

Adjuvant radiotherapy following radical prostatectomy: Genito-Urinary Radiation Oncologists of Canada Consensus Statement

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Abstract

Until the results of 3 randomized trials became known in 2005, the role of adjuvant postoperative radiation therapy following radical prostatectomy was poorly defined. After the publication of these trials, the Genito-Urinary Radiation Oncologists of Canada (GUROC) met and crafted a consensus statement regarding the current place of adjuvant radiation therapy. GUROC also identified gaps in current knowledge and strongly supports ongoing study protocols to further quantify the benefit of postoperative radiotherapy.

This report summarizes the main trial findings and the commentary provided during the consensus-building process. It also outlines the subsequent consensus statement.

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Introduction

The Genito-Urinary Radiation Oncologists of Canada (GUROC) meet every 2 years to discuss current issues and, where appropriate, develop consensus guidelines. Since the last meeting in December 2004,¹ new data have been published concerning the role of adjuvant radiation therapy after radical prostatectomy (RRP). Hence, the January 2007 meeting addressed the changing role of adjuvant and salvage radiation therapy. This article describes the background, the current evidence, the new trials under development and the consensus that was reached at this meeting regarding adjuvant radiation.

Background

RRP is an established curative management for men with low- and intermediate-risk prostate cancer; it is increasingly being used for selected men with high-risk cancers. When compared with watchful waiting in the clinically detected (as opposed to screen detected) population of men with prostate cancer, it has been shown to offer a survival advantage for men aged under 65 years.² For men with low-risk cancer as defined by the Canadian consensus definition,³ the 5-year prostate-specific antigen (PSA) control rates for no biological evidence of disease (bNED) exceed 80%–90%, but as risk category worsens, 5-year control falls to 60%–80%.^{4,5} In large case series from surgical

centres of excellence, 10-year relapse rates are 30%–50%,^{6,7} and 40% of patients will subsequently receive second-line androgen deprivation therapy (ADT).⁸ Survival rates for prostate cancer can be as high as 80% after 25 years, owing to the success of surgery and the indolent nature of prostate cancer in many.⁶

At radical prostatectomy, adverse features that predict increased risk for relapse include positive margins, extracapsular extension, high Gleason grade and seminal vesicle involvement.⁹ Positive margin rates vary not only with presurgery risk group but also with the case load of the surgeon and institution.⁸ In case series, typical margin positivity rates vary from 10% to 30%.¹⁰

It is therefore logical to consider whether a local treatment modality (adjuvant radiation) might provide additional benefits to cure where the risk of locally persistent disease exists. Factors predictive of local relapse after radical prostatectomy include positive margins and extracapsular extension of the tumour. Other adverse features, such as positive seminal vesicles and high Gleason grade, would be expected to predict increased risk of both local and metastatic relapse.

Local recurrence remains a significant problem after surgery. In patients with a rising PSA postoperatively, careful ultrasound-guided biopsies reveal cancer in 54% of those with negative CT scan and bone scan.¹¹ Of those who fail locally, one-third have had apparently negative margins at the time of surgery.¹¹ Molecular marker studies have shown that, even with negative pathological margins according to hematoxylin and eosin stains, 25% showed positive margins when molecular markers were used.¹²

Numerous small retrospective, and in some

cases prospective, observational studies of adjuvant radiation have been published.^{13,14} These small studies typically showed improvements in bNED rates from historic levels of about 50% up to 70%–90% when adjuvant radiation therapy was directed to the prostate bed. However, case-selection and other biases limit the ability to assess the true benefits of adjuvant radiotherapy.

In 2005, the results of 3 large prospective randomized controlled trials (RCTs) of adjuvant radiation therapy were presented orally, and 2 have since been published.^{15–17} On behalf of the Cancer Care Ontario Practice Guidelines Group, Dr. Scott Morgan performed a meta-analysis¹⁸ of RCTs, which was also presented and will be incorporated into a future Ontario clinical guideline. Following these presentations, open discussion led to consensus agreement.

Summary of RCTs

Southwest Oncology Group Study

All studies are summarized in Table 1. The most mature of these studies is the South West Oncology Group (SWOG) 8794 / National Cancer Institute of Canada PR2 study.¹⁵ A sample of 473 men with adverse pathological features (T3 cancer, positive margins or seminal vesicles) were randomized to either observation or immediate adjuvant post-operative radiation therapy (within 4 months). Radiation was delivered to a small volume (field sizes 9 cm × 9 cm or 10 cm × 10 cm) in a single phase to a dose of 60–64 Gy. Patients were conventionally simulated. After a median follow-up of 9.7 years, the PSA relapse rate was halved from

47% to 23% ($p < 0.001$). The bNED benefit was seen across all patient subgroups, with hazard ratios of 0.44 for positive margins, 0.23 for seminal vesicle involvement and 0.4 for the presence of both factors. The use of secondary ADT was reduced by more than one-half to 10% at 5 years.

