Timing of radiotherapy after radical prostatectomy (RADICALS-RT): a randomised, controlled phase 3 trial


Summary

Background The optimal timing of radiotherapy after radical prostatectomy for prostate cancer is uncertain. We aimed to compare the efficacy and safety of adjuvant radiotherapy versus an observation policy with salvage radiotherapy for prostate-specific antigen (PSA) biochemical progression.

Methods We did a randomised controlled trial enrolling patients with at least one risk factor (pathological T-stage 3 or 4, Gleason score of 7–10, positive margins, or preoperative PSA ≥10 ng/mL) for biochemical progression after radical prostatectomy (RADICALS-RT). The study took place in trial-accredited centres in Canada, Denmark, Ireland, and the UK. Patients were randomly assigned in a 1:1 ratio to adjuvant radiotherapy or an observation policy with salvage radiotherapy for PSA biochemical progression (PSA ≥0.1 ng/mL or three consecutive rises). Masking was not deemed feasible. Stratification factors were Gleason score, margin status, planned radiotherapy schedule (52.5 Gy in 20 fractions or 66 Gy in 33 fractions), and centre. The primary outcome measure was freedom from distant metastases, designed with 80% power to detect an improvement from 90% with salvage radiotherapy (control) to 95% at 10 years with adjuvant radiotherapy. We report on biochemical progression-free survival, freedom from non-proctocol hormone therapy, and patient-reported outcomes. Standard survival analysis methods were used. A hazard ratio (HR) of less than 1 favoured adjuvant radiotherapy. This study is registered with ClinicalTrials.gov, NCT00541047.

Findings Between Nov 22, 2007, and Dec 30, 2016, 1396 patients were randomly assigned, 699 (50%) to salvage radiotherapy and 697 (50%) to adjuvant radiotherapy. Allocated groups were balanced with a median age of 65 years (IQR 60–68). Median follow-up was 4–9 years (IQR 3–6–6.1). 649 (93%) of 697 participants in the adjuvant radiotherapy group reported radiotherapy within 6 months; 228 (33%) of 699 in the salvage radiotherapy group reported radiotherapy within 8 years after randomisation. With 169 events, 5-year biochemical progression-free survival was 85% for those in the adjuvant radiotherapy group and 88% for those in the salvage radiotherapy group (HR 1·10, 95% CI 0·81–1·49; p=0·56). Freedom from non-protocol hormone therapy at 5 years was 85% for those in the adjuvant radiotherapy group and 88% for those in the salvage radiotherapy group (HR 0·88, 95% CI 0·58–1·33; p=0·56). Self-reported urinary incontinence was worse at 1 year for those in the adjuvant radiotherapy group versus 92% for those in the salvage radiotherapy group (HR 0·88, 95% CI 0·58–1·33; p=0·56). Grade 3–4 urethral stricture within 2 years was reported in 6% of individuals in the adjuvant radiotherapy group versus 92% for those in the salvage radiotherapy group (HR 0·88, 95% CI 0·58–1·33; p=0·56). Freedom from non-protocol hormone therapy at 5 years was 93% for those in the adjuvant radiotherapy group and 88% for those in the salvage radiotherapy group (HR 1·10, 95% CI 0·81–1·49; p=0·56). Freedom from non-protocol hormone therapy at 5 years was 93% for those in the adjuvant radiotherapy group and 88% for those in the salvage radiotherapy group (HR 1·10, 95% CI 0·81–1·49; p=0·56).

Interpretation These initial results do not support routine administration of adjuvant radiotherapy after radical prostatectomy. Adjuvant radiotherapy increases the risk of urinary morbidity. An observation policy with salvage radiotherapy for PSA biochemical progression should be the current standard after radical prostatectomy.

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Introduction

Radical prostatectomy is a standard treatment for clinically localised prostate cancer, and is often followed by postoperative radiotherapy to the prostate bed.14 The optimal timing of radiotherapy after radical prostatectomy remains uncertain. Adjuvant radiotherapy can be given early, to those with no evidence of residual disease after surgery, to reduce the risk of subsequent recurrence. Alternatively, patients might be followed up after surgery, with salvage radiotherapy given later only to those men who develop a rising prostate-specific antigen (PSA) concentration. It is possible that earlier treatment with adjuvant radiotherapy might be more effective than a policy of delayed salvage radiotherapy for biochemical progression. However, the salvage radiotherapy policy avoids unnecessary treatment of those cured by surgery alone and can therefore result in less treatment-related morbidity.
Evidence before this study

