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

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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-protocol hormone therapy, safety, 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 3·0–6·1). 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 93% 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=0·53). Self-reported urinary incontinence was worse at 1 year for those in the adjuvant radiotherapy group (mean score 4·8 *vs* 4·0; p=0·0023). Grade 3–4 urethral stricture within 2 years was reported in 6% of individuals in the adjuvant radiotherapy group versus 4% in the salvage radiotherapy group (p=0·020).

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.

Funding Cancer Research UK, MRC Clinical Trials Unit, and Canadian Cancer Society.

Introduction

Radical prostatectomy is a standard treatment for clinically localised prostate cancer, and is often followed by postoperative radiotherapy to the prostate bed.[1,2] 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.

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Research in context

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.

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.

Previously reported randomised controlled trials of adjuvant radiotherapy after radical prostatectomy have shown a reduced risk of early disease recurrence, but have given conflicting results with regard to longer-term outcomes. Although the SWOG 8794 trial[3] found an overall survival benefit for adjuvant radiotherapy in a cohort of 425 patients recruited between 1988 and 1997, the EORTC 22911 trial[4,5] of 1005 patients recruited between 1992 and 2001 did not. Furthermore, these trials are of limited relevance to contemporary clinical practice because patients in the respective control groups did not receive timely salvage radiotherapy. Two further trials of adjuvant radiotherapy, the ARO 96-02 trial[6] and the Finnish Radiation Oncology Group trial,[7] were not designed to report with power on long-term outcomes. Clinical guidelines differ in their approach to post-operative radiotherapy timing. The European Society of Medical Oncology guideline states "immediate post-operative radiotherapy after radical prostatectomy is not routinely recommended", whereas the American Society for Radiation Oncology and American Urological Association guideline, while stopping short of recommending adjuvant radiotherapy, states "patients should be counselled that high-quality evidence indicates that... adjuvant radiotherapy...reduces the risk of biochemical recurrence, local recurrence, and clinical progression".[8] Not surprisingly, there has been poor consensus regarding the timing of postoperative radiotherapy.[9] A survey in 2018 of 88 North American radiation oncologists specialising in prostate cancer found that 55% recommend an adjuvant radiotherapy policy and 45% recommend a policy of salvage radiotherapy in the event of recurrence.[10] At the Advanced Prostate Cancer Consensus Conference 2017, faced with a range of clinical scenarios, up to 48% of the panel voted in favour of adjuvant radiotherapy.[11]

RADICALS-RT was designed to compare the efficacy and safety of adjuvant radiotherapy after radical prostatectomy versus a policy of observation with early salvage radiotherapy for PSA biochemical progression (referred to in the protocol as PSA failure), with a focus on long-term outcome measures. This is the first report from RADICALS-RT on early outcome measures, presented with the support of the independent data monitoring committee and the trial steering committee.

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[1] 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.[3,5] The RADICALS team instigated discussions with two other then-recruiting trials addressing radiotherapy timing, RAVES[13] and GETUG-AFU 17,[14] which led to the ARTISTIC[15] 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.

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For the **protocol** see http://www.radicals-trial.org/media/1128/radicals-protocol-version-60-14-dec-2018.pdf

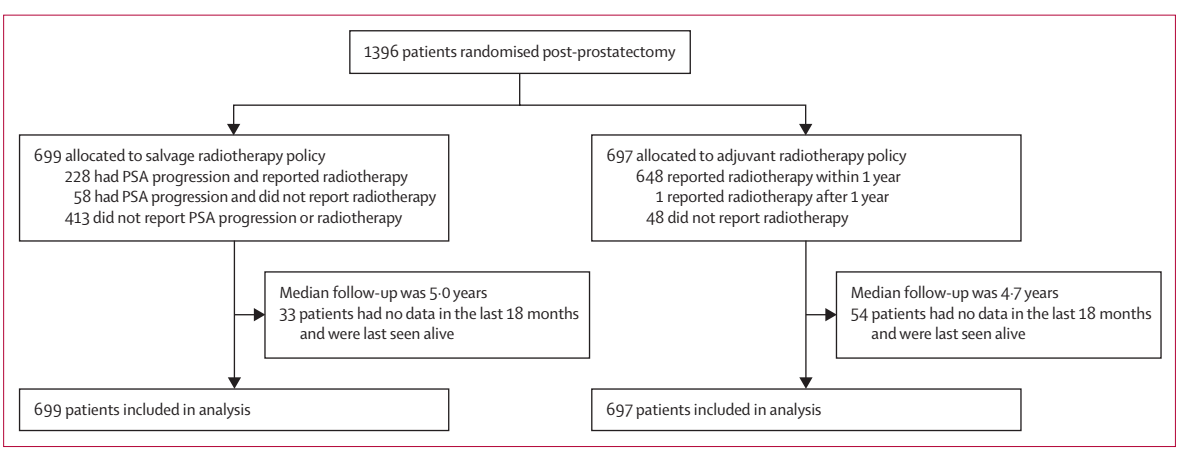

Figure 1: **Trial profile**
PSA=prostate-specific antigen.

