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Adjuvant radiotherapy following radical prostatectomy for prostate cancer (Review)

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TABLE OF CONTENTS

[Intervention Review]

Adjuvant radiotherapy following radical prostatectomy for prostate cancer

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ABSTRACT

Background

Men who have a radical prostatectomy (RP) for prostate cancer that does not involve lymph nodes, but extends beyond the prostate capsule into the seminal vesicles or to surgical margins, are at increased risk of relapse. In men with these high risk factors, radiotherapy (RT) directed at the prostate bed after surgery may reduce this risk, and be curative.

Objectives

To evaluate the effect of adjuvant RT following RP for prostate cancer in men with high risk features compared with RP.

Search methods

We searched the Cochrane Prostatic Diseases and Urological Cancers Specialised Register (23 February 2011), the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE (January 1966 to February 2011), PDQ® (Physician Data Query) trial registry databases for ongoing studies (2 November 2010), reference lists from selected studies and reviews, and handsearched relevant conference proceedings.

Selection criteria

Randomised controlled trials (RCT) comparing RP followed by RT with RP alone.

Data collection and analysis

Two authors independently assessed the studies for inclusion and bias and extracted data for analysis. Authors were contacted to clarify data and obtain missing information.

Main results

We found three RCTs involving 1815 men. Adjuvant RT following prostatectomy did not affect overall survival at 5 years (RD (risk difference) 0.00; 95% CI -0.03 to 0.03), but improved survival at 10 years (RD -0.11; 95% CI -0.20 to -0.02). Adjuvant RT did not improve prostate cancer-specific mortality at 5 years (RD -0.01; 95% CI -0.03 to 0.00). Adjuvant RT did not reduce metastatic disease at 5 years (RD -0.00; 95% CI -0.04 to 0.03), but reduced it at 10 years (RD -0.11; 95% CI -0.20 to -0.01). It improved local control

at 5 and 10 years (RD -0.10; 95% CI -0.13 to -0.06 and RD -0.14; 95% CI -0.21 to -0.07, respectively), and biochemical progression-free survival at 5 years and 10 years (RD -0.16; 95% CI -0.21 to -0.11 and RD -0.29; 95% CI -0.39 to -0.19, respectively). There were no data for clinical disease-free survival. Adjuvant RT increased acute and late gastrointestinal toxicity [do you have the rd for this?], urinary stricture (RD 0.05; 95% CI 0.01 to 0.09) and incontinence (RD 0.04; 95% CI 0.01 to 0.08). It did not increase erectile dysfunction or degrade quality of life (RD 0.01; 95% CI -0.06 to -0.26), but with limited data.

Authors' conclusions

Adjuvant RT after RP improves overall survival and reduces the rate of distant metastases, but these effects are only evident with longer follow up. At 5 and 10 years it improves local control and reduces the risk of biochemical failure, although the latter is not a clinical endpoint. Moderate or severe acute and late toxicity is minimal. There is an increased risk of urinary stricture and incontinence, but no detriment to quality of life, based on limited data. Given that the majority of men who have undergone a RP have a longer life expectancy, radiotherapy should be considered for those with high-risk features following radical prostatectomy. The optimal timing is unclear.

PLAIN LANGUAGE SUMMARY

Radiotherapy after surgery for prostate cancer

Surgical removal of the prostate has a high chance of cure when prostate cancer is confined to the prostate. High-risk features (ie, cancer that has spread through the capsule surrounding the prostate into the nearby seminal vesicles or to the edge of the surgical specimen) found at the time of surgery increase the risk of the cancer recurring. Recurrence of cancer might show up as an abnormal blood test (increased prostate-specific antigen (PSA)), local recurrence at the site of the prostate, or distant spread (most commonly to bones).

Radiotherapy, using external X-rays directed where the prostate was in the pelvis, has the potential to kill any prostate cancer cells left behind, and improve the chance of cure. On the other hand, it may cause problems with bladder, bowel or sexual function. In some men it may be futile if the prostate cancer cells have already spread beyond the pelvis. This review looked at whether radiotherapy given after surgery for prostate cancer with these high risk features was effective in reducing the risk of prostate cancer recurring, whether it made men live longer, and what the side effects were.

One trial with longer follow up (more than 10 years) showed improved survival with adjuvant radiotherapy but this improvement did not exist at 5 years follow up. Radiotherapy reduced the number of men whose cancer spread to other parts of the body (metastases). We found that radiotherapy improved local control in the prostate bed and did reduce the risk of cancer recurring. Radiotherapy reduced the number of men with an abnormal PSA blood test, but the importance of this is uncertain. Radiotherapy does increase the risk of side effects, (mostly mild) affecting bladder and bowel function.

It is not clear from these studies whether it is better to give radiotherapy immediately after surgery when these high risk features are present, or whether it would be just as good watching for a time, and only giving radiotherapy once the PSA blood test starts to rise. This is the subject of ongoing studies. Radiotherapy after radical prostatectomy should be considered if high risk features are present, but the optimal timing is unclear.

BACKGROUND

Globally, prostate cancer is the second most common malignancy diagnosed in men, with 903,500 estimated new cases worldwide in 2008 (Jemal 2011). It is the second most common cause of death after lung cancer in the United States (Jemal 2010)). The incidence has increased over the last few decades, largely due to the increasing use of prostate specific cancer antigen (PSA) screening. This has also led to an increase in the proportion of men diagnosed with prostate cancer who have clinically localized disease (Cooperberg 2004).

The natural history of prostate cancer varies considerably. Prostate cancer may behave aggressively, causing significant morbidity and

death. For many men, however, the disease has an indolent course. Given this, and the fact that prostate cancer occurs more often in older men in whom life threatening co-morbid conditions are more common, many men die with prostate cancer rather than from it. Appreciation of the variable behavior of prostate cancer has lead to considerable debate about optimal treatment.

There are a number of valid treatment options for men with localized prostate cancer (clinically confined to the prostate). These include RP, external beam radiotherapy (EBRT), interstitial prostate brachytherapy (radiation therapy delivered directly to the prostate, either using permanently implanted radioactive seeds or temporary catheters containing a radiation source), hormonal therapy, combinations of these, active surveillance, or observation.

There is evidence from randomised trials that radical prostatectomy reduces the risk of distant metastasis and death from prostate cancer compared to observation in men with prostate cancer detected primarily by methods other than PSA testing (Bill-Axelson 2011). No randomised trials have compared radical prostatectomy with contemporary radiotherapy, although large single and multi-institutional trials suggest similar 5 and 10-year survival (Kupelian 2004; Kupelian 1997a). For each man the choice of treatment depends on consideration of tumour, patient and treatment-related factors. Tumour-related factors, such as PSA and Gleason score, help to predict the natural history of the disease. Patient-related factors, including co-morbid conditions and life expectancy, may help to predict whether a man's cancer is likely to cause bother in his lifetime. Men also need to consider that treatments differ in their effect on urinary, sexual and bowel functioning.

Radical prostatectomy is a surgical procedure which involves the removal of the entire prostate gland with seminal vesicles and the ampulla of the vas deferens. Depending on the characteristics of the tumour and the man's sexual function, this may involve sparing of the neurovascular bundle, which increases the likelihood of preserving potency. Lymph node dissection may be performed if the risk of lymph node involvement is high, and if nodes are positive, the prostate would not necessarily be removed. Men most suitable for radical prostatectomy are those with a life expectancy of at least 10 years with disease that does not extend beyond the prostate capsule.

After radical prostatectomy, if all normal and malignant prostate tissue is removed, PSA levels should fall to undetectable levels by the sixth week postoperatively. Even in appropriately selected men, up to a third undergoing radical prostatectomy will experience PSA failure (biochemical progression), with persistently detectable or rising postoperative levels, within 10 years (Amling 2000; Han 2003; Hull 2002; Pound 1999; Roehl 2004; Ward 2003). PSA failure may reflect residual local disease, distant metastatic disease, or both. PSA failure predicts a higher risk of clinical failure and death from prostate cancer. Nearly two-thirds of men with PSA failure after radical prostatectomy who do not receive salvage therapy develop metastatic disease within 10 years. The median survival for men who develop metastatic disease is less than 5 years (Pound 1999).

Factors predicting a higher risk of relapse after radical prostatectomy have been identified. These include a high preoperative PSA (> 10 ng/mL (nanograms/millilitre), a short PSA doubling time (PSADT), and pathological factors such as a high Gleason grade (> 7), extracapsular extension, invasion of the seminal vesicle, positive margins, and lymph node involvement (Epstein 1996; Han 2003; Kausik 2002; Kupelian 1997b; Roehl 2004; Swindle 2005). These factors differ in their relative effect on the risk of local as opposed to distant relapse. While lymph node metastases and a short PSADT increase the risk of the development of distant metastases, positive margins, extra-capsular spread and seminal vesicle invasion increase the risk of local relapse. There is randomised trial evidence for improved survival for men with involved lymph nodes who receive androgen deprivation therapy postoperatively compared with patients in whom androgen deprivation therapy is deferred until the time of distant metastases or symptomatic recurrence (Messing 2006). The appropriate course of action for patients without involved lymph nodes but other high risk features is unclear. The conventional strategy for those at risk of relapse after radical prostatectomy is surveillance, with salvage therapy deferred until biochemical or clinical relapse is identified.

'Salvage' treatment refers to treatment of patients with detectable postoperative PSA beyond 6 weeks with or without palpable local disease, and may occur at any stage following radical prostatectomy. The optimal salvage treatment is controversial. Although treatment modalities, including hormonal therapy or chemotherapy, may be used when relapse is identified, radiotherapy is the only modality currently known to have the potential to cure for men with residual or recurrent disease localized to the radiotherapy treatment volume. Single institution, retrospective studies have shown that salvage external beam radiotherapy achieves durable disease control with up to 50% of men treated at relapse free from biochemical progression (Anscher 2000; Cadeddu 1998; Cheung 2005; Duchesne 2003; Pazona 2005; Pisanasky 2000; Stephenson 2004).

Description of the intervention

Adjuvant radiotherapy (treatment of the prostate with high energy X-rays) has been used for patients following radical prostatectomy with high risk features, such as extracapsular extension, seminal vesicle invasion, or positive margins, to prevent recurrence. 'Adjuvant' treatment is therapy given after surgery in men with an undetectable PSA, who are not known to have residual or recurrent disease, but deemed at high risk of microscopic residual disease. Adjuvant radiotherapy to the prostate tumour bed can potentially eradicate microscopic residual tumour in the periprostatic tissues, allowing cure for those men with isolated local residual disease. Re-

cent randomised controlled data shows that adjuvant radiotherapy significantly reduces the risk of PSA failure compared to surgery alone with salvage at recurrence (ARO; EORTC; SWOG). With longer follow up SWOG has shown significant improvements in metastasis-free survival and overall survival. Despite this, the use of adjuvant radiotherapy remains controversial, because of the following.

1. Randomised trials of adjuvant radiotherapy following radical prostatectomy have not uniformly identified significant differences in metastasis-free survival, cancer-specific survival or overall survival. While this may be due to inadequate follow up, reflecting the time lag between biochemical failure and clinical failure, not all men with PSA failure develop clinically evident local or distant recurrence, or they may do so only after a very long time. Not all patients with clinical progression die of prostate cancer.
2. Some men with high-risk features who are observed will not develop PSA failure, and would receive radiotherapy unnecessarily if all at-risk men were treated adjuvantly.
3. Radiotherapy is associated with well recognized toxicity, particularly in the postoperative setting where operative morbidity may be exacerbated (Hu 2006). Urethral strictures and the recovery of continence and potency are particular concerns.
4. Some men are at very high risk of distant metastatic disease, so radiotherapy to the periprostatic tissues may be futile, and the side effects of treatment unjustified.
5. Salvage treatment in the control arms of the abovementioned randomised trials may have been sub optimal. Retrospective evidence has shown that durable salvage is most likely achieved if radiotherapy is given at the earliest confirmation of biochemical relapse. A number of series have shown that cure rates with postoperative salvage radiotherapy steadily decline as the PSA rises (Cheung 2005; Duchesne 2003; Nudell 1999; Maier 2004; Stephenson 2004). The timing of salvage treatment was not specified in the large randomised trials. Careful surveillance and early radiotherapy may be as effective as adjuvant radiotherapy for high-risk patients.

Why it is important to do this review

The optimal approach for high-risk men following radical prostatectomy is not clear. Adjuvant radiotherapy significantly improves PSA failure, but there is inconsistent evidence that it prevents metastases or prostate-cancer death. Routine adjuvant radiotherapy may be overtreatment for many men. Existing studies have not been adequately powered or may have inadequate follow up to show survival differences. A systematic review and meta-analysis is essential to make a reliable estimate of the effect of adjuvant radiotherapy.

OBJECTIVES

To assess the effects of adjuvant RT for men with high risk prostate cancer who have had radical prostatectomy.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCT) comparing radical prostatectomy followed by adjuvant radiotherapy with radical prostatectomy alone.

Types of participants

Men with histologically confirmed invasive prostate adenocarcinoma without regional lymph node involvement or distant metastatic disease (AJCC (American Joint Committee on Cancer) T1 to T4 N0 M0), who have undergone radical prostatectomy.

Types of interventions

Radical prostatectomy followed by adjuvant radiotherapy was compared with radical prostatectomy alone. Radiotherapy refers to megavoltage external beam radiotherapy to a radical dose of at least 60 Gray (Gy) (in 1.8 to 2.0 Gy fractions) or the biological equivalent, to a volume that covers at least the prostate bed using two dimensional, three dimensional CT planning, IMRT or novel techniques. Trials using other therapy, such as androgen suppression therapy, could be included provided the additional therapy was given in both treatment groups, such that the analysis of the effect of radiotherapy was unconfounded.

Types of outcome measures

Primary outcomes

The primary endpoint was overall mortality.