The trial was developed by an international trial development group. The evidence before the development of the trial in 2005 was well known to the prostate cancer community from high-profile randomised controlled trials. Previous randomised controlled trials of adjuvant radiotherapy after radical prostatectomy showed a reduced risk of disease recurrence, but conflicting results for longer-term outcomes. These trials are difficult to interpret in the context of current practice due to their late use, if at all, of salvage radiotherapy in the control group. Clinical guidelines differed in their approach to postoperative radiotherapy timing, and surveys of clinical opinion did not find a consensus on this issue. The evidence before these results were developed with the ARTISTIC meta-analysis group in a systematic review set out in PROSPERO (CRD42019132669), which included searches of trial registers and major oncology conference proceedings.

Research in context

Evidence before this study

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Added value of this study

RADICALS-RT compared adjuvant radiotherapy against a policy of early salvage radiotherapy in the event of prostate-specific antigen biochemical progression. Adjuvant radiotherapy did not have any benefit in comparison with the salvage policy, but did increase the risk of urinary and bowel morbidity.

Implications of all the available evidence

These results are published in the context of two other trials that assessed radiotherapy timing and a prospectively planned meta-analysis, ARTISTIC. In the absence of any reliable evidence that adjuvant radiotherapy does more good than harm, observation with salvage treatment for prostate-specific antigen biochemical progression should be the current standard of care after radical prostatectomy.

Methods

Study design and participants

RADICALS is an international, phase 3, multicentre, open-label, randomised controlled trial in prostate cancer. The protocol contains two separate randomisations with overlapping patient groups and was implemented at 138 trial-accredited centres in Canada, Denmark, Ireland, and the UK. Participants were randomly assigned shortly after radical prostatectomy to adjuvant or salvage postoperative radiotherapy (RADICALS-RT), and, in patients planned for postoperative radiotherapy, to 0 versus 6 months versus 24 months of hormone therapy (RADICALS-HD). Here, we report results from the radiotherapy timing randomisation, RADICALS-RT, comparing the addition of immediate postoperative radiotherapy (research) to a salvage postoperative radiotherapy policy (control).

Patients with non-metastatic adenocarcinoma of the prostate were eligible for RADICALS-RT if they had undergone radical prostatectomy, had postoperative PSA of 0–2 ng/mL or less, and at least one specified risk factor (ie, pathological T-stage 3 or 4, Gleason score 7–10, positive margins, or preoperative PSA of 10 ng/mL or more). Appropriate ethical review was in place for each participating country. All participants gave written informed consent. The protocol is available online.
Randomisation and masking
Participants were randomly assigned, within 22 weeks after radical prostatectomy, to receive either adjuvant radiotherapy to the prostate bed with or without pelvis, or close observation with salvage radiotherapy to the prostate bed with or without pelvis given in the event of PSA biochemical progression, defined as either two consecutive rising PSA amounts with a PSA of greater than 0·1 ng/mL, or three consecutive rising PSA amounts. Randomisation, using a 1:1 allocation, was done centrally using minimisation with a random element, which was stratified by Gleason sum score, margin status, radiotherapy schedule, and study centre. No masking was used in the trial.

Procedures
Radiotherapy to the prostate bed used a non-randomised dose-fractionation schedule of either 66·0 Gy in 33 fractions or 52·5 Gy in 20 fractions. Radiotherapy was delivered once a day with five sessions per week. Treatment commenced within both 2 months after randomisation and 26 weeks of radical prostatectomy for patients on adjuvant radiotherapy, and within 2 months of PSA biochemical progression for patients on salvage radiotherapy. Radiotherapy could be delayed by up to 2 months if the patient was also due to receive hormone therapy.

Participants could also receive radiotherapy to the pelvic lymph nodes, at the investigator’s discretion. Radiotherapy was planned with the patient supine, with empty rectum and comfortably full bladder. Patients could also receive up to 2 years’ hormone therapy (either a luteinising hormone releasing hormone analogue or bicalutamide 150 mg once a day) starting before and continuing during and after their postoperative radiotherapy, either according to clinical judgment, or if participating in RADICALS-HD, randomly allocated to receive either no, 6 months, or 2 years of hormone therapy.