Rates of metastatic disease were reduced from 43% to 35.5% (hazard ratio [HR] 0.75, 95% confidence interval [CI] 0.55–1.02, $p = 0.06$). The observed reduction in death in the adjuvant arm approached statistical significance (HR 0.80, 95% CI 0.58–1.09, $p = 0.16$). Complication rates (which were not graded according to any scale) were doubled from 12% to 24% in the adjuvant radiation arm. Urinary incontinence was seen in 6.5% versus 2.8%, and urethral stricture in 18% versus 10%.

Comments

The SWOG trial suffered from a lower event rate than anticipated. The trial was underpowered to detect a metastasis-free or overall survival benefit. Because event rates were lower than anticipated, it was estimated that the trial would have needed 2900 men to show statistically significant survival benefits, given the magnitude of effect observed.

European Organisation for Research and Treatment of Cancer 22911 Trial

The second trial was carried out by the European Organization for Research and Treatment of Cancer (EORTC). With 1005 patients, it is the largest adjuvant trial to date, but its median follow-up of 5 years is relatively immature.¹⁶ Patients with capsule invasion (64%), positive margins (50%) or

Table 1. Summary of main trial results

Endpoint	Trial; RR (and 95%CI)*		
	SWOG trial ¹⁵	EORTC 22911 ¹⁶	ARO trial ¹⁷
PSA relapse	0.43 (0.31–1.58)	0.48 (0.37–0.62)	0.4 (HR not stated, $p < 0.001$)
Metastatic relapse	0.75 (0.55–1.02)	—	—
Secondary ADT	0.45 (0.29–0.68)	—	—
Clinical progression	0.62 (0.46–0.82)	0.61 (0.43–0.87)	—
Overall survival	0.8 (0.58–1.09)	1.09 (0.67–1.79)	—

ARO = German Cancer Society; ADT = androgen deprivation therapy; CI = confidence interval; EORTC = European Organization for Research and Treatment of Cancer; PSA = prostate-specific antigen; RR = risk ratio; SWOG = Southeast Oncology Group; — = no data.
*Where available.

seminal vesicle invasion (13%) were eligible. Radiation was directed to the prostate bed within 16 weeks of surgery, and conventional techniques were used: 50 Gy to the surgical bed with a "security margin," followed by a boost of 10 Gy to a smaller margin.

Results were consistent and very similar to those of the SWOG trial: bNED was reduced from 47% to 26% (HR 0.48). Of those who relapsed, just over one-half received salvage radiation therapy. Only 59 metastatic events were observed, with no difference between treatment arms. Twice as many men died of prostate cancer in the observation group, but there was no significant effect on overall survival (HR 1.09), as would be expected with such short follow-up.

Analysis by patient subgroup revealed that margin status is the strongest prognostic factor.¹⁹ Where pathology was centrally reviewed, the benefit of radiation was greatest with positive margins (HR for relapse was 0.38, 95% CI 0.26–0.54, $p < 0.001$), compared with a nonsignificant reduction in relapse of 13% with negative margins (HR 0.87, 95% CI 0.53–1.46, $p = \text{ns}$). The positive margin site (e.g., apex versus posterior) was not a significant factor.

Grade 3 toxicity rates were observed in 4.2% of adjuvant patients versus 2.6% of observation patients ($p = 0.7$). No grade 4 toxicity was observed. It is possible that the lower toxicity rates in the EORTC trial reflected the lower dose or more modern planning techniques or both.

Comments

The EORTC trial population likely does not reflect current North American practice because the trial was not performed in a screen-detected population. In addition, some treated patients had significantly high postoperative PSA levels (i.e., these patients were not in a truly adjuvant situation). There was no consistent management approach for those who relapsed (in either arm). Finally, although morbidity data were reported, there was no quality-of-life measurement. The importance of pathology review was shown by subsequent analysis.¹⁹

German Cancer Society Trial

The third trial, carried out by the German Cancer

Society (ARO 96–02), has only been published in abstract form to date.¹⁷ This is a small trial of less than 300 men, with a median follow-up of 3 years. Nonetheless, results are also very consistent with the above 2 trials: PSA relapse was reduced from 40% to 19% (HR 0.4). Grade 3 late toxicity was only 2%.

Comments

The median follow-up in this study is short, with limited information available from the abstract, and the full publication is awaited.

Meta-analysis of RCTs

Dr. Scott Morgan identified these 3 RCTs as being suitable for inclusion in meta-analysis. Only the SWOG and EORTC trials reported an overall survival end point. According to meta-analysis of these 2 studies, the HR was 0.91 (95% CI 0.67–1.22, $p = 0.52$). Notably, the EORTC data are immature for this end point, and longer follow-up is needed. For the biochemical control end point all 3 trials contributed data. The HR for biochemical control from these 3 studies was 0.45 (95% CI 0.38–0.54, $p < 0.001$). Unfortunately, heterogeneity precluded a pooled analysis of acute and late toxicity data. Specifically the SWOG toxicity data were not graded, and the German trial did not have toxicity data from the control arm.