Secondary outcomes

The secondary endpoints included:

1. prostate cancer-specific mortality;
2. clinical disease-free survival (defined as freedom from local or distant disease);
3. metastasis-free survival (defined as alive, with no evidence of distant disease);

4. local recurrence-free survival (defined as alive with no evidence of local recurrence);
5. biochemical progression-free survival;
6. adverse outcomes (radiation toxicity, specifically late genitourinary (continence and potency) and bowel toxicity, scored using trial specific instruments);
7. quality of life (scored using trial-specific instruments);
8. patient preferences.

Timing of outcome assessment

Outcomes were assessed at 5 and 10 years.

Search methods for identification of studies

See the Prostatic Diseases and Urologic Cancers Group's methods used in reviews.
The Cochrane Prostatic Diseases and Urological Cancers Group specialized register was searched (details of search strategies used by the group for the identification of studies and the procedure used to code references are outline in the group's module) on 2 June 2008. Studies coded as 'X' and 'Y' on the specialized register were extracted for consideration.
No language or publication restrictions were applied.

Electronic searches

Our search strategy included an electronic search of MEDLINE on OVID from 1966 to 23 February 2011, to identify all relevant published randomised trials that compare radical prostatectomy with radical prostatectomy followed by adjuvant radiotherapy for prostate cancer.
MEDLINE search strategy (see 'Appendix 1').
This search was modified for additional searches of the following electronic databases:

- Cochrane Central Register of Controlled Trials (Central);
- EMBASE (search date to 23 February 2011);
- PDQ® (search for open and closed trials) (2 November 2010).

Searching other resources

The following databases were searched for ongoing trials:

- Current Controlled Trials Register: http://www.controlled-trials.com (2 November 2010);
- European Organisation for Research and Treatment of Cancer (EORTC): http://www.eortc.be (searched 2 November 2010);
- United Kingdom Research Co-coordinating Committee on Cancer Research (UKCCCR): (2 November 2010);
- UK National Research Register of all NHS-funded research: http://www.doh.gov.uk/research/nrr.htm (2 November 2010);
- National Cancer Institute, America:(2 November 2010);
- National Cancer Institute, Canada: http://www.ctg.queensu.ca/ctg_home/htm;
- National Health and Medical Council of Australia: http://www.ctc.usyd.edu.au/ (searched 30 November 2010).

Handsearching

Relevant conference proceedings were manually searched to identify eligible trials, including ASCO (American Society of Clinical Oncology) 1995 to 2010), ASTRO (American Society for Therapeutic Radiology and Oncology) (2001 to 2010), ESTRO (European Society for Therapeutic Radiology and Oncology) (1990, 1993, 2002 to 2010), AUA (American Urology Association) (2000 to 2010) and EUA (European Association of Urology) (2010). Journal of Urology 1999 to 2000 inclusive, and 2010: 184 (1 to 3); 183 (1 to 6); 184 (1 to 3); 182 (1 to 6); 181 (1 to 6).

Reference lists

Citations from identified trials and review articles were checked.

Correspondence

Authors and researchers were contacted to determine if they were aware of other relevant studies.

Data collection and analysis

Selection of studies

All authors (TD, BH and ML) checked the titles and abstracts retrieved. Each author independently assessed the full text of studies relevant to this review. Disagreements were resolved through discussion.

Data extraction and management

Two authors (TD and BH) independently extracted data, with disagreements resolved by discussion. Where possible we extracted the following data: PSA prior to randomisation; pathological factors, including Gleason score, the presence of extra-capsular extension, seminal vesicle invasion, and positive margins; radiotherapy data, including total dose, dose per fraction, and volume. Data was checked and entered into RevMan 5.1.22 for statistical analysis.

Assessment of risk of bias in included studies

The quality of each study and the subsequent risk of bias were assessed independently by 2 reviewers (TD, BH) and 'Risk of bias' tables were constructed. ML reviewed the 'Risk of bias' tables and any differences in opinion were resolved through discussion. When there was insufficient detail about the study method, further information was sought from the authors.

Measures of treatment effect

We used the intention-to-treat principle to analyse data from the included trials.

Dichotomous data

Dichotomous outcomes were presented as risk differences (RD) with 95% confidence intervals (CI) for individual trials (Deeks 2002). The findings of each study were discussed and if deemed appropriate and feasible, data were pooled. Where results were significant, the absolute risk (DR) was calculated and the number needed-to-treat (NNT) to prevent or produce the relevant outcome (McQuay 1997).

Continuous data

Continuous data was dichotomised in the reports. In future updates, where continuous variables (such as quality of life) are available, we will use recommended methods to collect and combine the data. We will use the mean difference method, unless different scales are used in the trials, in which case we will use a standardized mean difference to summarize the data (Deeks 2002). [this dichotomised continuous data needs to be explained]

Dealing with missing data

When data could not be extracted from the text, or statistics were missing, the authors of the original articles were contacted to obtain the necessary information.

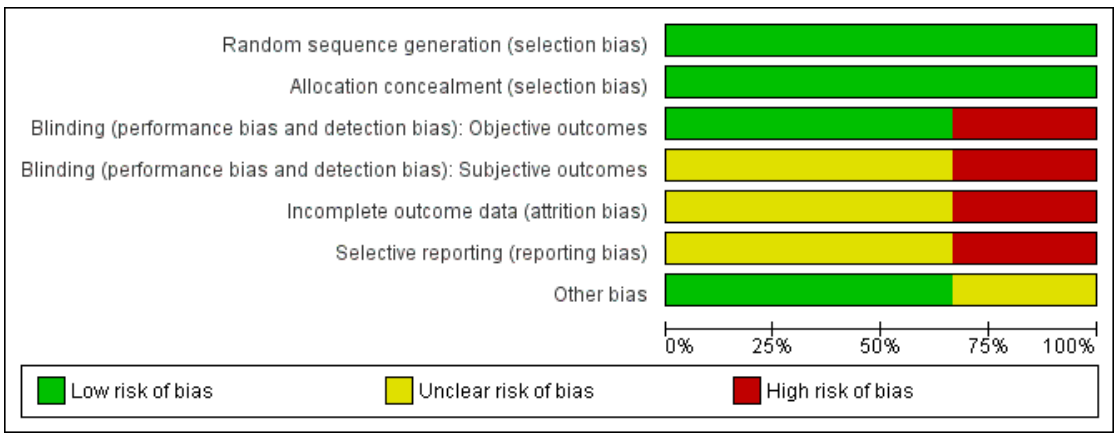
Assessment of heterogeneity

Heterogeneity (clinical and methodological diversity) were assessed both visually and statistically using the Chi^2 test of heterogeneity and the Higgins I^2 test (Higgins 2002; Higgins 2003). When heterogeneity was identified, reasons for it were explored and caution in the interpretation of our results was emphasized. We sought to reduce publication bias through our previously described search methods and by contact with authors and experts in the field.

Data synthesis

We used Mantel-Haenszel methods to calculate pooled results (when it was appropriate to do so) and determined a weighted average treatment effect by using the fixed-effect model to combine results (Greenland 1985; Mantel 1959).
In ARO, three different analyses were reported *(see 'Figure 1'):*

Figure 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



1. ITT1 - including all patients randomised according to intention to treat;
2. ITT2 - excluding those patients who did not achieve an undetectable PSA;
3. ITT3 - per protocol analysis.

We analysed the data using ITT1 for the outcome biochemical relapse, all other outcomes from ARO used ITT2, as data for other outcomes not reported by trial arm (ARO).

Where continuous variables were dichotomised (proctitis/ rectal bleeding, urethral stricture), the fixed-effect model was used to combine results. Where continence was reported using International Incontinence Scale (ICS) (see 'Table 1'), results were dichotomised, into grade 0 (dry) versus any higher grade of incontinence (EORTC). Other continuous variables were not able to be combined. As data from a single study was available, figures for the text were reported. In future updates, it may be possible to use the mean difference or the standardised mean difference to analyse the data.

Subgroup analysis and investigation of heterogeneity

We were not able to do subgroup analysis other than by length of follow up (5 years versus 10 years). If sufficient data is available for future updates we may perform subgroup analyses to investigate whether the effect of postprostatectomy radiotherapy differs depending on radiation dose (greater than 60 Gy), measures of tumour risk classification - including PSA at baseline, tumour stage, the presence of extracapsular spread, seminal vesicle invasion or positive margins - and histological grade and according to the timing of salvage radiotherapy in the control arm. [I believe you could expand this para and give the cut points for all these categories]

Sensitivity analysis

We performed two sensitivity analyses: the first was by length of follow up (5 years (ARO; EORTC) versus 10 years (SWOG)); the second was to examine the two data sets presented in ARO. For the outcome of biochemical relapse, they presented the results for all men randomised (ITT1), and for only those men who achieved an undetectable PSA postprostatectomy (ITT2). The rest of the outcomes in ARO were derived from ITT2, so further sensitivity analyses were not possible.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Results of the search

Our search strategy identified 2105 references. Screening of titles and abstracts identified 33 potentially eligible reports. Five of these (NCT00541047; NCT00860652; NCT00667069; Parker 2007; Parker 2007a refer to three ongoing studies (NCT00667069; RADICALS; RAVES) described in 'Characteristics of ongoing studies'. The remaining 28 reports (Abi Aad 1993; Bolla 2002; Bolla 2004; Bolla 2004a; Bolla 2005; Bolla 2007; Collette 2005; Davis 2002; Elias 1997; Jani 2005; Moinpour 2008; Swanson 2007; Swanson 2008; Swanson 2009; Thompson 2006; Thompson 2009; Tombal 2006; Van Cangh 1998 ; Van Der Kwast 2006; Van der Kwast 2006a; Van der Kwast 2007;Wiegel 1998; Wiegel 2008a; Wiegel 2005; Wiegel 2007; Wiegel 2007a; Wiegel 2009; Zurlo 2002) related to three randomised controlled trials (ARO; EORTC; SWOG). Two excluded studies (Elias 1997; Jani 2005) (see 'Excluded studies'). The three randomised controlled studies reported at different times with different durations of follow up (ARO; EORTC; SWOG). These are described in 'Characteristics of included studies'. The most recent publications report results with a median follow up of 53 months (ARO), 60 months (EORTC) and 12.5 years (SWOG). In all three trials, men were randomised postoperatively to a control arm of observation, or an experimental arm of external beam radiotherapy (ARO; EORTC; SWOG).

Included studies

Design

All three trials were randomised controlled trials (ARO; EORTC; SWOG) (see 'Characteristics of included studies').

Sample sizes

The three trials included in this review randomised a total of 1815 men, including 385 men in ARO, 1005 men in EORTC and 425 men in SWOG.

Setting

In all trials men were recruited from multiple centres, from Germany (ARO), Europe (EORTC), and USA and Canada (SWOG).

Participants

All studies included men who had radical prostatectomy for prostate adenocarcinoma with no lymph node or distant metastases (N0M0), with one or more of the following pathological risk factors: extracapsular extension; seminal vesicle invasion or positive margins (ARO; EORTC; SWOG). Lymph nodes were assessed by pelvic lymph node dissection in men recruited to EORTC and ARO, and in SWOG in men recruited prior to June 1995. After this those considered at low risk of pelvic lymph node

metastases ((1) clinical stage T1a or T2a, GS (Gleason score) 2 to 6 and PSA < 10 ng/mL (nanograms per millilitre), (2) stage T1b-c, GS 2 to 5, and PSA < 10 ng/mL, (3) stage T2b, GS 2 to 6 and PSA < 6 ng/mL and (4) stage T2c, GS 2 to 6, and PSA < 4 ng/mL) did not require pelvic lymphadenectomy. All men in the three studies had a negative bone scan to exclude distant bony metastatic disease.

The SWOG trial specified that men who had total urinary incontinence postoperatively, persistent urinary extravasation, pelvic injury or intraoperative rectal injury were excluded. ARO specified that men had no major voiding problems postoperatively.

Androgen deprivation therapy prior to surgery (neoadjuvant hormonal therapy) was permitted in all three trials, but was received by a minority of men in each trial (8% to 12%), and in similar numbers in each treatment arm.

An undetectable PSA prior to randomisation was not required in any of the studies.

Interventions

In all three trials men were randomised postoperatively to a control arm of observation, or an experimental arm of adjuvant RT (ARO; EORTC; SWOG).

In ARO, men were randomised immediately postoperatively. Men whose postoperative PSA became undetectable (< 0.1 ng/mL) were treated according to their allocation. Those in the experimental arm received external beam radiotherapy, starting within 6 to 12 weeks of surgery, to a dose of 60 Gy in 30 fractions, to a volume that included the surgical limits 'from the seminal vesicles, marked with clips intraoperatively, to the apex'. Men whose PSA did not become undetectable were excluded and immediate radiotherapy was given. The dose given to these men was not specified.

In EORTC men randomised to the experimental arm received external beam radiotherapy to a dose of 60 Gy in 30 fractions, starting within 16 weeks of surgery. A two phase technique was used. In phase one 50 Gy in 25 fractions was given to a volume "that included the surgical limits from the seminal vesicles to the apex" with a margin, and a 10 Gy boost was used to treat the previous limits of the prostate.

In SWOG the experimental arm received 60 to 64 Gy in 30 to 32 fractions, starting within 17 weeks of surgery (randomised within 16 weeks of surgery and starting radiotherapy within 10 days of randomisation). The "prostatic fossa and paraprostatic tissues" were treated.

Outcomes

ARO study

In ARO the primary outcome was biochemical progression free survival, defined as "two consecutive increases above the detection limit of the respective PSA assay used". All men whose PSA did not become undetectable were considered failures from the time of randomisation. The secondary endpoints were metastasis free survival, overall survival and acute and late toxicity. No distinction in the report is made between acute and late toxicity. Urinary incontinence was not assessed in ARO as it was not part of the RTOG/EORTC toxicity scoring system. Median duration of follow up was 53.7 months (ARO).