Outcomes
Patients were seen by a site investigator every 4 months from randomisation for 2 years, then 6-monthly until 5 years, then annually until 15 years. Clinician-reported data were collected at each follow-up visit on diarrhoea, proctitis, cystitis, haematuria, and urethral stricture, graded according to Radiation Therapy Oncology Group (RTOG) toxicity score.12 Data for other adverse events were collected if the event met the criteria to be classified as a serious adverse event. Patient-reported data were collected at baseline, 1, 5, and 10 years post-randomisation with use of standard questionnaires that included Vaizey (bowel) and International Continence Society Male Short-Form (urinary incontinence).

RADICALS was designed to focus on long-term outcomes, with the primary outcome measure of disease-specific survival for both the RADICALS-RT and RADICALS-HD randomisations, and freedom-from-distant metastases (FFDM) as a key secondary outcome measure. Distant metastases could be bone, liver, lung, distant node, or other metastases, but did not include pelvic nodes. It became apparent after the EORTC 22911 and SWOG 8794 trials were published that patient outcomes were better than previously reported.13,14 The RADICALS team instigated discussions with two other then-recruiting trials addressing radiotherapy timing, RAVES15 and GETUG-AFU 17,16 which led to the ARTISTIC17 meta-analysis. Given the ability of the meta-analysis to attain power for disease-specific survival, and based on the observed event rate from external sources, the RADICALS team amended the primary outcome of the RADICALS-RT comparison to FFDM that would have greater power at any given time. This change was made with all ethical and regulatory approvals in place, without reference to accumulating comparative data from RADICALS-RT, and was agreed with the trial steering committee (which includes independent members, including the chair) and gained favourable international peer review, through Cancer Research UK.

Figure 1: Trial profile
PSA=prostate-specific antigen.

<table>
<thead>
<tr>
<th>1136 patients randomised post-prostatectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>699 allocated to salvage radiotherapy policy</td>
</tr>
<tr>
<td>228 had PSA progression and reported radiotherapy</td>
</tr>
<tr>
<td>51 had PSA progression and did not report radiotherapy</td>
</tr>
<tr>
<td>411 did not report PSA progression or radiotherapy</td>
</tr>
<tr>
<td>Median follow-up was 5·0 years</td>
</tr>
<tr>
<td>33 patients had no data in the last 18 months and were last seen alive</td>
</tr>
<tr>
<td>699 patients included in analysis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>697 allocated to adjuvant radiotherapy policy</th>
</tr>
</thead>
<tbody>
<tr>
<td>648 reported radiotherapy within 1 year</td>
</tr>
<tr>
<td>1 reported radiotherapy after 1 year</td>
</tr>
<tr>
<td>48 did not report radiotherapy</td>
</tr>
<tr>
<td>Median follow-up was 4·7 years</td>
</tr>
<tr>
<td>54 patients had no data in the last 18 months and were last seen alive</td>
</tr>
<tr>
<td>697 patients included in analysis</td>
</tr>
</tbody>
</table>
Secondary outcomes were survival and disease-specific survival, initiation of non-protocol hormone therapy, treatment toxicity, and patient-reported outcomes. Freedom from biochemical progression was added as a secondary outcome measure in 2018 to facilitate the ARTISTIC meta-analysis without reference to the accumulating data and with the approval of the oversight committees. The other two trials, RAVES and GETUG-AFU 17, were both designed with a focus on biochemical progression.

Biochemical progression-free survival (bPFS) was defined as freedom from PSA of 0·4 ng/mL or greater following postoperative radiotherapy, or PSA of more than 2·0 ng/mL at any time, or clinical progression, or initiation of non-protocol hormone therapy, or death from any cause. This definition of bPFS was agreed in collaboration with the RAVES and GETUG-AFU 17 trial teams and registered in PROSPERO with the ARTISTIC meta-analysis protocol.¹⁶

Comparative data for long-term outcome measures remain confidential to the independent data monitoring committee and are not reported here.

### Statistical analysis

The sample size target was originally approximately 2600 patients recruited over 5-5 years and followed up for a further 7 years, to have 80% power to detect an improvement from 70% to 75%, or 90% power to detect an improvement from 80% to 85% in disease-specific survival. In 2011, the primary outcome of RADICALS-RT was brought forward to FFDM following a review of the expected event rate based on external publications. To target an improvement in patients free of distant metastases at 10 years from 90% to 95%, with 80% power at a two-sided 5% significance level would require 66 patients with distant metastases events, assuming still 5-5 years of accrual, a further 7 years of follow-up, and that 30% of patients would not be assessable for prostate cancer survival from 5 up to 10 years after randomisation. This target difference was anticipated to require 1063 patients at an accrual rate of 30 patients per month or 1160 patients at 25 patients per month. The trial management group continued to project and track combinations of accrual rates and expected time to accumulate interim data.