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]

	Salvage radiotherapy (n=699)	Adjuvant radiotherapy (n=697)	All (n=1396)
Age, years	65 (60–68)	65 (60–68)	65 (60–68)
PSA at diagnosis, ng/mL	8·0 (5·6–11·6)	7·8 (5·8–11·4)	7·9 (5·7–11·5)
Gleason score			
<7	48 (7%)	48 (7%)	96 (7%)
3+4	338 (48%)	349 (50%)	687 (49%)
4+3	190 (27%)	188 (27%)	378 (27%)
≥8	123 (18%)	112 (16%)	235 (17%)
Pathological T-stage			
2	176 (25%)	163 (23%)	339 (24%)
3a	389 (56%)	407 (58%)	796 (57%)
3b	130 (19%)	122 (18%)	252 (18%)
4	4 (1%)	5 (1%)	9 (1%)
Positive margins			
Present	443 (63%)	439 (63%)	882 (63%)
Absent	256 (37%)	258 (37%)	514 (37%)
Lymph node involvement			
Node positive	28 (4%)	38 (5%)	66 (5%)
Node negative	374 (54%)	335 (48%)	709 (51%)
No dissection	297 (42%)	322 (46%)	619 (44%)
CAPRA-S score			
Low (0–2)	55 (8%)	58 (8%)	113 (8%)
Intermediate (3–5)	384 (55%)	382 (55%)	766 (55%)
High (6+)	260 (37%)	257 (37%)	517 (37%)
Country			
UK	573 (82%)	574 (82%)	1147 (82%)
Denmark	92 (13%)	95 (14%)	187 (13%)
Canada	28 (4%)	22 (3%)	50 (4%)
Ireland	6 (1%)	6 (1%)	12 (1%)

Data are n (%) or median (IQR). PSA=prostate-specific antigen. CAPRA-S=Cancer of the Prostate Risk Assessment post-surgical.

Table 1: **Baseline characteristics**

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 the target number of events, without reference to any accumulating 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 χ^2 test. For patient-reported outcomes, groups were compared at 1 year and 5 years with use of analysis of covariance, adjusted for baseline score. Stata, version 16.1 was used for statistical analysis. An independent data monitoring committee was used. This study is registered with ClinicalTrials.gov, NCT00541047.

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[18] 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 years at the time of data freeze (March 21, 2019).

Most patients allocated to the adjuvant radiotherapy policy began treatment, as planned, shortly after randomisation (appendix p 5). 647 (93%) of 697 patients allocated to the adjuvant radiotherapy group reported starting radiotherapy within 6 months at a median of 4·9 months (IQR 4·1–5·7) after prostatectomy. At the time of analysis, 228 patients allocated to the salvage radiotherapy group had started treatment following PSA biochemical progression; 223 (32%) of 699 patients allocated to the salvage radiotherapy group started radiotherapy within 5 years after randomisation. The median PSA measurement at the time of starting salvage radiotherapy was 0·2 (IQR 0·1–0·3) ng/mL. Among patients allocated to the salvage radiotherapy policy, 58 (8%) of 699 met the protocol definition of PSA biochemical progression during follow-up but did not yet report starting radiotherapy. Most patients who had radiotherapy received 66 Gy in 30 fractions (n=536 [61%] of 877) or 52·5 Gy in 20 fractions (n=258 [29%] of 877), with similar proportions in both randomised groups. Most patients received radiotherapy to the prostate bed only, with radiotherapy additionally to pelvic lymph nodes in only 21 (3%) of 649 patients on salvage radiotherapy and 15 (7%) of 228 patients on adjuvant radiotherapy.

Of the 649 patients in the adjuvant radiotherapy group who began radiotherapy, 154 (24%) of 649 also reported receiving neo-adjuvant or adjuvant hormone therapy, 90 randomly assigned to 6 months and 45 to 2 years of treatment in RADICALS-HD, and a further 19 reported hormone therapy outside of RADICALS-HD. Of the 228 patients in the salvage radiotherapy group who began radiotherapy, 61 (27%) of 228 reported receiving neo-adjuvant or adjuvant hormone therapy, 33 to 6 months and 13 to 2 years of treatment in RADICALS-HD, and 15 outside of RADICALS-HD.

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=0·56). 5-year 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).