EORTC study

The primary endpoint of the EORTC study was also biochemical progression-free survival. When the trial started the primary endpoint was local recurrence, but this was subsequently changed to clinical progression-free survival, and then to biochemical progression-free survival on the basis of "evolving urological practice". Secondary endpoints were clinical progression free survival, local recurrence, and acute and late toxicity. Although not specified in the protocol, overall survival was analysed. For acute toxicity (occurring at less than six months post-treatment), the WHO scoring system was used (a five point scale) (EORTC). For late toxicity, the EORTC/RTOG scoring system was used (a five point scale) ('Table 2') (EORTC). Quality of life and sexual function were not assessed. Urinary incontinence was not evaluated in the entire cohort as it was not part of the RTOG/EORTC toxicity scoring system (EORTC). A subset of 100 men were evaluated for continence. These men were a subset of those randomised in the EORTC study, but all treated at a single institution. These men had a validated modified pad weighing test (Bates 1983) using the International Incontinence Scale (ICS) (see 'Table 1') and an interview. Baseline parameters do not suggest they differ significantly from the remainder of men randomised in the study (EORTC). Median duration of follow up was 60 months (EORTC).

SWOG study

The primary endpoint of the SWOG trial was metastasis-free survival. Secondary endpoints were biochemical relapse-free (RFS), clinical recurrence free survival and time to hormonal treatment. Although not specified in the protocol, overall survival was analysed. Complications, including rectal toxicity (proctitis or bleeding), urethral stricture or total urinary incontinence were recorded. Acute versus late complications are not clearly defined, and toxicity was not graded. Median duration of follow up was 12.7 years (SWOG).

Two hundred seventeen of four hundred twenty-five (217/425) men were enrolled in a companion health related quality of life study (HRQL). The trial was activated in August 1988. Men registered after February 1990 provided baseline HRQL, unless they required translation. A validated Spanish translation was available in 1995. HRQOL was evaluated at baseline (prior to randomisation), at 6 weeks, 6 months and annually to 5 years. Bowel function and genitourinary -specific symptom items were developed ('Table 3'). These were validated through pilot testing (Moinpour

1991; Rodriguez 1988), and have been shown to be sensitive to change with time and treatment arm (Moinpour 1998).Outcomes for bowel function, genitourinary-specific symptoms and global HRQL were reported as binary outcomes, recorded as present with a score of ≥ 3 for bowel and genitourinary-specific symptoms and < 5 for global HQRL as cut points. The clinically significant difference was defined as a ≥ 15% difference between the treatment arms. Although men enrolled in the ancillary study of HRQL were more likely to be African-American (24% versus 14%; P = 0.01), and less likely to have had preoperative hormone therapy, they were not significantly different with respect to other baseline factors (SWOG).

Differences between studies

A major difference in study design was that ARO randomised patients immediately postoperatively and excluded patients from their allocated treatment arm if they did not achieve an undetectable PSA within 6 weeks. They performed three separate analyses: by intention to treat, according to their initial allocation (ITT1); after exclusion of those men who did not achieve undetectable PSA (ITT2); and according to actual treatment received (ITT3).

Of relevance to the calculation of biochemical failure, the trials differed in:

1. the proportion of men for whom a postoperative PSA was recorded (In EORTC, a postoperative PSA was recorded in 99.4% (999/1005) of all men. In SWOG, a postoperative PSA value was recorded for 88% (376/425) of men randomised. In ARO, a postoperative PSA value was available for all patients (100%));
2. the definition of nadir (see 'Table 4');
3. the proportion of men whose PSA became undetectable postoperatively (achieved nadir) (In EORTC PSA was measured and undetectable (defined as < 0.2 ng/mL), in approximately 90% of men in each arm (EORTC). In SWOG the PSA was undetectable (< 0.2 ng/mL) postoperatively in 249 (66.2%) of 376 men who had a postoperative PSA recorded (SWOG). In ARO all the men analysed for biochemical relapse had undetectable PSA postoperatively (defined as ≥ 0.1 ng/mL) (ARO). See 'Table 5'. Conversely: in ARO 78/388 (20%) of men randomised the PSA remained detectable postoperatively. These men were considered to have progressed, and received radiotherapy, as per the study design (ARO). In SWOG 127/347 (33%) did not achieve PSA ≤ 0.2 ng/mL (SWOG). Ten per cent (108/1005) of men in EORTC did not nadir postoperatively) (see 'Table 5'));
4. the definition of biochemical relapse (In EORTC biochemical failure was defined as a rise of > 0.2ng/mL over the lowest postoperative value measured on three occasions at least two weeks apart, and was calculated for all randomised patients (EORTC). In SWOG it was defined as the first occurrence of a PSA of > 0.4 ng/mL (SWOG). In ARO it was defined as two consecutive rises in PSA (ARO))
5. the groups in whom that was calculated (In SWOG biochemical relapse was assessed in 347 men with a postoperative PSA ≤ 0.4 ng/mL (approximately 80% of men in each treatment arm) (SWOG). In ARO biochemical failure was calculated in two ways: ITT1 in all men randomised assuming that those who did not achieve an undetectable PSA postoperatively failed from the time of randomisation, and ITT2, in 310/388 men (80%) who did achieve an undetectable PSA postoperatively. In EORTC all men were included in analysis of biochemical relapse.).

Toxicity reporting

In ARO acute radiation toxicity was scored according to the RTOG scale ('Table 6'), and late toxicity according to the RTOG/EORTC late scoring scale ('Table 2'). As continence and potency are not included in this scoring system they were not assessed. The reported results do not distinguish between acute and late events. In SWOG the incidence of "total urinary continence" (defined as no ability to control urinary leakage), urethral stricture and "rectal complications" were measured, but no scoring system was used, and the timing of the assessments is unclear (SWOG). The SWOG quality of life sub study assessed urinary frequency, bowel movement tenderness and urgency, and erectile dysfunction ('Table 3'). In EORTC acute toxicity was measured using the WHO scoring scale, and late toxicity using the RTOG/EORTC scoring scale ('Table 2'). Urinary continence was assessed in a subset of 100 men from a single institution. Potency was not assessed.

Central pathology review was performed in all patients in ARO and 311/425 (73%) of men in SWOG, but not in EORTC.

The dose given for salvage radiotherapy in the EORTC trial was recommended (70 Gy in 35 fractions, with or without an LHRH agonist), but was not specified in the ARO or SWOG trials.

Quality assurance for RT was conducted for those men in EORTC and SWOG but not reported in ARO.

Risk of bias in included studies

Allocation

Randomisation was performed centrally for all studies (ARO; EORTC; SWOG). Allocation sequences were generated by using computer generated lists with permuted blocks of randomly varying size per stratum in ARO. This was concealed (confirmed by personal communication) (Morgan 2008). EORTC used a minimisation technique and SWOG did not indicate the method of sequence generation. The randomisation process was unlikely to be a source of bias in any of the trials ('Figure 1').

Blinding

See 'Characteristics of included studies'.

Patients and outcome assessors were not blinded to treatment allocation. This was stated for SWOG and assumed for ARO and EORTC.

Objective outcomes

Lack of blinding was unlikely to have introduced bias in the assessment of overall survival, given the objective nature of this outcome.

With regard to PSA failure, the time intervals for PSA tests were prespecified, and therefore it is unlikely that lack of blinding introduced bias (ARO; EORTC; SWOG).

There may have been some risk in the assessment of distant metastatic disease if there was more frequent radiological investigation in patients who did not receive adjuvant radiotherapy (ARO; EORTC; SWOG). Although information regarding the frequency of investigations was not available, we felt that the risk of bias from this was low.

Subjective outcomes

In EORTC, local recurrence was assessed using DRE (digital rectal exam). Given the subjective nature of this procedure, there is a high risk of bias in the absence of personnel blinding. Confirmation of local recurrence is best achieved with biopsy.

Lack of patient and assessor blinding may have had an effect on reporting of both acute and late toxicity, with a bias in favour of the observation arms in all three trials ('Figure 1'). We felt the risk of bias was unclear in ARO and EORTC. In SWOG recording of toxicity was neither graded nor pre-specified, and therefore there was greater potential for toxicity recording to be influenced by the interests or opinion of the involved clinician, increasing the risk of bias, and therefore we judged that there was a high risk of bias (SWOG) ('Figure 1').

Incomplete outcome data

As mentioned above, the trials differed in the proportion of men included in the analysis of biochemical failure, because of differing trial design. In EORTC a postoperative PSA was recorded for nearly all men, and all men were included in the analysis of biochemical failure. In ARO in ITT1 all men are included, but in ITT2, those men who did not achieve undetectable PSA postoperatively were excluded. This makes data reported on the ITT2 analysis at high risk of bias; this includes the following outcomes: overall survival, distant metastases and urethral stricture . We performed a sensitivity analysis of both groups (ITT1 and ITT2) for the outcome biochemical relapse. Given that ITT3 is not according to randomised allocation there is significant risk of bias, and this analysis has not been used in our summary statistic. In SWOG approximately 20% of men were excluded from analysis of biochemical failure in each arm, largely due to changing practice over time. Given that proportions were similar, and the reason for exclusion was similar, bias is unlikely.

With respect to toxicity reporting, a sub study of quality of life outcomes in men recruited to SWOG was reported. Although the analysis included only half of total number of men recruited to SWOG for whom baseline quality of life data was available, the authors reported no significant difference in baseline characteristics between the two treatment arms, or between the men included in the quality of life sub study and those men who were not ('Figure 1').

Selective reporting

For ARO, all outcomes reported in the paper had been specified in the methods section. Overall survival, distant metastases and local control are not reported for the entire cohort of randomised men, which increases the risk of bias for these outcomes. Biochemical relapse is reported for the entire cohort of randomised men. The toxicity reporting is unclear, as it is not possible to distinguish whether acute or late toxicity is reported in the ARO trial. In both SWOG and EORTC, overall survival was reported despite not being specified in the methods, but given the objective nature of this outcome, bias is unlikely. There were insufficient details available to make a judgement about whether there was incomplete outcome data for the three trials (ARO; EORTC; SWOG) ('Figure 1').

Other potential sources of bias

Early stopping occurred in EORTC based on O'Brien-Flemming stopping rule (EORTC). They reported their planned sample size (1000), and randomised 1005 men. The trial was stopped by an independent data monitoring committee when the pre-specified P value of < 0.02 was reached. Although the treatment effect size was large: (HR 0.48; 0.37, 0.62; P < 0.0001), this represented 365 events. Early stopping is unlikely to have introduced bias, therefore we judged the risk of bias to be low (EORTC) ('Figure 1').

Effects of interventions

Results are presented as risk differences (RD), with the RD < 0 evidence of a benefit to the experimental arm. The fixed-effect model was used to pool results where appropriate.

Primary outcome

Overall survival

We studied 300 deaths in 1737 men.

Adjuvant RT postprostatectomy did not improve survival at 5 years: (RD -0.00; 95% CI -0.03 to 0.02; P = 0.95) There was no heterogeneity detected (P = 0.41, I^2 = 0%) (ARO; EORTC) ('Analysis 1.1').
Adjuvant RT postprostatectomy did improve survival at 10 years: RD -0.11 (95% CI -0.20 to -0.02; P = 0.02) (SWOG). Testing for heterogeneity was not applicable. NNT = 10: it is expected that one less person will die (from any cause) by 10 years for every ten men who have prostate cancer with high risk features and receive postprostatectomy RT ('Analysis 1.1').

Secondary outcomes

Prostate cancer-specific mortality

Adjuvant RT did not improve prostate cancer-specific survival at 5 years (data from one study) (EORTC) (RD -0.01; 95% CI -0.03 to 0.00) ('Analysis 1.2').

Clinical disease-free survival

(defined as freedom from local or distant disease)
No data.

Metastasis-free survival

(defined as alive, with no evidence of distant disease)
Two hundred sixteen of seven hundred thirty-two (216/732) men developed distant metastases.
Adjuvant RT postprostatectomy did not improve metastasis-free survival at 5 years: (RD -0.01; 95% CI -0.03 to 0.0; P = 0.42). There was no heterogeneity detected (ARO; EORTC; SWOG) ('Analysis 1.2').
Adjuvant RT postprostatectomy improved metastasis-free survival at 10 years: RD -0.11 (95% CI -0.2 to -0.01; P = 0.03). Testing for heterogeneity was not applicable (SWOG). NNT = 10: it is expected that one less person will develop metastases by 10 years for every 10 men who have prostate cancer with high risk features and receive postprostatectomy RT ('Analysis 1.2').

Local recurrence-free survival

(defined as alive with no evidence of local recurrence)
There were 154 local recurrences were reported in 1379 men.
Adjuvant RT postprostatectomy decreased local recurrence at 5 years: RD -0.10 (95% CI -0.13 to -0.06; P < 0.00001) (EORTC). Testing for heterogeneity was not applicable. NNT = 10; it is expected that one less person will develop local recurrence by 5 years for every ten men who have prostate cancer with high risk features and receive postprostatectomy RT ('Analysis 1.3').
Adjuvant RT postprostatectomy decreased local recurrence at 10 years: RD -0.14; 95% CI -0.21 to -0.07); P = 0.00001) (SWOG). Testing for heterogeneity was not applicable. NNT = 8; it is expected that one less person will develop local recurrence by 5 years for every 8 men who have prostate cancer with high risk features and receive postprostatectomy RT ('Analysis 1.3').

Biochemical progression-free survival

When all randomised men were studied (ITT1), biochemical progression-free survival improved with adjuvant RT at:

1. 5 years ((RD -0.15; 95% CI -0.20 to -0.11; P < 0.00001). Heterogeneity was detected: P = 0.09, I^2 = 66% (ARO; EORTC) ('Analysis 1.4'). NNT = 7; it is expected that one less person will develop biochemical relapse by 5 years for every seven men who have prostate cancer with high risk features and receive postprostatectomy RT.);
2. 10 years ((RD -0.29; 95% CI -0.39 to -0.19; P < 0.00001). Testing for heterogeneity was not applicable (SWOG) ('Analysis 1.4'). NNT = 4; it is expected that one less person will develop biochemical relapse by 10 years for every four men who have prostate cancer with high risk features and receive postprostatectomy RT.).

