**Editorial**

**RADICALS (Radiotherapy and Androgen Deprivation in Combination after Local Surgery)**


(The RADICALS Trial Management Group)

*Academic Unit of Radiotherapy and Oncology, Institute of Cancer Research and the Royal Marsden NHS Foundation Trust, Downs Road, Sutton, Surrey SM2 5PT, UK; †Salford Royal Hospitals NHS Trust, Salford M6 8HD, UK; ‡Christie Hospital NHS Trust, Manchester M20 4BX, UK; ‖Department of Oncology, UCH, 250 Euston Road, London NW1 2PQ, UK; ¶Princess Margaret Hospital, 610 University Avenue, Toronto, ON, Canada M5G 2M9;  Department of Urology, University Hospital of Wales, Heath Park, Cardiff CF14 4XW, UK; **MRC Clinical Trials Unit, 222 Euston Road, London NW1 2DA, UK; ††University of Ottawa, The Ottawa Hospital General Campus, 501 Smyth Road, Ottawa, ON, Canada K1H 8L6; §§National Cancer Institute of Canada (NCIC) Clinical Trials Group, 10 Stuart Street, Kingston, Ontario, Canada K7L 3N6; §§PCaSO Prostate Cancer Network, PO Box 66, Emsworth, Hampshire PO10 7ZP, UK

**Introduction**

Radical prostatectomy is a standard of care for men with localised prostate cancer. The routine use of postoperative adjuvant therapy has shown survival benefits in other cancer types, such as breast and colorectal cancer, but has not been well studied in prostate cancer. This article describes the background to, and the design of, RADICALS (Radiotherapy and Androgen Deprivation in Combination after Local Surgery), an international, phase III randomised controlled trial of adjuvant treatment after radical prostatectomy.

**Background**

**Radiotherapy Timing**

There are just two published randomised controlled trials of adjuvant radiotherapy in prostate cancer [1,2]. EORTC 22911 randomised 1005 patients with pT3 disease at radical prostatectomy between adjuvant radiotherapy and a ‘wait and see’ policy. Patients in the ‘wait and see’ arm of the trial were recommended to have salvage radiotherapy only in the event of local recurrence (and not for prostate-specific antigen [PSA] failure alone). At a median follow-up of 5 years, a statistically significant advantage was reported for adjuvant treatment in terms of biochemical progression-free survival (74% vs 53%; hazards ratio [HR] 0.48, 98% confidence interval [CI] 0.37–0.62; \( P < 0.0001 \)) and clinical progression-free survival (87% vs 77%; HR 0.61, 98% CI 0.43–0.87; \( P = 0.004 \)). Follow-up was relatively short, and just 37 patients had developed metastatic disease, 19 in the adjuvant radiotherapy arm and 18 in the ‘wait and see’ arm. Similarly, there were only 64 deaths reported, 32 in each trial arm. The quality-of-life data from this trial has yet to be published, but ‘all types and all grades of late effects [of treatment on bladder and bowel function] were more common in the postoperative irradiation group’ [1].

SWOG 8794 (NCIC PR-2) had a similar design: 425 men with pT3 disease were randomised to either adjuvant radiotherapy or observation to the prostate bed, with a median follow-up at the time of analysis of 10.6 years. Once again, adjuvant radiotherapy was associated with a statistically significant improvement in biochemical control (HR 0.43, 95% CI 0.31–0.58, \( P < 0.001 \)). Interestingly, adjuvant radiotherapy was also associated with a trend towards better metastasis-free survival (HR 0.75, 95% CI 0.55–1.02, \( P = 0.06 \)), and overall survival (HR 0.80, 95% CI 0.58–1.09, \( P = 0.16 \)). Proctitis (3.3% vs 0%; \( P = 0.02 \)), urethral stricture (17.8% vs 9.5%; relative risk [RR] 1.9, 95% CI 1.1–3.1, \( P = 0.02 \)) and urinary incontinence (6.5% vs 2.8%; RR 2.3, 95% CI 0.9–5.9, \( P = 0.11 \)) were seen more often in the adjuvant radiotherapy arm.