The other two relevant trials, RAVES and GETUG-AFU 17, had bPFS as their primary outcome measure. The RADICALS trial management group agreed, with support of the independent members of the oversight committees, to assess and report on bPFS before the analysis of RADICALS-RT’s primary outcome measure. This analysis would be timed to coincide with the planned reporting of the other trials and to facilitate a timely meta-analysis. We calculated having approximately 80% power to detect a hazard ratio (HR) of 0-70 if 5-year bPFS was 0-86 in the early salvage group.

All analyses were done on an intention-to-treat basis. For time-to-event analysis of bPFS, patients without events were censored at the date of their most recent PSA measurement and groups were compared with use of the log-rank test. The HR is reported as the measure of effect, and analyses are stratified by randomisation stratification factors. Kaplan-Meier graphs are structured in the KMunicate format.¹⁷ Toxicity data are divided into events reported as within 2 years after randomisation, and subsequently. Within each period, the highest grade of event experienced by patients was compared between randomised groups using the χ² test. Adjusted for baseline score. Analyses are stratified by randomisation. Stata, version 16.1 was used for statistical analysis. An independent data monitoring committee was used. This study is registered with ClinicalTrials.gov, NCT00541047.

#### Table 1: Baseline characteristics

<table>
<thead>
<tr>
<th>Country</th>
<th>Salvage radiotherapy (n=699)</th>
<th>Adjuvant radiotherapy (n=697)</th>
<th>All (n=1396)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>65 (60-68)</td>
<td>65 (60-68)</td>
<td>65 (60-68)</td>
</tr>
<tr>
<td>PSA at diagnosis, ng/mL</td>
<td>8 (5-11.6)</td>
<td>7 (5-11.4)</td>
<td>7 (5-11.5)</td>
</tr>
<tr>
<td>Gleason score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;7</td>
<td>48 (7%)</td>
<td>48 (7%)</td>
<td>96 (7%)</td>
</tr>
<tr>
<td>3 + 4</td>
<td>338 (48%)</td>
<td>349 (50%)</td>
<td>687 (49%)</td>
</tr>
<tr>
<td>4 + 3</td>
<td>190 (27%)</td>
<td>188 (27%)</td>
<td>378 (27%)</td>
</tr>
<tr>
<td>≥8</td>
<td>123 (18%)</td>
<td>112 (16%)</td>
<td>235 (17%)</td>
</tr>
<tr>
<td>Pathological T-stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>176 (25%)</td>
<td>163 (23%)</td>
<td>339 (24%)</td>
</tr>
<tr>
<td>3a</td>
<td>389 (56%)</td>
<td>407 (58%)</td>
<td>796 (57%)</td>
</tr>
<tr>
<td>3b</td>
<td>130 (19%)</td>
<td>122 (18%)</td>
<td>252 (18%)</td>
</tr>
<tr>
<td>4</td>
<td>4 (1%)</td>
<td>5 (1%)</td>
<td>9 (1%)</td>
</tr>
<tr>
<td>Positive margins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>443 (63%)</td>
<td>439 (63%)</td>
<td>882 (63%)</td>
</tr>
<tr>
<td>Absent</td>
<td>256 (37%)</td>
<td>258 (37%)</td>
<td>514 (37%)</td>
</tr>
<tr>
<td>Lymph node involvement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Node positive</td>
<td>28 (4%)</td>
<td>38 (5%)</td>
<td>66 (5%)</td>
</tr>
<tr>
<td>Node negative</td>
<td>374 (54%)</td>
<td>335 (48%)</td>
<td>709 (51%)</td>
</tr>
<tr>
<td>No dissection</td>
<td>297 (42%)</td>
<td>322 (46%)</td>
<td>619 (44%)</td>
</tr>
<tr>
<td>CAPRA-S score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (0-2)</td>
<td>55 (8%)</td>
<td>58 (8%)</td>
<td>112 (8%)</td>
</tr>
<tr>
<td>Intermediate (3-5)</td>
<td>384 (55%)</td>
<td>382 (55%)</td>
<td>766 (55%)</td>
</tr>
<tr>
<td>High (6+)</td>
<td>260 (37%)</td>
<td>257 (37%)</td>
<td>517 (37%)</td>
</tr>
<tr>
<td>Country</td>
<td>573 (82%)</td>
<td>574 (82%)</td>
<td>1147 (82%)</td>
</tr>
<tr>
<td>Denmark</td>
<td>92 (13%)</td>
<td>95 (14%)</td>
<td>187 (13%)</td>
</tr>
<tr>
<td>Canada</td>
<td>28 (4%)</td>
<td>22 (3%)</td>
<td>50 (4%)</td>
</tr>
<tr>
<td>Ireland</td>
<td>6 (1%)</td>
<td>6 (1%)</td>
<td>12 (1%)</td>
</tr>
</tbody>
</table>