We performed a sensitivity analysis: when only those men whose PSA nadired postprostatectomy (ITT2) (ARO) were studied, biochemical progression-free survival improved with adjuvant RT at 5 years: (RD -0.18; 95% CI -0.23 to -0.13; P $\leq$ 0.00001) or 10 years:(RD -0.29; 95% CI -0.39 to -0.19). There was no heterogeneity detected: P = 0.69, I^2 = 0% (ARO; EORTC) ('Analysis 1.5').

Adverse outcomes

Nearly twenty-four per cent (51/214) men reported non-specific adverse effects during follow up in the adjuvant RT arm compared with 11.7% (25/211) men in the observation arm (SWOG). Non-specific adverse effects during follow up (no time reported) were more common after RT: RD 0.12 (95% CI 0.05 to 0.19; P = 0.001). Testing for heterogeneity was not applicable (SWOG). NNT = 9: it is expected that one more person will develop non-specific adverse effects for every nine men who have prostate cancer with high risk features and receive postprostatectomy RT.

Acute effects: (toxicity occurring within 90 days of treatment)

Gastrointestinal toxicity

In the SWOG quality of life sub study "significantly more men had tenderness and urgency with bowel movements at six weeks in the adjuvant RT group" (47% versus 5%, no P value reported) (SWOG). In EORTC 24/457 (5.3%) men having radiotherapy had grade 3 diarrhoea.

Genitourinary toxicity

Urinary frequency and dysuria

Urinary frequency was more common after RT in the 217/425 men in the SWOG quality of life sub study (a clinically significant difference was defined as ≥ 15% difference between treatment arms) (SWOG). This difference remained constant over time (see 'Characteristics of included studies'). In EORTC 15/457 (3.3%) men reported WHO Grade III urinary frequency and 2/457 (0.4%) reported WHO Grade IV urinary frequency (EORTC). 5/457 (1.1%) reported WHO Grade III dysuria (EORTC).

Late effects:(toxicity occurring later than 90 days after RT)

Grade II or III late effects (genitourinary and gastrointestinal) were more frequent after RT (no figures reported, P = 0.0005) (EORTC). Grade III toxicity (genitourinary and gastrointestinal) was increased at 5 years after RT: 4.2% versus 2.6%, P = 0.0726 (figures from text). No Grade IV toxicity was reported (EORTC).

Gastrointestinal toxicity

Rectal complications (proctitis and rectal bleeding)

Seven of two hundred fourteen (3.2%) of men who received adjuvant RT reported proctitis and rectal bleeding compared to 0/211(0%) in the observation arm (SWOG). Proctitis and rectal bleeding were more common after RT: RD 0.03 (95% CI 0.01 to 0.06; P = 0.01). Testing for heterogeneity was not applicable (SWOG). NNT = 34: it is expected that one more person will develop proctitis and rectal bleeding for every 34 men who have prostate cancer with high risk features and receive postprostatectomy RT.
"Tenderness and urgency of bowel movement" settled with time; by 2 years the authors reported "little difference between groups" (no figures or P value reported) (SWOG).

Genitourinary toxicity

Grade II genitourinary toxicity
Three of one hundred fifty-nine (3/159) (1.8%) men in the adjuvant RT arm reported Grade II genitourinary toxicity compared with 0/148 (0%) men in the observation arm (ARO).Grade II genitourinary toxicity was not increased after RT: RD 2% (95% CI -1% to 4%; P = 0.13). Testing for heterogeneity was not applicable (ARO).

Urethral stricture

Forty of three hundred seventy-three (40/373) (10%) (range 1.3% to 17%) men had urethral strictures in the adjuvant RT arm compared with 21/359 (5.8%) (range 0.7% to 9%) men in the observation arm (ARO; SWOG).
Urethral strictures at:

1. 5 years did not differ between the two groups ((RD 0.01; 95% CI -0.02 to 0.03; P = 0.6) (ARO). Testing for heterogeneity was not applicable ('Analysis 1.5'));
2. 10 years were increased with adjuvant RT ((RD 0.08; 95% CI 0.02 to 0.15; P = 0.01) (SWOG). Testing for heterogeneity was not applicable. NNT = 13: it is expected that one more person will develop urethral stricture for every 13 men (at 10 years) who have prostate cancer with high risk features and receive postprostatectomy RT ('Analysis 1.5')).

Urinary incontinence

Eighteen of two hundred sixty-two (18/262) (6.8%) (range 6% to 8%) men who received adjuvant RT reported urinary incontinence compared with 7/263 (2.6%) (range 2-2%) [check range] men in the observation arm (EORTC; SWOG).
Urinary incontinence at:
1) 5 years was not increased for men who received adjuvant RT ((RD 0.06; 95% CI -0.02 to 0.15)RD 0.06; P = 0.15) (EORTC). Testing for heterogeneity was not applicable ('Analysis 1.6'));
2) 10 years was not increased for men who received adjuvant RT ((RD 0.04; 95% CI -0.00 to 0.08; P = 0.07) (SWOG). Testing for heterogeneity was not applicable ('Analysis 1.6')).

Erectile dysfunction

The proportion of men with erectile dysfunction significantly decreased over time (P = 0.02), but did not vary significantly according to treatment arm (P = 0.16), figures from text (SWOG).

Quality of life (scored using trial-specific instruments)

Global health related quality of life (GHRQL)

Fewer men who had RT reported normal GHRQL at six weeks: RD -0.16 (95% CI -0.30 to -0.02; P = 0.02). Testing for heterogeneity was not applicable (SWOG).
The number of men with normal GHRQL at 5 years did not differ between the groups: RD 0.1 (95% CI -0.06 to 0.26; P = 0.21). Testing for heterogeneity was not applicable (SWOG).

Patient preference

No data.

DISCUSSION

Summary of main results

In this review we found no overall survival benefit at 5 years for men who have had prostatectomy for cancer with high-risk features (positive margins, extra-capsular spread and seminal vesicle invasion) treated with adjuvant radiotherapy postprostatectomy: RD 0 (95% CI -0.03 to 0.02; P = 0.95). At 10 years however, adjuvant RT postprostatectomy did improve survival: RD -0.11 (95% CI -0.20 to -0.02; P = 0.02) ('Analysis 1.1').

Prostate cancer-specific mortality at 5 years was not improved by adjuvant RT: (RD -0.01; 95% CI -0.03 to 0.00). For clinical disease-free survival, there was no data.

Metastasis-free survival was not improved by adjuvant RT postprostatectomy at 5 years: (RD -0.01; 95% CI -0.03 to 0.01), but was improved at 10 years: (RD -0.11; 95% CI -0.20 to -0.01; P = 0.03) ('Analysis 1.2').

Adjuvant RT postprostatectomy decreased local recurrence at 5 years: (RD -0.10; 95% CI -0.13 to -0.06; P < 0.00001) and at 10 years: (RD -0.14; 95% CI -0.21 to -0.07; P = 0.00001) ('Analysis 1.3').

Biochemical progression-free survival was decreased by adjuvant postprostatectomy radiation therapy at 5 years:(RD -0.15; 95% CI -0.20 to -0.11) and 10 years (RD -0.29; 95% CI -0.39 to -0.19) ('Analysis 1.4').

There was a significant increase in mild acute genitourinary and gastrointestinal toxicity with adjuvant radiotherapy, and fewer men reported normal global HRQOL at 6 weeks. There was also a significant increase in the risk of late genitourinary and gastrointestinal toxicity with proctitis and rectal bleeding more common, but tenderness and urgency settled with time, and little difference was evident with time.

Urethral strictures at 5 years were not increased by adjuvant RT: (RD 0.01; 95% CI -0.02 to 0.03) but strictures at 10 years were increased with adjuvant RT:(RD 0.08; 95% CI 0.02 to 0.1; P = 0.01) (SWOG).

Urinary incontinence was not increased at 5 years for men who received adjuvant RT: (RD 0.06; 95% CI -0.02 to 0.15; P = 0.15) (EORTC) or 10 years for men who received adjuvant RT: (RD 0.04; 95% CI -0.00 to 0.08; P = 0.07) (SWOG).

Although erectile dysfunction significantly decreased with time (P = 0.02), it did not vary according to treatment arm (P = 0.16, figures from text) (SWOG). At 5 years the number of men with normal GHRQL did not differ (SWOG).

Overall completeness and applicability of evidence

Radical prostatectomy is frequently used for the treatment of localised prostate cancer (Cooperberg 2010). About one third of men who have radical prostatectomy fail biochemically (PSA rises), and are at risk of subsequent clinical failure (Pound 1999). Adjuvant RT may improve cure rates after radical prostatectomy in men who have isolated local residual disease. Men with prostate cancer who choose radical prostatectomy want cure with preservation of urinary continence and sexual function. Ideally, the addition of postprostatectomy radiotherapy would improve their chance of cure without adding significant morbidity. This review set out to determine if the addition of postoperative radiotherapy for men with high risk localised prostate cancer treated with radical prostatectomy improved survival without significant toxicity or detriment to quality of life. The comparison studied was: men with early prostate cancer treated with radical prostatectomy and postoperative adjuvant RT versus surgery alone.

Two of these trials started before the widespread use of PSA testing. The common use of PSA testing (ad hoc or in screening programmes) means that contemporary practice would include men with earlier stage disease and lower tumour burden. Despite this, almost 50% of men having radical prostatectomy in modern series (even with PSA detected disease) will have cancer that extends beyond the prostate capsule, or positive margins (Karakiewicz 2005). The term 'adjuvant' radiotherapy following radical prostatectomy describes radiotherapy given in the absence of measurable residual prostate cancer based on an undetectable PSA level 6 weeks postoperatively. In contrast the term 'salvage' radiotherapy postprostatectomy is used in men with PSA which is detectable or rising at 6 weeks postoperatively. As EORTC and SWOG were initiated at a time when PSA was not widely used, not all participants in the three studies achieved undetectable PSA levels postoperatively, and therefore the intervention arms include patients treated adjuvantly and for salvage.

The definition of an undetectable PSA was not uniform in the included studies (ARO; EORTC; SWOG) ('Table 4'). The proportion of men who did achieve an undetectable PSA and thus were treated with adjuvant RT differed among the included studies (ARO; EORTC; SWOG) ('Table 5'). The inclusion of 313/1769 (17%) men who did not nadir (achieve PSA $\leq$ 0.2 ng/dL (nanograms/decilitre) may have diluted the effect that adjuvant RT may have on the clinically important endpoints of overall and metastasis-free survival. This difference in trial design may explain in part the heterogeneity seen in biochemical relapse-free survival at 5 years. This is supported by our sensitivity analysis incorporating ITT2 (which comprised only those men who had undetectable PSA postoperatively) (ARO).

The gold standard endpoint for evidence of clinical benefit is overall survival. We found an improvement in overall survival with adjuvant radiotherapy at 10 years, but not 5 years. While the absence of an improvement at 5 years may reflect inadequate sample size, the improvement evident with longer follow up would be consistent with the variable and sometimes long natural history of prostate cancer. For men with PSA failure after radical prostatectomy the median time between biochemical failure and metas-

tases is 8 years, and between metastases and death; 5 years (Pound 1999). SWOG reported that adjuvant radiotherapy postprostatectomy improved survival: this study had significantly longer follow up (12.5 years) than the other included studies, median follow up: 53.7 months (ARO) and 60 months (EORTC). The finding of early reduction in local recurrence with delayed smaller improvement in survival parallels the findings when adjuvant RT is used in breast cancer. When RT is given after breast conservative surgery or postmastectomy, local recurrence is reduced by two thirds, but the smaller gain in survival (five percent) is not seen till after 10 to 15 years follow up. Given that the majority of men who undergo radical prostatectomy would be expected to have a life expectancy of at least 10 years, the benefit at 10 years should be relevant.

The development of metastatic disease is a clinically important outcome; it increases the risk of developing symptoms, and of dying from prostate cancer. The National Cancer Institute PSA Working Group recommend that the development of metastases be used to measure the clinical efficacy of therapy postprostatectomy (Scher 2004).

Biochemical progression-free survival was increased by adjuvant postprostatectomy RT. The clinical significance of this finding is uncertain. The clinical relevance of PSA failure has been debated (Jhaveri 1999). PSA failure universally antedates metastases and prostate cancer death, but not all men who fail biochemically will develop clinically evident disease, or die of their prostate cancer. There may be a significant lag time between the development of PSA failure and clinically measurable or symptomatic disease. This long natural history promotes the use of surrogate endpoints. Although PSA is a sensitive marker for early treatment failure, given the variable natural history, and competing risks for death in older men, biochemical failure is not a validated surrogate endpoint for prostate cancer specific survival or overall survival in metastatic prostate cancer (Collette 2005). Its value in non-metastatic disease has not been validated and does not predict survival in this setting (Jhaveri 1999). These conclusions may not apply however in a younger cohort of men with fewer competing risks.

Considerable variation in the definition of PSA failure adds to the confusion. Cookson 2007 found up to 53 definitions of PSA failure following radical prostatectomy used in the literature. Definitions vary in the cutoff used, and the need for confirmatory measurements, or an increase. The most common was $\geq$ 0.2 ng/mL. In 2007 the American Urological Association recommended that a value of $\geq$ 0.2 ng/mL be accepted as the definition of biochemical relapse post RP (confirmed with second specimen $\geq$ 0.2 ng/mL) (Cookson 2007). The definition of what constituted biochemical relapse differed in the included studies (See 'Characteristics of included studies'). This may have contributed to the heterogeneity we found.

Comparisons of toxicity between adjuvant radiotherapy and surgery alone were limited by a number of factors including:

1. Insufficient distinction between acute versus late toxicity in both ARO and SWOG. While acute radiation effects (those seen within 90 days of RT) may cause significant morbidity, they often resolve with time after completion of radiotherapy. Late radiation effects, however, are usually irreversible.
2. Aggregate toxicity rates were given, without distinction between gastrointestinal and genitourinary side effects (EORTC).
3. There was variation in the RT morbidity scoring systems used.
4. Sexual function and continence following treatment was not assessed (ARO; EORTC).