What can we learn from these two trials? They provide good evidence that postoperative radiotherapy can reduce the risk of PSA failure, albeit at the price of increased toxicity. There is also a real suggestion from the SWOG trial that, in comparison with observation plus late salvage radiotherapy, adjuvant radiotherapy may lead to a meaningful improvement in overall survival.

However, clinical practice after radical prostatectomy has evolved since the SWOG and the EORTC trials were designed in the 1980s. In particular, salvage radiotherapy is now typically given early (at the time of biochemical relapse), rather than when local recurrence is clinically

---

0936-6555/07/190167-05 $35.00/0 © 2007 The Royal College of Radiologists. Published by Elsevier Ltd. All rights reserved.
palpable: this may lead to a significant improvement in the efficacy of salvage treatment. For this reason, the 'benefit' seen for adjuvant radiotherapy should not lead to the general acceptance of treatment in the adjuvant setting. Instead, the results provide a strong rationale for a comparison between adjuvant radiotherapy and the current standard of care, which is observation with early salvage radiation for biochemical failure.

Hormone Duration

One question that has received little or no attention to date is that of the optimum duration of hormone treatment in patients receiving postoperative radiotherapy to the prostate bed. Several randomised controlled trials have shown that the addition of hormone therapy improves overall survival in men receiving primary (not postoperative) radiotherapy for prostate cancer [3–5]. However, there are no completed randomised controlled trials addressing the role of hormone therapy in men receiving postoperative radiotherapy to the prostate bed. Three retrospective studies have compared the outcome of salvage radiotherapy alone vs salvage radiotherapy plus short-term (4–6 months) androgen deprivation, and have observed improved biochemical control rates with the addition of androgen deprivation [6–8]. In addition, RTOG 96-01 recruited 840 patients with PSA failure after radical prostatectomy, who were randomised between early salvage radiotherapy alone vs early salvage radiotherapy plus 2 years of bicalutamide 150 mg daily, with overall survival as the main outcome measure. The first outcome data are expected in 2008. In the context of primary radiotherapy for prostate cancer, there may be a benefit to longer, rather than shorter, durations of hormone therapy. RTOG 92-02 randomised 1554 men receiving radiotherapy as primary treatment for locally advanced disease between short-term (4 months) and long-term (28 months) androgen deprivation. Long-term therapy was associated with improved 5-year cause-specific survival (95% vs 91%, \( P = 0.006 \)), although with no evidence to date of a significant difference in overall survival at 5 years (80% vs 79%, \( P = 0.73 \)) [9].

Rationale

Radical prostatectomy is a common operation. Hospital episodes’ statistics report that 3413 such operations were carried out in England in 2004. This is a significant underestimate because it does not include operations carried out outside the National Health Service. SWOG 8794 and EORTC 22911 have shown that immediate postoperative radiotherapy may have a meaningful benefit compared with surgery alone, but a policy of early salvage radiotherapy for PSA failure has not been tested in a randomised controlled trial. The lack of randomised controlled trials addressing the optimum duration of hormone therapy in combination with postoperative radiotherapy is an important omission. The popularity of radical prostatectomy presents an opportunity for a large, randomised controlled trial addressing both the timing of postoperative treatment (immediate vs early salvage) and the duration of hormone therapy (none vs short term vs long term) used in addition to prostate bed radiotherapy. The overall aim is to define the optimum management for men after radical prostatectomy, avoiding both the cost and morbidity of over-treatment, and the risks of disease progression associated with under-treatment.