Data are n (%) or median (IQR). PSA=prostate-specific antigen. CAPRA-S=Cancer of the Prostate Risk Assessment post-surgical.
Role of the funding source
The funder of the study had no role in study design, data
collection, data analysis, data interpretation, or writing of
the report. The corresponding author had full access to
all the data in the study and had final responsibility for
the decision to submit for publication.

Results
RADICALS-RT recruited 1396 patients over 9 years
between Nov 22, 2007, and Dec 30, 2016, with participants
being randomly assigned to an adjuvant radiotherapy
(n=697 [50%]) or salvage radiotherapy policy (n=699 [50%]).
The trial profile is shown in figure 1 (see also appendix
p 2). Median age was 65 years (IQR 60–68), median PSA
at diagnosis was 7.9 ng/mL, and 517 (37%) of 1396 had
a Cancer of the Prostate Risk Assessment post-surgical
(CAPRA-S) score of 6 or greater (table 1, appendix
pp 3–4). Median PSA at randomisation was undetectable
in both randomised groups. Median follow-up was
4.9 months (IQR 4.1–5.7) after prostatectomy. At the
time of analysis, 228 patients allocated to the salvage
radiotherapy group who began radiotherapy, 154 (24%) of 649 also reported
starting radiotherapy within 6 months at a median of
21 (3%) of 649 patients on salvage radiotherapy
with similar proportions in both randomised groups.
Median follow-up was 0.2 (IQR 0.1–0.3) ng/mL. Among
patients allocated to the salvage radiotherapy group, 52.5 Gy in 20 fractions
(n=258 [29%] of 877) or 58 Gy in 28 fractions (n=320 [36%] of 877)
radiotherapy received 66 Gy in 30 fractions (n=536 [61%]
of 877) or 52.5 Gy in 20 fractions (n=258 [29%] of 877),
radiotherapy was 0.2 (IQR 0.1–0.3) ng/mL. Among
patients initiated non-protocol hormone therapy between Nov 22, 2007, and Dec 30, 2016, with participants
being randomly assigned to an adjuvant radiotherapy
(n=697 [50%]) or salvage radiotherapy policy (n=699 [50%]).
Regarding early efficacy outcome measures, 169 biochemical progression
events were reported—87 events in
patients in the adjuvant radiotherapy group and 82 in
patients in the salvage radiotherapy group (figure 2A). No
evidence was seen of a difference between the adjuvant
and salvage groups in terms of bPFS (HR for adjuvant
radiotherapy 1.10, 95% CI 0.81–1.49; p=0.53). Five-year
bPFS was 85% for those in the adjuvant radiotherapy
group and 88% for those in the salvage radiotherapy
group.

Figure 2: Biochemical progression-free survival (A) and freedom from non-protocol HT (B)
HT=hormone therapy.

Regarding long-term efficacy outcome measures, at the
time of analysis, data for the primary outcome measure of

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bPFS was 85% for those in the adjuvant radiotherapy
group and 88% for those in the salvage radiotherapy
group.

Among patients with a bPFS event, 91 (54%) of
169 reported initiation of non-protocol hormone therapy
(42 (48%) of 87 in the adjuvant group, 49 (60%) of 82 in the
salvage group). At 5 years, 7% of patients in the adjuvant
group and 8% of patients in the salvage group had
initiated non-protocol hormone therapy (HR for adjuvant
group 0.88, 95% CI 0.58–1.33; p=0.53; figure 2B).