The American Urological Association Prostate Cancer Guideline Update Panel reviewed reporting of erectile function outcomes used in the literature (Burnett 2007).They found great variation in the measurement of sexual function outcomes used, hindering useful comparisons between treatments. They recommended use of a validated standardised scoring system, such as the International Index of Erectile Function Questionnaire (IIEF) (Rosen 1997), to allow comparisons in future trials. Additionally there is no consensus on the definition of incontinence.

There remain some unanswered questions:

1. Is early salvage radiotherapy as good as adjuvant radiotherapy?

The studies included in this review (ARO; EORTC; SWOG) were not designed to compare adjuvant RT postprostatectomy with salvage RT. Although salvage RT was encouraged for those men randomised to observation who failed clinically or biochemically, RT details were not specified in the protocol, and there were no pre-defined triggers for instituting salvage. Thirty three per cent (70/211) of men in the observation arm received salvage RT in SWOG**.** PSA values before RT, within 6 months of commencement were available for 65% and the median value was 1.0 ng/mL. Forty one per cent (207/502) of men randomised to observation developed biochemical relapse in EORTC**.** Fifty four per cent (113/207) of those men with biochemical relapse received salvage RT (EORTC). In ARO 33 men who did not achieve undetectable PSA postoperatively received RT. No details are reported about salvage RT for the men (63/175) (36%) in the observation arm who relapsed (ARO).

The success of salvage RT for men with biochemical relapse postprostatectomy in achieving PSA control is greatest when given early, when the PSA is very low. This has lead to the concept of 'early salvage' RT. More than half the men in the control arms in the included studies did not fail biochemically, so did not need salvage RT (ARO; EORTC; SWOG). PSA monitoring may allow early identification of those men with residual disease confined to the operative bed for whom RT is necessary. This approach avoids unnecessary RT in those men who will not fail and delays RT. This delay may allow recovery of continence and sexual function. Three ongoing trials compare adjuvant RT postprostatectomy with observation and early salvage (NCT00667069; RADICALS; RAVES). RADICALS aims to randomise men postprostatectomy (with PSA < 0.4 ng/mL) to immediate adjuvant RT or observation with early salvage RT. RAVES compares immediate adjuvant RT

postprostatectomy (PSA undetectable postoperatively) to immediate adjuvant RT or early salvage. The triggers for salvage are prespecified (see 'Characteristics of ongoing studies'). NCT00667069 compares immediate RT postprostatectomy plus androgen deprivation (in men with PSA < 0.2 ng/mL) to early salvage (PSA <0.2 ng/mL) plus androgen deprivation.

2. What is the optimal radiotherapy dose, volume and technique?

Developments in RT delivery mean that the RT given in the included studies may be sub-optimal by current standards. Two-dimensional planning was used in SWOG, 3D conformal RT was used in ARO. Three dimensional (3D) conformal (fields shaped to exclude normal tissues) and intensity modulated RT (IMRT) (multi-beam RT which allows sparing of normal tissues) have become the standard of care in the radiation treatment of prostate cancer. These techniques allow sparing of dose to surrounding normal tissues, reducing RT related toxicity, and allow dose escalation in RT for the intact prostate (Cozzarini 2003; Dearnaley 1999). With modern RT techniques, it may be possible to deliver the same or higher RT doses with less morbidity in the postprostatectomy setting.

The volumes treated in the included studies are not clearly described. The clinical target volume at risk can be difficult to define postprostatectomy. Published guidelines defining the clinical target volume at risk now exist (Mickalski 2010; Mirabell 2007; Poortmans 2007; Sidhom 2008; Wiltshire 2007); they were not available when the men in the included studies were treated.

The radiation dose used in these studies (60 Gy in ARO and EORTC, 60 to 64 Gy in SWOG) may be insufficient. A number of retrospective trials have shown that lower doses, with varying cutoffs between 60 and 70 Gy, are associated with higher rates of biochemical failure in the adjuvant (PSA undetectable postoperative PSA) and salvage setting (detectable PSA) (Cozzarini 2009; Bernard 2010; King 2008; Tomita 2009; Valicenti 1998). Further randomised trials are needed to determine the most effective dose. Quality assurance was performed for EORTC and SWOG, but not reported for ARO.

3) Are other adjuvant therapies required?

Postoperative RT can only be curative if residual or recurrent disease is localised to the volume treated. Failure after RT may reflect insufficient dose, but it can also represent distant metastatic disease. Adjuvant androgen deprivation therapy (blocking the action of testosterone) improves survival in men with involved pelvic nodes who have had radical prostatectomy (Messing 2006). Prolonged androgen deprivation after definitive radiation therapy improves survival in men with high risk and locally advanced prostate cancer (Bolla 2002; Pilepich 2001; Pilepich 2005). Given the benefit in these settings, it has been hypothesised that adjuvant RT plus androgen deprivation postprostatectomy may benefit those men who are node negative but have other high risk features. This hypothesis is currently the subject of two ongoing trials (RADICALS; NCT00949962) (see 'Characteristics of ongoing studies').

Quality of the evidence

We included data from three studies with median follow up of 60 months (EORTC), 53 months (ARO) and 12.5 years (SWOG). The studies included 1815 men who had radical prostatectomy for prostate cancer. All three studies had pre-determined follow up intervals and performed PSA levels at each visit (see 'Included studies'). A test of funnel plot symmetry was not possible or appropriate, as there were only three studies found (Cochrane Handbook) (Higgins 2008). The three included studies were of moderate to high quality, except for the high risk of bias for subjective outcomes which were not blinded.

Potential biases in the review process

The major potential sources of bias in all three trials related to the lack of blinding for assessment of subjective outcomes. For metastasis-free survival, the lack of blinding was a potential source of bias, as unblinded investigators may have ordered bone scans earlier and therefore introduced lead-time bias, shortening metastasis-free survival. We thought there was high risk of bias in determination of local recurrence (and subsequently also of clinical recurrence, which includes local recurrence), particularly considering subjective nature of interpretation of DRE. Confirmation of local recurrence is best achieved with biopsy.

Lack of patient and assessor blinding may also have had an effect on reporting of acute and late toxicity, so we felt the risk of bias was unclear. Patients having RT had more frequent assessment of toxicity, and patient and assessors more likely to report toxicity in RT arm. The information about continence was reported in a subset of 100 men treated at a single institution, representing 100/1815 (5.5%) men studied (EORTC).

There was high risk of bias from selective and incomplete outcome reporting in one study (ARO), which made all outcomes other than biochemical relapse at high risk of bias.

Agreements and disagreements with other studies or reviews

Our findings are consistent with those of Morgan 2008 and Roque 2008. They did both a systematic review and meta-analysis on the same topic which included the same three trials (with shorter follow up). Morgan 2008 excluded studies not published in English. This did not introduce language bias, as the three included studies were all published in English. They reported no difference in survival with adjuvant RT postprostatectomy: HR 0.91 (95% CI 0.67, 1.22; P = 0.52) (Morgan 2008), P = 0.26 (Roque 2008). They reported no difference in metastasis-free survival: HR = 0.75 (95% CI 0.55-1.02; P = 0.06) (Morgan 2008) (using figures from the text) for one study (SWOG), P = 0.27 (Roque 2008). They confirm our finding of improvement in biochemical RFS with adjuvant RT postprostatectomy: HR 0.47 (95% CI 0.40,

0.561; P < 0.00001) (Morgan 2008) and HR 0.37 (95% CI 0.29, 0.46; P < 0.00001) (Roque 2008). We found an improvement in overall survival and metastasis free survival at 10 years, which may be explained by the longer follow up.

AUTHORS' CONCLUSIONS

Implications for practice

Radiotherapy following radical prostatectomy in men with high risk features should be considered for men who have a life expectancy of more than 10 years. The optimum timing (adjuvant or early salvage) is unknown. Consideration should be given to recruitment to a clinical trial in progress.

Implications for research

Studies designed to adequately address all-cause and prostate cancer-specific mortality are needed. Better information regarding patient related outcomes is desirable. Patient-reported toxicity and quality of life related outcomes, (in particular: incontinence, potency, sexual function and patient satisfaction) should be reported and scored using validated scales. Clear description of volumes treated, techniques, dose prescription and quality assurance are required for RT trials. Ongoing trials are addressing the question of whether adjuvant RT is better than early salvage (RAVES; RADICALS) and the effect of the addition of androgen deprivation to postprostatectomy RT (NCT00667069; RADICALS).

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

ARO

Methods	Randomised controlled trial, median follow up 53.7 months.
Participants	385 men who have had a radical prostatectomy for prostate adenocarcinoma with pT3-4N0M0 with positive or negative margins (ie. cancer extending beyond the capsule, into seminal vesicles or invading other adjacent tissues, with or without positive margins) Median age 64 (50 to 77). No data re race or comorbidities. Median preoperative PSA: 10.4. Gleason Score (GS) surgical specimen < 6: 32%, 7: 54%, >8: 14%. Positive surgical margin (PSM): 68%, Seminal vesicle invasion (SVI): 28%
Interventions	Experimental arm: (if reached nadir) 60 Gy in 30 # external beam radiotherapy (EBRT) , if did not nadir, received upfront EBRT Control arm: if did not nadir EBRT (60 Gy in 30 #), if nadir reached, observed
Outcomes	Primary endpoint: biochemical progression free survival. Biochemical progression was defined as "two consecutive PSA increases above the detection limit of the assay used". Men who did not achieve undetectable PSA were counted as failures from the time of randomisation Secondary endpoints: metastasis free survival, overall survival and acute and late toxicity
Notes	Central pathology review performed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "We did a randomised trial" (Abstract 1062, IJROBP 2007) Quote: "randomly assigned" p 2925, para 7. Quote: "using computer generated lists with permuted blocks of randomly varying size per stratum" p2925, para 7 Quote: "Patients were stratified for Gleason-score, margin status, neoadjuvant hormonal treatment and stage (pT3A+B versus C)." Methods section abstract (Wiegel 2007a, Wiegel 2007). Sequence generation probably adequate, knowing history of well organised and established trials group
Allocation concealment (selection bias)	Low risk	Quote: "We did a randomised trial" Abstract (Wiegel 2007). Quote: '385 men with prostate cancer were randomised" (Materials and Methods section of ab-

		stract (Abstract 1062, IJROBP 2007). Quote: "men with prostate cancer were randomised" (Abstract 1062, IJROBP 2007) Quote: Randomisation was performed centrally..." p 2925, para 7 Allocation concealed (personal communication with authors)
Blinding (performance bias and detection bias) Objective outcomes	Low risk	Not mentioned, probably not done. "Clinical examinations, including digital rectal examinations, and PSA tests were done every 3 months for 2 years, then every 6 months until the end of the fifth year, then every year." PSA failure: As the time intervals for PSA tests were pre-specified, lack of blinding unlikely to contribute to bias. Some risk if more frequent investigation for distant metastatic disease in observation arm, but low risk
Blinding (performance bias and detection bias) Subjective outcomes	Unclear risk	Patient and assessor blinding: not mentioned, probably not done (there is insufficient information to permit judgement) . May have had an effect on reporting of acute and late toxicity
Incomplete outcome data (attrition bias) All outcomes	High risk	388 men randomised, 3 excluded because ineligible (1 in control arm received AD, 2 in adjuvant RT arm received AD) 3 different analyses reported - 1) ITT1 - including all patients randomised according to intention to treat 2) ITT2 - excluding those patients who did not achieve an undetectable PSA 3) ITT3 - according to treatment actually received (per protocol analysis) Adjuvant RT arm n = 194 (includes ineligible 2 receiving AD) 45 excluded because of progressive disease (PSA did not become undetectable) 34 did not receive RT 148 analysed ITT2 114 analysed ITT3 Control arm n = 194 (includes ineligible 1 receiving AD) 33 excluded because of progressive disease (PSA did not become undetectable) 5 received postoperative RT

ARO (*Continued*)

		159 analysed ITT2 154 analysed ITT3 Most concern regarding bias is with ITT3, because there are large differences in the proportions of patients excluded from each arm. The data reported for overall survival and distant metastases are from ITT2. In this analysis, those men who did not nadir were excluded after randomisation. 45/194 (23%) in adjuvant RT arm and 33/194 (17%) in observation arm were excluded postrandomisation, making these analyses at high risk of bias. For the outcome of biochemical relapse, data was available for all randomised men
Selective reporting (reporting bias)	High risk	Outcomes specified in methods: Primary endpoint: biochemical progression-free survival (bNED PFS) Secondary endpoints: metastasis-free survival, overall survival, acute and late toxicity. These outcomes were reported for a group which did not include all randomised men, increasing the risk of bias (Wiegel CJO 27 (18) p 2925, para 10) Outcomes actually reported in paper: bNED PFS distant metastases, deaths. Toxicity - report % with grade > 1 GI or bladder adverse effects in each group. Unclear whether acute or late. Urethral stricture: 2 in experimental arm, 1 in control arm We did not review the study protocol.
Other bias	Unclear risk	Unclear

EORTC

Methods	Randomised controlled trial, median follow up 60 months.
Participants	503 men with pT0-3N0M0 prostate cancer (post radical prostatectomy) with one of: extra-capsular spread, seminal vesicle involvement or positive margins Median age 65. No data regarding race. Associated chronic disease in 26.8%. Median preoperative PSA: 12.3. WHO G1:13%, G2: 63%, G3:24%. PSM: 63%. SVI: 26%
Interventions	Experimental arm: EBRT, 60Gy in 30 # (started within 16 weeks of surgery). Control arm: Observation

EORTC (*Continued*)