Trial Design

RADICALS is a large phase III randomised controlled trial with two randomisations (Fig. 1). The first randomisation, carried out within the 3 months after radical prostatectomy, is defined as the Radiotherapy Timing Randomisation. The second randomisation, carried out before the administration of radiotherapy, is defined as the Hormone Duration Randomisation. Patients may be entered into one or both randomisations. The eligibility criteria are deliberately broad, to allow any patient who has a radical prostatectomy to take part, where there is uncertainty about the appropriate postoperative treatment.

Trial Entry

After radical prostatectomy, some men are at low risk of recurrence (e.g. pT3, Gleason score 6, margin negative, pre-operative PSA < 10 ng/ml) and they would normally be managed by observation with PSA monitoring. At the other end of the spectrum, patients with a persistently detectable PSA ≥ 0.2 ng/ml may typically be recommended to receive immediate additional therapy. That leaves the remainder, who have a postoperative PSA < 0.2 ng/ml, but some risk factors for disease recurrence (e.g. pT3 or positive margins or Gleason score > 6 or pre-operative PSA > 10 or a combination of these) in whom there is uncertainty about the use of immediate postoperative treatment. These patients may be randomised within 3 months of radical prostatectomy between immediate radiotherapy and early salvage radiotherapy for PSA failure (Radiotherapy Timing Randomisation).

Before postoperative radiotherapy (whether immediate or early salvage), patients may be randomised between no hormone therapy, short-term hormone therapy (6 months duration) and long-term hormone therapy (24 months duration) (Hormone Duration Randomisation). This means that for patients receiving early salvage radiotherapy, the Hormone Duration Randomisation may take place months or even years after radical prostatectomy. Patients who were following a postoperative early salvage radiotherapy policy (PSA monitoring) off-trial and who develop PSA failure for which they are due to receive early salvage radiotherapy, may join RADICALS at the time of radiotherapy to take part in the Hormone Duration Randomisation. The overall trial schema is shown in Fig. 2. At least during the pilot stage of the trial, patients can elect to be randomised between two rather than all three of the hormone duration arms.

Radiotherapy Treatment

'Immediate' radiotherapy to the prostate bed will start within 2 months after the Radiotherapy Timing Randomisation.
Radical prostatectomy

Assess need: Is immediate post-operative RT required?

Uncertain

Yes

No

Trial follow-up

Hormone duration

RANDOMISATION

Radiotherapy

Alone

Radiotherapy + 6 months hormone therapy

Radiotherapy + 2 years hormone therapy

Salvage RT Policy

(RT for PSA failure)

Fig. 1 — The RADICALS trial has two separate randomisations. Patients may take part in one or both.

Radical prostatectomy

- overall design

Yes

Immediate RT

Immediate RT

RT timing

RANDOMISATION

Hormone duration

RANDOMISATION

Trial follow-up

Outcome measures

Key

On trial

Off trial

Treatment

RT + no HT

RT + 6mo HT

RT + 2yr HT

Salvage RT Policy

Monitor on trial

At rising PSA

Monitor off trial

Fig. 2 — Overall trial design.
Patients randomised to follow a policy of selective early salvage radiotherapy will be closely monitored, with radiotherapy to the prostate bed given in the event of biochemical failure. Serum PSA will be tested at each follow-up visit and more often if a rising PSA is detected. Biochemical failure is defined as either two consecutive rises in PSA level and a PSA > 0.1 ng/ml, or three consecutive rising PSA levels. If postoperative biochemical failure is confirmed, patients will receive prostate bed radiotherapy. The treatment will be computed tomography planned, and given to a dose of 66 Gy in 33 daily fractions over 6.5 weeks. Alternatively, centres may use a 4-week schedule of 52.5 Gy in 20 fractions. Defining the target volume for prostate bed radiotherapy has proved controversial, and the protocol includes clear guidelines on target localisation, based on the technique developed by Wiltshire and colleagues [10] from the National Cancer Institute of Canada, modified according to feedback at the 2006 British Uro-oncology Group annual meeting.