Regarding long-term efficacy outcome measures, at the
time of analysis, data for the primary outcome measure of

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FFDM were not sufficiently mature (number of events observed was not yet near the target number of events) for comparison of randomised groups. Patients randomly assigned to the control group (salvage radiotherapy group) were noted to have 91% (95% CI 83–95) FFDM at 9 years. Data for overall survival were similarly immature, with 26 (4%) of 699 deaths among the control group (salvage radiotherapy group) patients, eight that were attributed by site investigators to prostate cancer.

RTOG toxicity events were more commonly reported in the group randomised to adjuvant radiotherapy in comparison with the salvage radiotherapy group (table 2). Most diarrhoea, proctitis, and cystitis events were low severity, with grade 3 or 4 events reported for approximately 1% of patients. In the first 2 years after randomisation, grade 3–4 haematuria was reported for 20 (3%) patients in the adjuvant radiotherapy group and two (<1%) patients in the salvage radiotherapy group. Beyond 2 years after randomisation, grade 3–4 haematuria was reported for 24 (4%) patients in the adjuvant radiotherapy group and 2 (<1%) patients in the salvage radiotherapy group. Grade 3–4 urethral stricture was also more commonly reported among patients in the adjuvant radiotherapy group within 2 years post-randomisation (39 [6%] patients in the adjuvant radiotherapy group and 30 [4%] patients in the salvage radiotherapy group). Events meeting the serious adverse event criteria were uncommon, with 46 events reported in total (33 adjuvant, 13 salvage; appendix p 6), only three of which were judged by the site investigator to be probably treatment-related.

Patient-reported outcome measures for urinary and bowel function were shown to be similar for both randomised groups at baseline (appendix p 8), a small but significant worsening of symptoms with adjuvant radiotherapy 1 year after randomisation (figure 3), but no evidence of a difference at later times.

**Table 2: Radiation Therapy Oncology Group toxicity**

<table>
<thead>
<tr>
<th>Event</th>
<th>Adjuvant radiotherapy</th>
<th>Salvage radiotherapy</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Early (&lt;2 years)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All (n=1372)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1 or 2</td>
<td>372 (27%)</td>
<td>112 (16%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Grade 3</td>
<td>13 (1%)</td>
<td>3 (&lt;1%)</td>
<td></td>
</tr>
<tr>
<td>Grade 4</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Proctitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1 or 2</td>
<td>196 (14%)</td>
<td>47 (7%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Grade 3</td>
<td>11 (1%)</td>
<td>3 (&lt;1%)</td>
<td></td>
</tr>
<tr>
<td>Grade 4</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Cystitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1 or 2</td>
<td>255 (19%)</td>
<td>84 (12%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Grade 3</td>
<td>16 (1%)</td>
<td>5 (1%)</td>
<td></td>
</tr>
<tr>
<td>Grade 4</td>
<td>1 (&lt;1%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Haematuria</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1 or 2</td>
<td>96 (7%)</td>
<td>25 (4%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Grade 3</td>
<td>22 (2%)</td>
<td>2 (&lt;1%)</td>
<td></td>
</tr>
<tr>
<td>Grade 4</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Urethral stricture</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1 or 2</td>
<td>62 (5%)</td>
<td>21 (3%)</td>
<td>0.020</td>
</tr>
<tr>
<td>Grade 3</td>
<td>64 (5%)</td>
<td>27 (4%)</td>
<td></td>
</tr>
<tr>
<td>Grade 4</td>
<td>5 (&lt;1%)</td>
<td>3 (&lt;1%)</td>
<td></td>
</tr>
</tbody>
</table>

Data are n (%). p values represent adjuvant versus salvage, χ² test. No grade 5 events reported.
Discussion
This initial analysis of RADICALS-RT has not shown any benefit for adjuvant radiotherapy after radical prostatectomy. No advantage was seen in biochemical control after radiotherapy, or in delaying the need for subsequent hormone therapy. Although additional follow-up is required to assess the effect of adjuvant radiotherapy on long-term outcome measures, the low metastatic event rate observed in the control group to date suggests poor scope for improvement in this patient group. Adjuvant radiotherapy does have adverse effects, with an increased risk both of urinary incontinence and urethral strictures. These findings strengthen the case for a policy of observation after radical prostatectomy, with early salvage radiotherapy reserved for use only in patients with PSA biochemical progression. Most individuals following such a policy will avoid the need for radiotherapy.