Outcomes	Primary endpoint: biochemical progression-free survival (PFS) (was initially local control, then changed to clinical PFS, then changed to biochemical PFS). Biochemical PFS = biochemical progression (increase in PSA > 0.2 ng/mL over the lowest postoperative value measured on 3 occasions at least 2 weeks apart), or "clinical progression, or start of treatment in the absence of progression, if any" Secondary endpoints: clinical PFS, survival. Toxicity: Acute: (WHO scoring system used) Late (EORTC/RTOG scoring system used), Quality of life assessed. Sexual function not assessed
Notes	Biochemical PFS definition: rise of 2ng/dl over nadir on three occasions two weeks apart. Ten percent of men in all arms did not ever reach nadir. Recommended salvage: 70GY in 35 # plus or minus LHRH agonist

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "were randomly assigned" (abstract p 572) Quote: "were randomly assigned" (Para 4, page 573) Probably done (EORTC is known by authors as a rigorous and experienced trials group)
Allocation concealment (selection bias)	Low risk	Quote: "Randomisation was centralised at the EORTC data center. After verification of all eligibility criteria, a minimisation technique was used with stratification for institution, capsule invasion, positive margins, and invasion of the seminal vesicles." (Para 4, page 573) Probably done, as EORTC is known by the authors to be an experienced international trials group
Blinding (performance bias and detection bias) Objective outcomes	Low risk	Not mentioned, probably not done. Quote: "Clinical examinations with DRE and PSA test were done at 4, 8 and 12 months after surgery (randomisation), then every year until death. Chest X-ray and bone scans were done every year or in case of clinical or biochemical suspicion of progression. CT scan and liver ultrasound were used for confirmation of suspected progression." PSA failure: As the time intervals for PSA tests were pre-specified, lack of blinding

EORTC (*Continued*)

		unlikely to contribute to bias. Some risk if more frequent investigation for distant metastatic disease in observation arm, but low risk Low risk of bias in overall survival estimation.
Blinding (performance bias and detection bias) Subjective outcomes	Unclear risk	Quote: "Local recurrence had to be documented by DRE (with or without biopsy) and distant relapse by sonography or scintigraphic imaging." High risk of bias in determination of local recurrence (and subsequently also of clinical recurrence, which includes local recurrence), particularly considering subjective nature of interpretation of DRE. Confirmation of local recurrence best with biopsy Some risk of bias in calculation of distant failure, if more frequent radiological investigation in men who have not had RT if clinical symptoms
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	RT arm: 17 ineligible (2 inadequate disease stage, 8 previous or concurrent cancer, 3 prior treatment, 1 lack of baseline data, 3 incomplete work-up) Control arm: 20 ineligible (6 inadequate disease stage, 8 previous or concurrent cancer, 2 prior treatments, 3 missing of baseline data, 1 incomplete work-up) No information available about what happened to people during the course of the trial, did any go missing? Experimental arm: 41 switched to wait and see policy (21 refused, 8 postop complications, 10 advanced disease, 2 unknown) 4 no information Control arm: 5 switched to postop RT 1 no information
Selective reporting (reporting bias)	Unclear risk	**Pre-specified endpoints:** Primary endpoint: Initially local control. Amended to "clinical progression-free survival in March 1995, because potential improvement in local control might benefit clinical progression-

EORTC (*Continued*)

		free survival". Amended in April 2003: "independent data monitoring committee accepted biochemical progression-free survival as primary endpoint (on grounds of evolving urological practice, to take into account biochemical relapse as well)." Although there was a change in primary outcome from that specified at start of trial, the new endpoint was specified in amended protocols, and was justified. Low risk of bias as a result of changed primary endpoint Secondary endpoints: clinical progression free survival local recurrence toxicity (acute and late) **Reported results:** Biochemical progression-free survival. In protocol authors state deaths without PSA failure were censored, but clearly included as event in results Therapy at salvage Clinical progression free survival Loco-regional failure Distant failure Overall survival, death due to prostate ca. Cumulative incidence of late toxicity Protocol not reviewed
Other bias	Low risk	Early stopping occurred, based on O'Brien Flemming rule. The trial was stopped by the independent data monitoring committee when the pre-specified P value < 0.02 was reached. They reported the required sample size (1000) and randomised 1005 men. The treatment effect size was large: HR 0.48 (95% CI 0.37, 0.62; P < 0.0001) , this represented 365 events

SWOG

Methods	Randomised controlled trial, median follow up 12.5 years.
Participants	Dates of data collection: August 1988 to January 1997 Setting: multiple institutions throughout USA and Canada Inclusion criteria: Men who had RP for prostate adenocarcinoma with extra-capsular spread, positive margins or seminal vesicle invasion, and no lymph node metastases detected by pelvic lymphadenectomy (unless 'low risk'*), or distant metastases on bone scan *From June 1995 men at low risk of lymph node metastases were not required to undergo

SWOG (*Continued*)

	lymphadenectomy, including: 1) clinical stage T1a or T2a, Gleason score(GS) 2-6, and PSA < 10 ng/mL, 2) T1b-c, GS 2 to 5 and PSA <10 ng/mL, 3)T2b, GS 2-6 and PSA < 6 ng/mL, and 4) T2c, GS 2-6, and PSA < 4ng/mL Exclusion criteria: RP >16 weeks from randomisation, total urinary incontinence, intraoperative rectal injury, persistent urinary extravasation, pelvic radiotherapy, previous RT or chemotherapy for prostate cancer Median age: 65 (observation) and 64 (RT). Race: 72% white, 19% black, 9% other. No data regarding co-morbidities. Preoperative PSA >10ng/mL: 48% (observation) and 53% (RT). GS <6: 57%, 7: 34%, >8: 9%. Unclear % PSM. SVI 33% (obs) and 32% (RT).
Interventions	EBRT to the pelvic fossa, 60 to 64 Gy in 30 to 32 fractions vs observation
Outcomes	Primary endpoint: metastasis-free survival (bony or visceral metastases, extrapelvic nodal metastases or death from any cause) Secondary endpoints: biochemical relapse-free (RFS), recurrence free survival (objective recurrence not including PSA relapse only or death from any cause), time to hormonal treatment, overall survival, toxicity. Quality of life and sexual function assessed in companion study
Notes	Quality assurance conducted. Central pathology review. About 33% of men in both arms did not achieve undetectable PSA postop

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"central randomisation occurred at SWOG Statistical Center" "were randomised" (abstract) "S8794 was a randomised multi-institutional study" (Para 2, page 957) They have not indicated the method of sequence generation, but the trials organisation is known by the authors to be rigorous and experienced
Allocation concealment (selection bias)	Low risk	"Central randomisation" "A dynamically balanced method was used to minimise imbalance in treatment assignment between the levels of the stratification factors" "Patients were stratified by extent of tumour (I.e. tumour at inked surgical margins or beyond the anatomical capsule and within the seminal vesicle) and by pre-prostatectomy hormonal use." (Para 4, page 2330)

Blinding (performance bias and detection bias) Objective outcomes	High risk	"Patients and investigators were not blinded as to treatment assignment" (Para 4, page 2330) "Follow-up visits at participating institutions were scheduled every 3 months" for 1 year, every 6 months for 2 years, and annually thereafter." Quote: " At each visit, PSA level was obtained, as were additional staging studies (e. g. bone scans) as clinically indicated" For primary endpoint (metastasis-free survival):This is a source of bias, as unblinded investigators may order bone scans earlier and therefore introduce lead-time bias, and shorten metastasis-free survival PSA relapse-free interval less likely to be biased by this policy given prespecified intervals for PSA measurement Death would be unaffected given objective outcome
Blinding (performance bias and detection bias) Subjective outcomes	High risk	Quote: "Toxicity monitored weekly during RT" (Para 3, page 2330) This is a source of bias, as these patients having RT had more frequent assessment of toxicity, and patient and assessors more likely to report toxicity in RT arm "Rectal complications and urinary strictures were not graded but were recorded if annotated on study flow sheets. Total urinary incontinence, while not predefined, was interpreted as no ability to control urinary leakage". Thompson 2006, page 2330, para 5 This is a source of bias, as the recording of toxicity was not either graded or pre-specifed, so depends on the interests or biases of the involved clinician
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"431 men enrolled, of these men, 425 were eligible for analysis" (Para 5, page 957) According to 'Figure 1', 425 were randomised, after exclusion of 6 ineligible patients "6 ineligible subjects, 2 did not undergo lymphadenectomy, 2 did not have pathology report, 1 had residual disease at bladder neck and 1 had positive pelvic nodes neck" (Para 5, page 957) "all 425 eligible patients were used for each

		endpoint analysis" (Analysed at median follow up of 10.6 years) (Para 2, page 2331) Quote: "PSA relapse-free interval assessed in 347/425 men (those with postsurgical PSA 0.4 ng/mL or lower)" (Para 2, page 2331) Although many patients were excluded from the analysis of biochemical failure, this was prespecified in the protocol, and probably due to the increased use and availability of PSA over the time course of the trial. Table shows similar % in each group had postop PSA measured, and similar % (78% control and 83% RT) had postop PSA <0.4 ng/dL and were included in the analysis of PSA failure ('Figure 2'). It is unlikely that the exclusions would cause bias 217/425 men registered to QoL companion trial. "Table 2 lists the demographic and clinical characteristics for the HRQOL sample. Distributions of these are similar for the two treatment arms and for the HRQOL sample versus the larger therapeutic sample". (Para 10, page 114) Although there are many exclusions from QoL analysis, the % and characteristics are similar in each group, with similar rates of follow up. Hence unlikely to have introduced bias Experimental arm: 19 had > 18 months since last contact 4 had < 5 years of follow up Control Arm: 22 > 18 months since last contact 5 had < 5 years of follow up ('Figure 1', page 2331)
Selective reporting (reporting bias)	Unclear risk	Outcomes specified in methods (protocol not reviewed) Primary: 1. Metastasis-free survival 2. Secondary: 3. PSA relapse-free interval 4. Recurrence-free survival 5. Time to hormone therapy 6. Postoperative complications Outcomes actually reported in paper 1. Metastasis-free survival

SWOG (*Continued)*

		2. PSA relapse-free interval 3. Recurrence-free survival 4. Overall survival (addition of this unlikely to cause bias as objective outcome) 5. Time to hormone therapy 6. Postoperative complications
Other bias	Low risk	None

Characteristics of excluded studies *[ordered by year of study]*

Study	Reason for exclusion
Elias 1997	Not RCT
Jani 2005	Not RCT

Characteristics of ongoing studies *[ordered by study ID]*

NCT00667069

Trial name or title	
Methods	Open label, randomised controlled trial
Participants	DISEASE CHARACTERISTICS: • Histologically confirmed adenocarcinoma of the prostate pT3a, pT3b (or pT4 by reaching the bladder neck), or R1 disease (stage III or IV). Localized disease: pN0 or pNx (lymph nodes resected during negative prostatectomy or lymph nodes not resected). No histologically confirmed nodal involvement during initial surgery (pN1 disease). No pT2 disease No tumors of other histology than adenocarcinoma • Must have undergone curative surgery in the past 6 months. Positive margins (tumoral glands in contact with contour ink) • No current clinical or biochemical disease. PSA <0.1 ng/mL after prostatectomy (confirmed at 1 month) • Gleason score < 8 with no seminal vesicles involved PATIENT CHARACTERISTICS • ECOG performance status 0 or 1. Life expectancy >10 years. Affiliated with social security program. No history of cancer within 5 years of surgery except basal cell skin cancer. No known severe hypertension uncontrolled by appropriate therapy (< 160 mm Hg systolic and/or < 90 mm Hg diastolic). No known hypersensitivity to gonadotropin-releasing hormone or its analogs. No contraindication of intramuscular injection. No patients who are deprived of liberty or under guardianship. Not unable to undergo medical monitoring due to geographical, social, or psychological reasons. • PRIOR CONCURRENT THERAPY: No prior surgical or chemical castration. No prior hormonal

NCT00667069 (*Continued*)

	therapy. No prior radiotherapy within 3 months after radical prostatectomy. No prior pelvic radiotherapy. No concurrent participation in another study
Interventions	• Arm I (delayed treatment): Patients receive triptorelin intramuscularly on day 1 and then 3 months later. Patients also undergo conformal radiotherapy daily, 5 days a week, for 7 weeks. Treatment begins at biochemical relapse (PSA is more than 0.2 ng/mL) and before PSA is more than 2 ng/mL. • Arm II (immediate treatment): Patients receive treatment as in arm I, but treatment begins within 6 months after surgery.
Outcomes	Primary Outcome Measures: Event-free survival (clinical progression, biochemical progression, death) at 5 years Secondary Outcome Measures: Overall survival Metastases-free survival Acute or chronic toxicity Quality of life Functional dependence in patients over 75 years old
Starting date	
Contact information	
Notes	Bordeaux, France, 33076

RADICALS

Trial name or title	RADICALS - Radiotherapy and Androgen Deprivation In Combination After Local Surgery
Methods	Treatment, Randomized, Open Label, Active Control
Participants	Genders Eligible for Study: male DISEASE CHARACTERISTICS: Inclusion criteria: • Diagnosis of nonmetastatic adenocarcinoma of the prostate • Must have undergone radical prostatectomy • Postoperative serum prostate-specific antigen (PSA) < 0.4 ng/mL • No postoperative biochemical failure, defined as EITHER two consecutive rises in PSA and final PSA > 0.1 ng/mL OR three consecutive rises in PSA (for patients undergoing hormone therapy duration randomisation) Exclusion criteria: • Known distant metastases from prostate cancer • PSA > 5 ng/mL at the time of hormone randomisation (for patients undergoing hormone therapy duration randomisation) PATIENT CHARACTERISTICS: • No other active malignancy likely to interfere with protocol treatment or follow up PRIOR CONCURRENT THERAPY: Inclusion criteria: • See Disease Characteristics • Co-enrollment to other trials is permitted, providing this does not interfere with the outcome measures

RADICALS (*Continued*)

