORTC 22043-30041 is a phase 3 randomized trial to evaluate the impact of 6 mo of concurrent/adjuvant ADT for node-negative men receiving adjuvant RT for extraprostatic extension, SVI, and/or PSMs. RTG 9601 evaluated the role of adjuvant high-dose (150 mg) bicalutamide for 2 yr in combination with conventional salvage RT (64.8 Gy) in 771 men with BCR after RP with either extraprostatic extension or PSMs. At median follow-up of 7.1 yr, no significant difference in OS was observed among men who did and did not receive adjuvant bicalutamide (91% vs 86%), although the former experienced improved freedom from PSA progression (57% vs 40%, \( p < 0.001 \)) and lower incidence of distant metastasis (7% vs 13%, \( p < 0.041 \)) but more gynecomastia (89% vs 15%).

It is not clear how high-dose bicalutamide will be incorporated into salvage RT paradigms. Similar evidence exists for adjuvant high-dose bicalutamide in high-risk patients after RP [56], but this treatment approach has not been widely embraced due to concerns of accelerated deaths and gynecomastia [57]. Health Canada has recommended that clinicians discontinue bicalutamide 150 mg in patients with localized PCa based on data from a planned secondary analysis of the Early Prostate Cancer program showing a trend toward accelerated deaths compared with placebo [57]. In RTOG 9601, the combined grade 3–4 toxicities for men who did and did not receive adjuvant bicalutamide were bladder (6% vs 5%), bowel (2% vs 1%), and cardiac (3% vs 2%).

Lastly, the use of postoperative RT in men with pelvic lymph node metastasis after RP is highly controversial. Conventional wisdom has excluded these patients from previous adjuvant RT trials, and few of these patients have been reported in the observational series of adjuvant and salvage RT. This is due to the historical concept that patients with node-positive PCa have coexistent systemic disease. As discussed, several series have suggested a cancer-specific survival benefit with the addition of postoperative RT to ADT in patients with evidence of lymph node metastasis after RP [58,59]. However, evidence of similar benefit from randomized trials is needed for this practice to be widely adopted.

4. Conclusions

Accumulating evidence indicates that postoperative RT to the prostate bed favorably influences the course of disease in men with adverse pathologic features. Three phase 3 randomized trials of adjuvant RT versus observation have reported improved freedom from BCR and local control. SWOG 8794 has reported improved metastasis-free survival and OS with adjuvant RT, although it appeared to have no impact on these end points in EORTC 22911. Similar evidence from randomized trials for salvage RT is lacking. However, several observational studies have reported durable responses to salvage RT in a substantial proportion of high-risk patients (provided that it is administered at the earliest evidence of BCR) and reduced PCSM.
It is unlikely the existing controversy regarding adjuvant versus salvage RT will be resolved in the absence of data from well-designed phase 3 randomized trials showing a clear benefit of one approach over the other in terms of quantity and/or quality of life. The senior author designed a concept for a phase 3 noninferiority trial in SWOG of adjuvant versus salvage RT in a similar patient population to that in SWOG 8794 with similar end points. Due to the substantially improved prognosis of contemporary patients caused by widespread PSA screening and the anticipated low event rate for metastasis and death, an estimated 8000 patients with 20 yr of follow-up would be required to adequately power such a trial. Given current accrual rates to randomized trials within the US cooperative groups, it is unlikely that a trial such would accrue sufficient patients to reach its primary end point. Two phase 3 randomized trials are currently being conducted by the Medical Research Council (RADICALS, Radiotherapy and Combined Androgen Deprivation after Local Surgery) and the Trans-Tasman Radiation Oncology Group (RAVES, Radiotherapy Adjuvant vs Early Salvage following Radical Prostatectomy) that seek to determine whether adjuvant versus salvage RT is associated with differences in PCSM and freedom from PSA progression, respectively. The results of these trials are eagerly anticipated to inform physicians regarding the merits of adjuvant versus salvage RT for men with an elevated risk of cancer recurrence after RP.

Given the lack of conclusive evidence demonstrating the superiority of adjuvant RT over observation (with early salvage RT) in men with risk factors for cancer recurrence after RP, we advocate multidisciplinary input and shared decision making among patients, urologists, and radiation oncologists regarding the relative advantages and disadvantages of each approach. Ideally, patients should be informed of the risks of BCR and PCSM using validated nomograms [47,48] and the impact of either adjuvant RT or salvage RT on reduction of these risks and on quality of life.

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**Study concept and design:** Stephenson, Bolla, Briganti, Cozzarini, Moul, Roach, van Poppel, Zietman.

**Acquisition of data:** Stephenson, Bolla, Briganti, Cozzarini, Moul, Roach, van Poppel, Zietman.

**Analysis and interpretation of data:** Stephenson, Bolla, Briganti, Cozzarini, Moul, Roach, van Poppel, Zietman.

**Drafting of the manuscript:** Stephenson, Bolla, Briganti, Cozzarini, Moul, Roach, van Poppel, Zietman.

**Critical revision of the manuscript for important intellectual content:** Stephenson, Bolla, Briganti, Cozzarini, Moul, Roach, van Poppel, Zietman.

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