The RADICALS-RT design differs from that of previous trials of adjuvant radiotherapy. In essence, SWOG 8794 and EORTC 22911 each compared adjuvant radiotherapy to observation alone. Salvage radiotherapy was not mandated for PSA biochemical progression in the observation group, and when it was given, it was typically given late. For example, in the SWOG trial, only 39 (18%) of 211 patients received salvage radiotherapy for PSA biochemical progression, and the median PSA at the time of salvage radiotherapy was 0.75 ng/mL. By contrast, the median PSA amount in RADICALS-RT at the time of salvage treatment was 0.2 ng/mL. It is possible that the late use, if at all, of timely salvage radiotherapy might have contributed to the overall survival benefit reported with adjuvant radiotherapy in the SWOG trial. These older trials are therefore of limited use in determining the optimum timing of postoperative radiotherapy.

The ARO 96-02 trial and the Finnish Radiation Oncology Group trial each include timely salvage radiotherapy in the control group, but were relatively small trials, with a combined total of 557 patients. Both trials found that adjuvant radiotherapy reduced the risk of biochemical progression. However, PSA biochemical progression at any time was regarded as an event, even in patients who subsequently went on to receive successful salvage radiotherapy. In other words, the trigger for salvage radiotherapy also counted as an event. Therefore, a benefit in biochemical progression defined by this measure simply shows that radiotherapy has activity, but does not shed any light on its optimal timing. Indeed, this point is well illustrated by the EORTC 22911 trial, which first showed a substantial benefit for adjuvant radiotherapy in bPFS (HR 0.48, 95% CI 0.37–0.62), but no benefit in overall survival (HR 1.09, 0.67–1.79). By contrast, the definition of biochemical progression in RADICALS-RT was designed to be a fairer comparison between the two groups, by focusing on PSA biochemical progression after radiotherapy. In RADICALS-RT, a small initial PSA rise in patients in the salvage radiotherapy group was regarded not as biochemical progression, but rather only as an indication for salvage radiotherapy. A subsequent PSA rise, after radiotherapy, or a rise to more than 2 ng/mL at any time, was regarded as biochemical progression.

Advocates of adjuvant radiotherapy might expect any benefit to be greatest in those patients with locally advanced disease. Recruitment of the 425 patients in SWOG 8794, the only trial to report a survival benefit, was restricted to those with pathological T-stage 3 or 4 or margin-positive disease. RADICALS-RT included 984 (70%) of 1396 patients with these features, and a further 412 (30%) of 1396 patients in which the clinical team was uncertain about the use of postoperative radiotherapy in the absence of these features (appendix pp 2–4). The prospective ARTISTIC meta-analysis collaboration has been developed to include all the relevant randomised trials of postoperative radiotherapy timing. The meta-analysis will enable subgroup analyses to investigate whether any effect of adjuvant radiotherapy is consistent across risk groups.

We do not yet have good quality evidence concerning the effect of postoperative radiotherapy timing on longer-term outcomes such as FFDM. The ARO 96-02 trial (n=307) had only 47 metastatic events at the time of the latest update, with 22 in the control group and 25 in the adjuvant radiotherapy group (p=0.53). The Finnish Radiation Oncology Group trial (n=250) had just six metastatic events. Although bPFS is not a surrogate for FFDM, typically, trials of prostate radiotherapy show a greater treatment effect in terms of bPFS than for longer-term outcomes. In the MRC PR07 trial, the point estimate of the HR for radiotherapy effect was 0.31 for bPFS, and 0.70 for overall survival. In RADICALS-RT, if we had observed a significant bPFS benefit, it would not have been safe to conclude that there will be an FFDM benefit. However, the observed absence of benefit in terms of bPFS makes it unlikely that a benefit in FFDM will emerge. Taken together with the absence of demonstrable benefit in RADICALS-RT with regard to time to subsequent hormone therapy, the weight of current evidence does not suggest that adjuvant radiotherapy confers a worthwhile long-term benefit in comparison with a salvage radiotherapy policy. With continued follow-up of all trials, the ARTISTIC meta-analysis will be powered to report on overall survival.

RADICALS-RT has several strengths. It is the largest randomised controlled trial of adjuvant radiotherapy after radical prostatectomy, it mandates salvage radiotherapy in the control group, and is powered to study—in due course—the long-term outcome measure of FFDM. The patient population, recruited primarily from Canada, Denmark, and the UK, is representative of men undergoing radical prostatectomy in high-income countries. Compliance with allocated treatment and follow-up was high and was consistent across both groups. Outcome
measures included not only physician-assessed toxicity, but also patient-reported functional outcomes.