	• 5-alpha reductase inhibitors, soya, selenium, and vitamin E are acceptable non-trial therapies Exclusion criteria: • Prior hormone therapy • Bilateral orchidectomy • Prior pelvic radiotherapy • Neoadjuvant treatment • Other concurrent therapies for prostate cancer (e.g., estrogens or cytotoxic chemotherapy) prior to disease progression
Interventions	2X2 randomisation 1) if postoperative uncertainty about the need for immediate radiotherapy, men randomised to • immediate radiotherapy or • salvage radiotherapy for PSA failure Radiotherapy = 66 Gy in 33 fractions over 6.5 weeks to the prostate bed PSA failure = 2 consecutive rises in PSA and PSA >0.1 ng/mL or 3 consecutive rises in PSA 2) when radiotherapy to be given, men randomised to • radiotherapy alone • radiotherapy with 6 months of hormone therapy • radiotherapy with 2 years of hormone therapy Hormone therapy = gonadotrophin releasing hormone analogue with 3 weeks of antiandrogen at initiation, or bicalutamide 150 mg
Outcomes	Primary Outcome Measures: Disease-specific survival (i.e., death due to prostate cancer) Secondary Outcome Measures: Freedom from treatment failure Clinical progression-free survival Overall survival Non-protocol hormone therapy Treatment toxicity Patient reported outcomes
Starting date	October 2007
Contact information	Christopher Parker, MD Royal Marsden NHS Foundation Trust
Notes	

RAVES

Trial name or title	A Phase III multi-centre randomised trial comparing adjuvant radiotherapy (RT) with early salvage RT in patients with positive margins or extraprostatic disease following radical prostatectomy. RAVES (Radiotherapy Adjuvant Versus Early Salvage)
Methods	Design: A two-arm, randomised phase III multicentre, non-inferiority trial. Patients were stratified according to the following criteria: Pre-operative PSA (as a continuous variable), Gleason score (from RP specimen; as a continuous variable), surgical margins (positive/negative), seminal vesicle involvement (pT3b) (yes/no) and radiotherapy institution

RAVES (*Continued*)

Participants	Inclusion Criteria All of the following must apply 1. Prior Radical Prostatectomy (RP) for adenocarcinoma of the prostate. 2. Histological confirmation of adenocarcinoma of the prostate with the Gleason score reported (Radical Prostatectomy specimen). 3. Patients must have at least one of the following risk factors: i) Positive margins ii) Extraprostatic extension (EPE) with or without seminal vesicle involvement (pT3a or pT3b) ('Appendix I') 4. Capable of starting RT within 4 months of RP (a requirement if randomised to adjuvant RT arm) 5. Most recent PSA $\leq$ 0.1 ng/mL following RP and prior to randomisation 6. Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1 ('Appendix II') 7. Patient able to adhere to the specified follow-up schedule and complete the Quality of Life and anxiety/depression self-assessments 8. Written informed consent obtained prior to randomisation 9. Completion of all pre-treatment evaluations 10. 18 years or older Exclusion Criteria None of the following must apply: 1. Previous pelvic RT 2. Concurrent or previous malignancy within 5 years prior to randomisation (except non-melanomatous skin cancer) 3. Androgen deprivation (AD) prior to or following RP 4. Evidence of nodal or distant metastases 5. Co-morbidities that would interfere with the completion of treatment or 5 years of follow up 6. Concurrent cytotoxic medication 7. Hip prosthesis
Interventions	Eligible patients will be randomised to either: Arm A (standard arm) - adjuvant RT commenced within 4 months of RP; or Arm B (experimental arm) - active surveillance with early salvage RT following a rising PSA (PSA level >0.2 ng/mL prior to radiotherapy)
Outcomes	Primary outcome measure: biochemical failure (bF) Secondary 1. Secondary objectives will include a comparison of the two treatment arms with respect to each of the secondary endpoints: QoL, adverse events, anxiety/depression, biochemical failure-free survival, overall survival, disease-specific survival, time to distant failure, time to local failure, time to the initiation of androgen deprivation, quality-adjusted life years and cost utility 2. In addition, a prognostic factors analysis will be performed for each time-to-event.
Starting date	30 March 2009
Contact information	Dr Maria Pearse Department of Radiation Oncology Auckland City Hospital P.O BOX 92-024 Auckland 1142 New Zealand

RAVES (*Continued*)

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Notes	

DATA AND ANALYSES

Comparison 1. Adjuvant RT versus nil postprostatectomy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	3		Risk Difference (M-H, Fixed, 95% CI)	Subtotals only
1.1 Overall survival at 5 years	3	1737	Risk Difference (M-H, Fixed, 95% CI)	-0.00 [-0.03, 0.02]
1.2 Overall survival at 10 years	1	425	Risk Difference (M-H, Fixed, 95% CI)	-0.11 [-0.20, -0.02]
2 Metastases	3		Risk Difference (M-H, Fixed, 95% CI)	Subtotals only
2.1 Metastases at 5 years	3	1737	Risk Difference (M-H, Fixed, 95% CI)	-0.01 [-0.03, 0.01]
2.2 Metastases at 10 years	1	425	Risk Difference (M-H, Fixed, 95% CI)	-0.11 [-0.20, -0.01]
3 Local recurrence	2	1379	Risk Difference (M-H, Fixed, 95% CI)	-0.11 [-0.14, -0.08]
3.1 Local recurrence at 5 years	1	1005	Risk Difference (M-H, Fixed, 95% CI)	-0.10 [-0.13, -0.06]
3.2 Local recurrence at 10 years	1	374	Risk Difference (M-H, Fixed, 95% CI)	-0.14 [-0.21, -0.07]
4 Biochemical relapse ITT1	3	2084	Risk Difference (M-H, Fixed, 95% CI)	-0.18 [-0.22, -0.14]
4.1 Biochemical relapse at 5 years	3	1737	Risk Difference (M-H, Fixed, 95% CI)	-0.15 [-0.20, -0.11]
4.2 Biochemical relapse at 10 years	1	347	Risk Difference (M-H, Fixed, 95% CI)	-0.29 [-0.39, -0.19]
5 Urethral stricture	2		Risk Difference (M-H, Fixed, 95% CI)	Subtotals only
5.1 Urethral stricture at 5 years	1	307	Risk Difference (M-H, Fixed, 95% CI)	0.01 [-0.02, 0.03]
5.2 Urethral stricture at 10 years	1	425	Risk Difference (M-H, Fixed, 95% CI)	0.08 [0.02, 0.15]
6 Urinary incontinence	2	525	Risk Difference (M-H, Fixed, 95% CI)	0.04 [0.01, 0.08]
6.1 Urinary incontinence at 5 years	1	100	Risk Difference (M-H, Fixed, 95% CI)	0.06 [-0.02, 0.15]
6.2 Urinary incontinence at 10 years	1	425	Risk Difference (M-H, Fixed, 95% CI)	0.04 [-0.00, 0.08]
7 Prostate cancer specific survival	1	1005	Risk Difference (M-H, Fixed, 95% CI)	-0.01 [-0.03, 0.00]

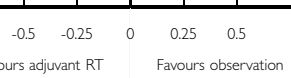
Analysis 1.1. Comparison 1 Adjuvant RT versus nil postprostatectomy, Outcome 1 Overall survival.

Review: Adjuvant radiotherapy following radical prostatectomy for prostate cancer

Comparison: 1 Adjuvant RT versus nil postprostatectomy

Outcome: 1 Overall survival

Study or subgroup	Adjuvant RT n/N	No RT n/N	Risk Difference M-H,Fixed,95% CI	Weight	Risk Difference M-H,Fixed,95% CI
1 Overall survival at 5 years					
ARO	5/148	8/159		17.7 %	-0.02 [-0.06, 0.03]
EORTC	46/502	43/503		57.9 %	0.01 [-0.03, 0.04]
SWOG	20/214	23/211		24.5 %	-0.02 [-0.07, 0.04]
Subtotal (95% CI)	**864**	**873**		**100.0 %**	**0.00 [-0.03, 0.02]**
Total events: 71 (Adjuvant RT), 74 (No RT)					
Heterogeneity: Chi^2 = 0.79, df = 2 (P = 0.67); I^2 =0.0%					
Test for overall effect: Z = 0.24 (P = 0.81)					
2 Overall survival at 10 years					
SWOG	88/214	110/211		100.0 %	-0.11 [-0.20, -0.02]
Subtotal (95% CI)	**214**	**211**		**100.0 %**	**-0.11 [-0.20, -0.02]**
Total events: 88 (Adjuvant RT), 110 (No RT)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.29 (P = 0.022)					
Test for subgroup differences: Chi^2 = 4.59, df = 1 (P = 0.03), I^2 =78%					



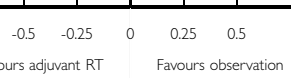
Analysis 1.2. Comparison 1 Adjuvant RT versus nil postprostatectomy, Outcome 2 Metastases.

Review: Adjuvant radiotherapy following radical prostatectomy for prostate cancer

Comparison: 1 Adjuvant RT versus nil postprostatectomy

Outcome: 2 Metastases

Study or subgroup	Adjuvant RT n/N	No RT n/N	Risk Difference M-H,Fixed,95% CI	Weight	Risk Difference M-H,Fixed,95% CI
1 Metastases at 5 years					
ARO	4/148	5/159		17.7 %	0.00 [-0.04, 0.03]
EORTC	19/502	18/503		57.9 %	0.00 [-0.02, 0.03]
SWOG	29/214	37/211		24.5 %	-0.04 [-0.11, 0.03]
Subtotal (95% CI)	**864**	**873**		**100.0 %**	**-0.01 [-0.03, 0.01]**
Total events: 52 (Adjuvant RT), 60 (No RT)					
Heterogeneity: Chi^2 = 1.74, df = 2 (P = 0.42); I^2 =0.0%					
Test for overall effect: Z = 0.81 (P = 0.42)					
2 Metastases at 10 years					
SWOG	93/214	114/211		100.0 %	-0.11 [-0.20, -0.01]
Subtotal (95% CI)	**214**	**211**		**100.0 %**	**-0.11 [-0.20, -0.01]**
Total events: 93 (Adjuvant RT), 114 (No RT)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.19 (P = 0.028)					
Test for subgroup differences: Chi^2 = 3.78, df = 1 (P = 0.05), I^2 =74%					



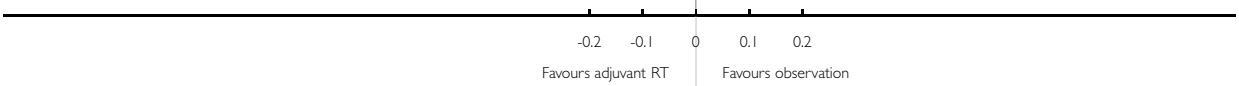
Analysis 1.3. Comparison 1 Adjuvant RT versus nil postprostatectomy, Outcome 3 Local recurrence.

Review: Adjuvant radiotherapy following radical prostatectomy for prostate cancer

Comparison: 1 Adjuvant RT versus nil postprostatectomy

Outcome: 3 Local recurrence

Study or subgroup	Adjuvant RT n/N	Observation n/N	Risk Difference M-H,Fixed,95% CI	Weight	Risk Difference M-H,Fixed,95% CI
1 Local recurrence at 5 years					
EORTC	25/502	74/503		72.9 %	-0.10 [-0.13, -0.06]
Subtotal (95% CI)	**502**	**503**		**72.9 %**	**-0.10 [-0.13, -0.06]**
Total events: 25 (Adjuvant RT), 74 (Observation)					
Heterogeneity: not applicable					
Test for overall effect: Z = 5.25 (P < 0.00001)					
2 Local recurrence at 10 years					
SWOG	15/190	40/184		27.1 %	-0.14 [-0.21, -0.07]
Subtotal (95% CI)	**190**	**184**		**27.1 %**	**-0.14 [-0.21, -0.07]**
Total events: 15 (Adjuvant RT), 40 (Observation)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.83 (P = 0.00013)					
Total (95% CI)	**692**	**687**		**100.0 %**	**-0.11 [-0.14, -0.08]**
Total events: 40 (Adjuvant RT), 114 (Observation)					
Heterogeneity: Chi^2 = 1.05, df = 1 (P = 0.31); I^2 =5%					
Test for overall effect: Z = 6.50 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 1.02, df = 1 (P = 0.31), I^2 =2%					



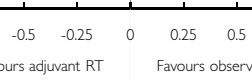
Analysis 1.4. Comparison 1 Adjuvant RT versus nil postprostatectomy, Outcome 4 Biochemical relapse ITT1.