Overall conclusions in regard to published studies

Adjuvant radiation therapy following radical prostatectomy reduces risk of biochemical failure and locoregional recurrence. It prolongs the time to initiation of ADT.

A rising PSA is common for pT3 tumours after radical prostatectomy. The benefit is seen when margins are negative as well as positive and also when seminal vesicles are involved. Adjuvant radiation therapy reduces the risk of clinical failure by 15%; although no survival advantage has been identified to date, it is too early to assess the effect on survival. Morbidity appears to be slightly increased, although this was noted as being predominantly an increase in grade 2 toxicity. The roles of intensity-modulated radiation therapy, nodal irradiation or androgen deprivation are unclear, given the absence of data.

Current and planned trials

Ongoing and planned trials will address some of the unresolved issues that were presented and discussed. The possible role of ADT in addition to salvage radiation has been studied in the Radiation Therapy Oncology Group (RTOG) trial 9601, with results pending. However, the experimental arm uses bicalutamide, not a luteinizing hormone-releasing hormone agonist, and prior studies in this population were negative.²⁰ EORTC trial 22043 has opened and will accrue 600 men to be randomized between adjuvant radiation and the same with 6 months of adjuvant ADT.

Radiation trials under development include the RADICALS trial in the United Kingdom. This large trial of 1600 men uses a 2 × 3 design randomizing between early versus delayed radiation and short, long or no adjuvant ADT. In 2007, the trial was opened within Canada by the National Cancer Institute of Canada (as PR13). The RTOG is also developing a 2 × 2 design trial to address the role of whole-pelvic radiation and adjuvant ADT in addition to local prostate bed irradiation. A competing trial of adjuvant taxotere given postprostatectomy, sponsored by Sanofi-Aventis, opened briefly in 2007 before closing. The trial was designed to detect a relative progression-free survival improvement of 30%. Because adjuvant trials of radiation have already demonstrated a halving of recurrence rates, accrual to this trial proved difficult.

Summary and group consensus

The natural history of PSA relapse is a median time to metastatic disease of 8 years,⁷ with variation dependant on PSA kinetics postoperatively and Gleason grade.⁹ There is thus a long latent (asymptomatic) interval before clinical disease becomes apparent. During this interval, radiation may be given early (adjuvant) or when PSA relapse becomes evident (early salvage) or when the PSA has risen significantly (delayed salvage) or when the disease has manifested clinically ("too late salvage"). The efficacy of delayed or late salvage radiation is significantly poorer than when given adjutantly or with early PSA relapse. Complication rates are increased after adjuvant radiation therapy, and many patients will be overtreated. Careful case selection and discussion with a radiation

oncologist about the advantages and disadvantages of adjuvant or salvage treatment is essential.

The main topic of debate at the meeting was whether or not early salvage radiation (i.e., when biochemical relapse is first detected, as defined by a rising PSA greater than 0.2 ng/mL) might achieve outcomes similar to those of adjuvant radiotherapy. It was noted that the randomized studies to date likely represented a randomization between adjuvant radiotherapy and a heterogeneous group of PSA failures (early PSA failures, patients with moderate PSA elevation and later PSA failures). It was recognized that, until ongoing and planned trials are completed and matured, the role of adjuvant radiotherapy as opposed to true early PSA salvage therapy will remain unresolved.

There was general agreement that ADT was not usually indicated in the adjuvant setting. It was noted that men who have received RRP had previously chosen a curative approach to their disease and that the evidence of benefit and toxicity should be discussed with them.

Consensus statement

After these presentations and discussion, the following consensus statement was approved:

Preamble:

- Three RCTs have established the benefit of adjuvant radiotherapy following prostatectomy where adverse pathological features exist (margin positive or seminal vesicle positive or T3a).
- Adjuvant radiation therapy has been shown to improve relapse-free survival (bNED) and decrease local relapse and use of secondary androgen ablation therapy. Similar benefits were consistent across all prognostic subgroups. The absolute improvement in relapse-free survival was 25%. In the most mature study, metastatic rate was reduced by an absolute 10% ($p = 0.06$).
- The impact on survival has not been determined. Trials were either underpowered or have had inadequate follow-up for this end point, and longer follow-up is required.

On the basis of the available evidence, the following are GUROC recommendations:

- Consultation with a radiation oncologist early in the postoperative period is advised to discuss benefits and side effects of adjuvant radiotherapy in those with adverse pathological features at prostatectomy.

- It is recommended that patients should be offered adjuvant external beam radiotherapy (within 6 months of surgery) and should be informed that it reduces the risk of biochemical failure and locoregional failure and delays or reduces the need for androgen deprivation therapy.
- Patients should be offered entry into RCTs to address:
 - the role of early salvage compared with adjuvant radiotherapy
 - the role of adjuvant radiotherapy combined with ADT.

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Correction

The correct order of authors for an abstract published in the *Canadian Urological Association Journal*^a is G. Godoy, H. Hajian, CJ Zappavigna, A. Hurtado-Coll, RF Paterson, BH Chew, SL Goldenberg.

Reference

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