RADICALS-RT also has some limitations. Although recruitment started in 2007, follow-up is at this time insufficient to reliably report long-term outcomes such as FFDM. During the period since RADICALS-RT started recruitment, new evidence has suggested that men receiving salvage radiotherapy benefit from the addition of hormone therapy: RTOG 9601 showed an advantage in overall survival for 2 years of bicalutamide and GETUG-16 showed an advantage for 6 months of goserelin in progression-free survival. Around 30% of patients in RADICALS-RT reported receiving hormone therapy with their postoperative radiotherapy. Although greater use of hormone therapy might have improved outcomes, there is no evidence that it would have had a differential effect on the two arms of the trial. Similarly, evidence from the RTOG SPPORT trial suggests a benefit to treating not just the prostate bed, but also the pelvic lymph nodes in men receiving salvage radiotherapy. This option was permitted in RADICALS-RT, but more than 95% of patients received treatment to the prostate bed alone. Once again, there is no evidence that pelvic nodal radiotherapy would have a differential effect in the adjuvant or salvage setting. Advances in treatment, such as these, provide another argument in favour of a salvage radiotherapy policy. Given that patients might receive salvage radiotherapy years after their prostatectomy, they could benefit from new knowledge not available in the immediate postoperative period.

The prospective ARTISTIC meta-analysis collaboration has been developed to include all the relevant randomised trials of postoperative radiotherapy timing, and, with continued follow-up of all trials, will be powered to report on FFDM and overall survival. The meta-analysis will also enable subgroup analyses to investigate whether any effect of adjuvant radiotherapy is consistent across CAPRA-S scores. The RADICALS-RT trial has not shown any benefit for adjuvant radiotherapy in comparison to a policy of salvage radiotherapy for PSA biochemical progression; however, adjuvant radiotherapy does increase the risk of urinary and bowel morbidity. In the absence of any reliable evidence that adjuvant radiotherapy does more good than harm, observation with salvage treatment for PSA biochemical progression should be the current standard of care after radical prostatectomy.

Contributors
CCP was the chief investigator. CCP, MRS, NWC, HGK, CC, and MKBP were responsible for trial design. CCP, MRS, NWC, HGK, MKBP were grant holders (UK) and CC, WP were grant holders (Canada). CCP, NWC, AC, HGK, PMP, CC, WC, JL, WP, HP, RP, HP, FS, MKBP, and MRS were TMG members. HP was responsible for trial operations. CCP, AC, MRS, CB, and MKBP were responsible for the analysis plan. AC, MRS, and CB did the analyses. CCP, MRS, and AC wrote essential sections of the manuscript. All authors collated data, interpreted data, and edited, reviewed, and approved the final manuscript. All authors affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Declaration of interests
CCP reports grants, personal fees, and other from Bayer, other from AAA, and personal fees from Janssen, outside the submitted work. NWC reports personal fees from Janssen, during the conduct of the study; and personal fees from Janssen, outside the submitted work. CC reports grants from Canadian Cancer Trials Group, during the conduct of the study; personal fees from Bayer, grants from AstaZeneeca, and personal fees from AbbVie, Janssen, and Astellas, outside the submitted work. HP reports personal fees from Janssen, Astellas, AstaZeneeca, Ferring, and Ipsen, outside the submitted work. FS reports grants, personal fees, and non-financial support from Astellas, Amgen, Janssen, Bayer, Sanofi, Pfizer, AstraZeneca, and Myovant, outside the submitted work. HL reports personal fees and non-financial support from Astellas Pharma, Bayer, Janssen, and Sanofi Aventis, and personal fees from Roche, outside the submitted work. AZ reports other fees from Bayer, personal fees from Pfizer, Janssen, Astellas, and EUSA Pharma, and grants from Sanofi, outside the submitted work. MKBP reports grants and non-financial support from Astellas, Clovis Oncology, Novartis, Pfizer, and Sanofi, outside the submitted work. MRS reports grants and non-financial support from Astellas, Clovis Oncology, Novartis, Pfizer, and Sanofi, personal fees from Eli Lilly, and grants, personal fees, and non-financial support from Janssen, outside the submitted work. All other authors declare no competing interests.

Data sharing
The dataset and technical appendices are available upon request as per the controlled access approach of the MRC Clinical Trials Unit at UCL. Please contact the corresponding author for more information.

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