Review: Adjuvant radiotherapy following radical prostatectomy for prostate cancer

Comparison: 1 Adjuvant RT versus nil postprostatectomy

Outcome: 4 Biochemical relapse ITT1

Study or subgroup	Adjuvant RT n/N	No RT n/N	Risk Difference M-H,Fixed,95% CI	Weight	Risk Difference M-H,Fixed,95% CI
1 Biochemical relapse at 5 years					
ARO	83/193	100/192		18.5 %	-0.09 [-0.19, 0.01]
EORTC	93/502	188/503		48.2 %	-0.19 [-0.24, -0.13]
SWOG	44/172	67/175		16.6 %	-0.13 [-0.22, -0.03]
Subtotal (95% CI)	**867**	**870**		**83.4 %**	**-0.15 [-0.20, -0.11]**
Total events: 220 (Adjuvant RT), 355 (No RT)					
Heterogeneity: Chi^2 = 3.39, df = 2 (P = 0.18); I^2 =41%					
Test for overall effect: Z = 7.05 (P < 0.00001)					
2 Biochemical relapse at 10 years					
SWOG	60/172	112/175		16.6 %	-0.29 [-0.39, -0.19]
Subtotal (95% CI)	**172**	**175**		**16.6 %**	**-0.29 [-0.39, -0.19]**
Total events: 60 (Adjuvant RT), 112 (No RT)					
Heterogeneity: not applicable					
Test for overall effect: Z = 5.67 (P < 0.00001)					
Total (95% CI)	**1039**	**1045**		**100.0 %**	**-0.18 [-0.22, -0.14]**
Total events: 280 (Adjuvant RT), 467 (No RT)					
Heterogeneity: Chi^2 = 9.02, df = 3 (P = 0.03); I^2 =67%					
Test for overall effect: Z = 8.79 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 5.98, df = 1 (P = 0.01), I^2 =83%					

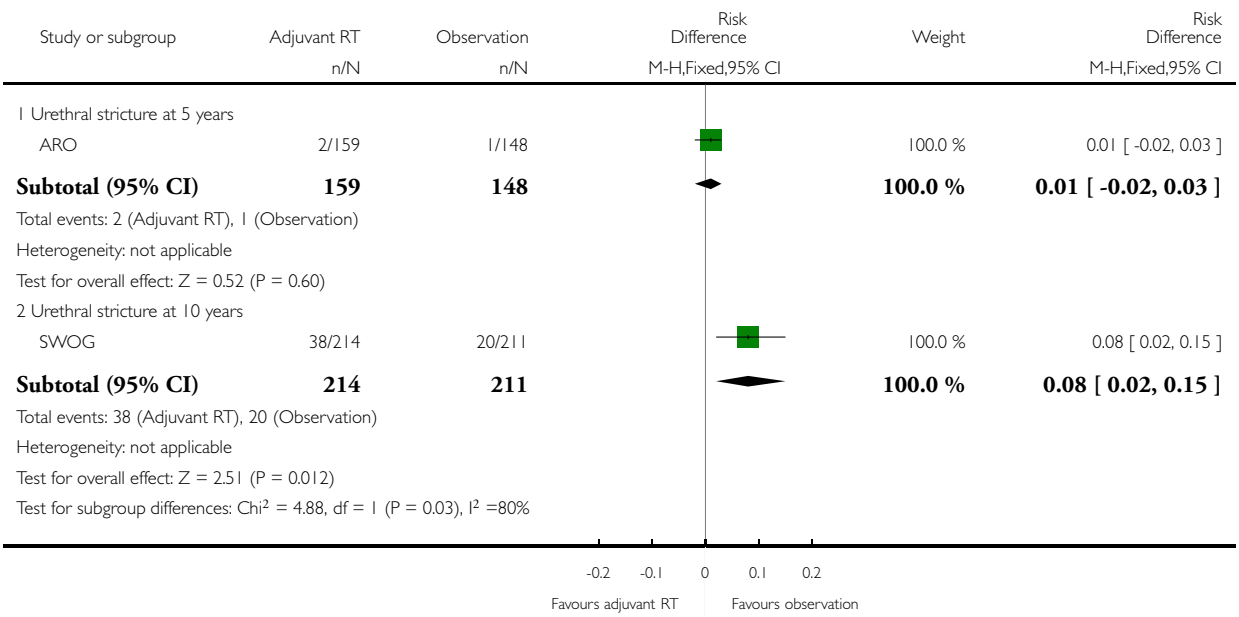


Analysis 1.5. Comparison 1 Adjuvant RT versus nil postprostatectomy, Outcome 5 Urethral stricture.

Review: Adjuvant radiotherapy following radical prostatectomy for prostate cancer

Comparison: 1 Adjuvant RT versus nil postprostatectomy

Outcome: 5 Urethral stricture



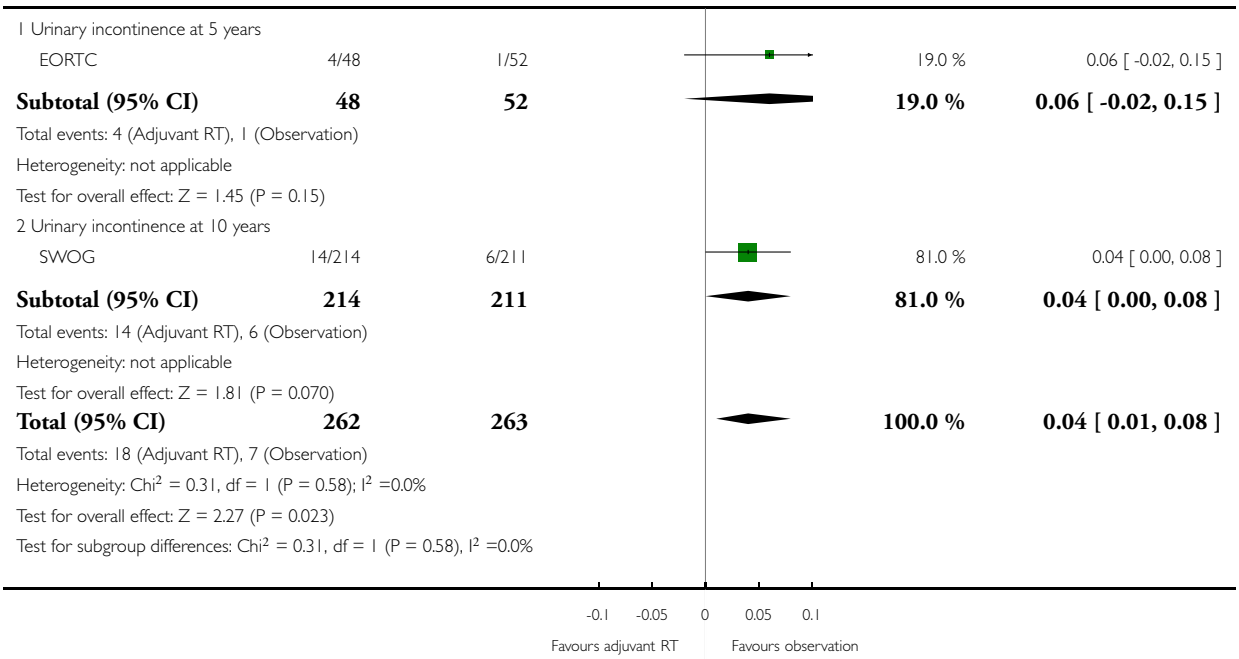
Analysis 1.6. Comparison 1 Adjuvant RT versus nil postprostatectomy, Outcome 6 Urinary incontinence.

Review: Adjuvant radiotherapy following radical prostatectomy for prostate cancer

Comparison: 1 Adjuvant RT versus nil postprostatectomy

Outcome: 6 Urinary incontinence

Study or subgroup	Adjuvant RT n/N	Observation n/N	Risk Difference M-H,Fixed,95% CI	Weight	Risk Difference M-H,Fixed,95% CI
1 Urinary incontinence at 5 years					
EORTC	4/48	1/52		19.0 %	0.06 [-0.02, 0.15]
Subtotal (95% CI)	**48**	**52**		**19.0 %**	**0.06 [-0.02, 0.15]**
Total events: 4 (Adjuvant RT), 1 (Observation)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.45 (P = 0.15)					
2 Urinary incontinence at 10 years					
SWOG	14/214	6/211		81.0 %	0.04 [0.00, 0.08]
Subtotal (95% CI)	**214**	**211**		**81.0 %**	**0.04 [0.00, 0.08]**
Total events: 14 (Adjuvant RT), 6 (Observation)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.81 (P = 0.070)					
Total (95% CI)	**262**	**263**		**100.0 %**	**0.04 [0.01, 0.08]**
Total events: 18 (Adjuvant RT), 7 (Observation)					
Heterogeneity: Chi^2 = 0.31, df = 1 (P = 0.58); I^2 =0.0%					
Test for overall effect: Z = 2.27 (P = 0.023)					
Test for subgroup differences: Chi^2 = 0.31, df = 1 (P = 0.58), I^2 =0.0%					



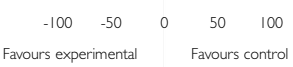
Analysis 1.7. Comparison 1 Adjuvant RT versus nil postprostatectomy, Outcome 7 Prostate cancer specific survival.

Review: Adjuvant radiotherapy following radical prostatectomy for prostate cancer

Comparison: 1 Adjuvant RT versus nil postprostatectomy

Outcome: 7 Prostate cancer specific survival

Study or subgroup	Adjuvant RT n/N	Control n/N	Risk Difference M-H,Fixed,95% CI	Weight	Risk Difference M-H,Fixed,95% CI
EORTC	8/502	15/503		100.0 %	-0.01 [-0.03, 0.00]
Total (95% CI)	**502**	**503**		**100.0 %**	**-0.01 [-0.03, 0.00]**
Total events: 8 (Adjuvant RT), 15 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.47 (P = 0.14)					
Test for subgroup differences: Not applicable					



ADDITIONAL TABLES

Table 1. International Incontinence Scale

Grade	Definition
0	dry < 1 gm (gram) no pads
1	minimal 1 to 9 gm 1 to 4 pads (humid)
2	moderate 10 to 50 gm 1 to 4 pads (soaked)
3	severe > 50 gm with > 4 pads

Table 2. RTOG/EORTC Late RT score Bladder

	0	1	2	3	4
Symptom	None	Slight epithelial atrophy; Minor telangiectasia (microscopic hematuria)	Moderate frequency; Generalized telangiectasia; Intermittent macroscopic hematuria	Severe frequency and dysuria; Severe generalized telangiectasia (often with petechiae); Frequent hematuria; Reduction in bladder capacity (< 150 cc)	Necrosis/Contracted bladder (capacity <100 cc); Severe hemorrhagic cystitis

Table 3. HQRL - dichotomous measures

Symptom	Scale
Tenderness and urgency with bowel movements	1. normal 2. occasionally mild 3. frequently mild 4. mild to moderate 5. frequent, severe urgency, pain, or bleeding 6. had to have a colostomy
Urinary frequency	1. $\leq$ 4 times/day 2. 5 to 8 times/day 3. 9 to 12 times/day 4. > 12 times/day 5. indwelling catheter
Erectile dysfunction	1. normal 2. weaker 3. insufficient 4. unable
Global HQRL: rating of how life is affected by the state of your health	1. extremely unpleasant 2. unpleasant 3. moderately unpleasant 4. slightly unpleasant 5. normal (no change)

Table 4. Definition of nadir

Study	Definition of nadir
ARO	postoperative PSA < 0.1ng/dL
EORTC	PSA < 0.2 ng/dL
SWOG	PSA ≤ 0.4 ng/dL

Table 5. Number of men who did not nadir

Study	Number of men who did not nadir
ARO	78/388 (20%)
EORTC	108/1005 (10%)
SWOG	127/376 (33%) did not achieve PSA ≤ 0.2 ng/dL 29/376 (7%) of men did not achieve PSA ≤ 0.4ng/dL (which is the definition they used for nadir) NB: only had PSA information for 376/425 men postoperatively

Table 6. Acute G/U toxicity (RTOG)

Grade	Symptoms
0	No change from baseline
1	urinary frequency and nocturia 2 times pretreatment habit, urgency, no medications
2	frequency, urgency and nocturia, medications required
3	frequency urgency and nocturia with spasms and frequent medications required
4	Haematuria requiring transfusion, acute bladder obstruction ulceration/necrosis
5	Death secondary to radiation side effects

APPENDICES

Appendix 1. MEDLINE search strategy

For MEDLINE, the search strategy will be as follows:

1. randomised controlled trial.pt
2. controlled clinical trial.pt
3. exp randomised controlled trials/
4. exp random allocation
5. exp double blind method/
6. exp single-blind method/
7. 1 OR 2 OR 3 OR 4 OR 5 OR 6
8. (animal not human).sh
9. 7 NOT 8
10. clinical trial.pt
11. exp clinical trial.pt
12. (clin$ adj25 trial$).tw
13. ((single OR double OR triple OR treble) adj25 blind$ or mask$)).tw
14. exp placebos/
15. placebo$.tw
16. Rrandom$.tw
17. exp research design/
18. 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17
19. 18 not 8
20. 9 OR 19
21. exp comparative study/
22. exp evaluation studies/
23. exp follow-up studies/
24. exp prospective studies/
25. (control$ OR prospective$ OR volunteer$).tw
26. 21 OR 22 OR 23 OR 24 OR 25
27. 26 NOT 8
28. 20 OR 27
29. exp prostatic neoplasms/
30. prostatic neoplasms.tw
31. exp Prostatic intrapiethelial neoplasia/
32. prostatic intraepithelial neoplasia.tw
33. exp Carcinoma/
34. carcinoma.tw
35. exp prostate/
36. prostate.tw
37. neoplasm$ or cancer$ or carcinoma$ or neoplasia$ or tumor$ or tumour$ or malignan$
38. 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36 OR 37
39. NOT 8
40. 28 AND 39
41. exp prostatectomy/
42. prostatectomy.tw
43. 41 OR 42
44. exp radiotherapy/
45. radiation therapy.tw
46. exp chemotherapy, adjuvant/
47. exp neoadjuvant therapy/
48. exp antineoplastic agents, hormonal/

49. exp androgen antagonists/
50. 44 OR 45 OR 46 OR 47 OR 48 OR 49
51. 43 AND 50
52. NOT 8
53. AND 40

HISTORY

Protocol first published: Issue 3, 2008

Review first published: Issue 12, 2011

CONTRIBUTIONS OF AUTHORS

TD wrote the protocol, reviewed results of search and abstracts, extracted and checked data and 'Risk of bias' tables, co-wrote the discussion and edited review.

BH edited protocol, reviewed results of search and abstracts, extracted and checked data, constructed Risk of bias tables, entered data into RevMan, analysed data, co-wrote and edited discussion.

ML edited protocol, reviewed results of search and abstracts, edited review.

DECLARATIONS OF INTEREST

None.

SOURCES OF SUPPORT

Internal sources

- Princess Alexandra Cancer Collaborative Group, Australia.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We reported risk difference not odds ratio as we proposed to do in the protocol (based on peer reviewer's recommendation).

INDEX TERMS

Medical Subject Headings (MeSH)

Prostatectomy [*methods]; Prostatic Neoplasms [mortality; *radiotherapy; surgery]; Radiotherapy, Adjuvant [mortality]; Randomized Controlled Trials as Topic; Time Factors

MeSH check words

Humans; Male