Hormone Therapy

Patients randomised to short-term hormone therapy in conjunction with postoperative radiotherapy should receive treatment using a gonadotrophin-releasing hormone analogue (GnRHa) for 6 months. Because of the possibility of tumour ‘flare’, an anti-androgen (such as cyproterone acetate 100 mg tds) should be used for 1 week before the first GnRHa administration, and continued for a total of 3 weeks. The choice of GnRHa may vary according to local practice (e.g. goserelin, leuprorelin), but where possible, 1-month preparations (e.g. goserelin 3.6 mg, leuprorelin 3.75 mg) should be used rather than longer-acting preparations in order to hasten testosterone recovery after the treatment period. Bicalutamide monotherapy 150 mg daily for 6 months is a satisfactory alternative. The choice of either a GnRHa or anti-androgen monotherapy will be a stratification variable.

Patients randomised to long-term hormone therapy with postoperative radiotherapy should receive treatment using a GnRHa for 24 months. In this context, the use of 3-month depot preparations (e.g. goserelin 10.8 mg, leuprorelin 11.25 mg) is encouraged in the interests of patient convenience, but 1-month or 2-month depots are acceptable. Bicalutamide monotherapy 150 mg daily for 24 months is once again a satisfactory alternative, but, in this case, patients should receive prophylactic radiotherapy to the breast buds to prevent painful gynaecomastia.

Outcome Measures and Sample Size

The primary outcome measure will be cause-specific survival. Secondary outcomes will include overall survival, non-protocol androgen deprivation, and patient-reported treatment toxicity. RADICALS is designed to identify treatment options with an absolute increase in 10-year cause-specific survival of at least 5%. A total of 2600 patients in the Radiotherapy Timing Randomisation could detect an increase in 10-year cause-specific survival from 80% to 85% with 90% power and a 5% significance level. This can be achieved with a recruitment rate of about 500 patients per year. About 3100 patients would be required for the Hormone Duration Randomisation.

Quality-of-life Studies

There are limited patient-reported data on symptoms and morbidities associated with treatments after prostatectomy. The RADICALS trial presents an important opportunity to collect these data prospectively. Two specific questions will be addressed:

- What is the long-term effect of postoperative radiotherapy on sexual function, urinary function and bowel function?
- How does the duration of androgen deprivation affect long-term sexual function and overall quality of life?

Patients will be asked to complete four short questionnaires: the SF-12 (general quality of life), ICSSex (sexual functioning), ICSSmaleSF (urinary functioning) and the Vaisey (bowel function). In total, patients will be asked around 50 questions at each quality-of-life assessment. These assessments will only be carried out at baseline, 1 year, 5 years and 10 years, as it is the long-term legacy of treatment, rather than the reversible short-term effects, that matter most in relation to patient decision-making.

Summary

RADICALS is a large, international randomised controlled trial addressing two of the most important questions in postoperative management after radical prostatectomy: the timing of postoperative radiotherapy (immediate vs early salvage) and the duration of hormone therapy (none vs short term vs long term) used in addition to prostate bed radiotherapy. It has been funded by the Clinical Trials Awards Advisory Committee and will be run by the Medical Research Council Clinical Trials Unit, in collaboration with the National Cancer Institute of Canada Clinical Trials Group and the Trial Management Group. Additional international collaborative groups are also being invited to take part. RADICALS is an ambitious trial, aiming to recruit over 4000 patients. Widespread support from the urological and oncological communities will be required. More information relating to this study is available from the Medical Research Council Clinical Trials Unit via: radicals@ctu.mrc.ac.uk.

Author for correspondence: Chris Parker, Academic Unit of Radiotherapy and Oncology, Institute of Cancer Research, Downs Road, Sutton, Surrey SM2 5PT, UK. Tel: +44-208-661-3425; E-mail: chris.parker@icr.ac.uk

Received 14 December 2006; received in revised form 22 December 2006; accepted 9 January 2007

References