See Online for appendix

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

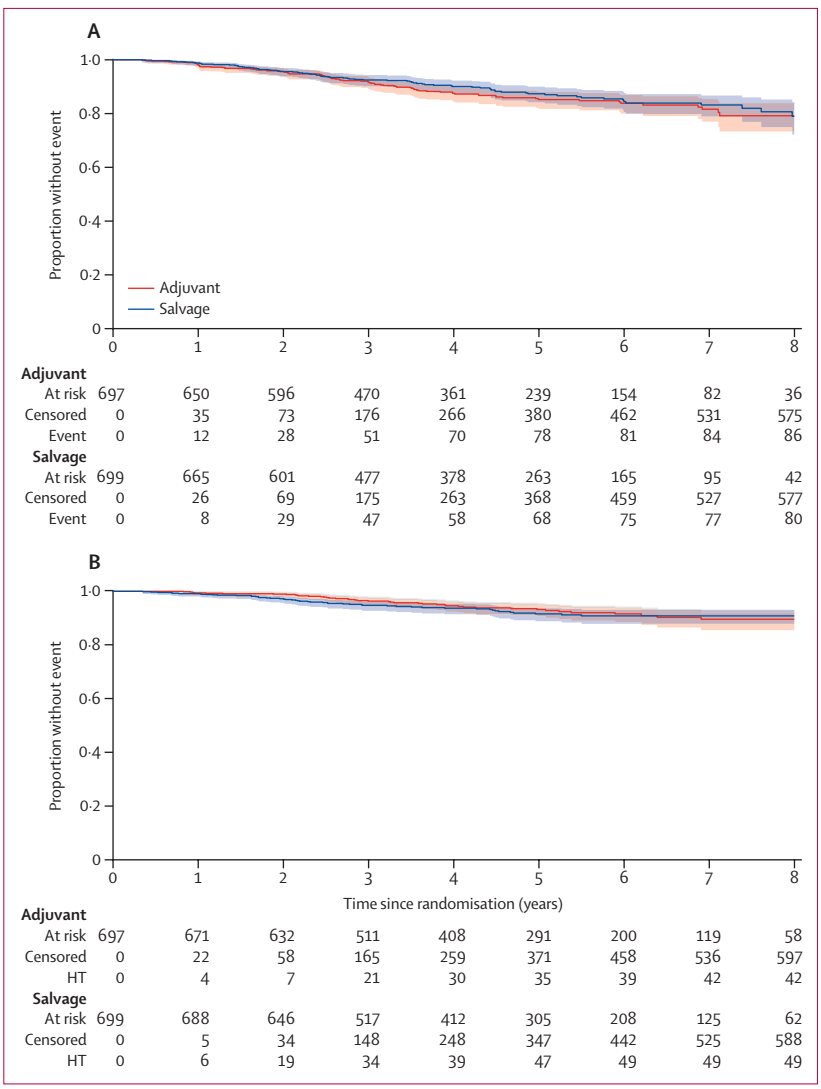

Figure 2: **Biochemical progression-free survival (A) and freedom from non-protocol HT (B)**
HT=hormone therapy.

	Early (<2 years)				Late (≥2 years)			
	All (n=1372)	Salvage radiotherapy (n=696)	Adjuvant radiotherapy (n=676)	p value	All (n=1220)	Salvage radiotherapy (n=621)	Adjuvant radiotherapy (n=599)	p value
Diarrhoea								
Grade 1 or 2	372 (27%)	112 (16%)	260 (38%)	<0·0001	153 (13%)	50 (8%)	103 (17%)	<0·0001
Grade 3	13 (1%)	3 (<1%)	10 (1%)	..	7 (1%)	2 (<1%)	5 (1%)	..
Grade 4	0	0	0	..	1 (<1%)	0	1 (<1%)	..
Proctitis								
Grade 1 or 2	196 (14%)	47 (7%)	149 (22%)	<0·0001	111 (9%)	34 (5%)	77 (13%)	<0·0001
Grade 3	11 (1%)	3 (<1%)	8 (1%)	..	7 (1%)	1 (<1%)	6 (1%)	..
Grade 4	0	0	0	..	0	0	0	..
Cystitis								
Grade 1 or 2	255 (19%)	84 (12%)	171 (25%)	<0·0001	122 (10%)	42 (7%)	80 (13%)	<0·0005
Grade 3	16 (1%)	5 (1%)	11 (2%)	..	10 (1%)	4 (1%)	6 (1%)	..
Grade 4	1 (<1%)	0	1 (<1%)	..	0	0	0	..
Haematuria								
Grade 1 or 2	96 (7%)	25 (4%)	71 (11%)	<0·0001	95 (8%)	25 (4%)	70 (12%)	<0·0001
Grade 3	22 (2%)	2 (<1%)	20 (3%)	..	26 (2%)	2 (<1%)	24 (4%)	..
Grade 4	0	0	0	..	0	0	0	..
Urethral stricture								
Grade 1 or 2	62 (5%)	21 (3%)	41 (6%)	0·020	55 (5%)	19 (3%)	36 (6%)	0·0025
Grade 3	64 (5%)	27 (4%)	37 (5%)	..	39 (3%)	13 (2%)	26 (4%)	..
Grade 4	5 (<1%)	3 (<1%)	2 (<1%)	..	3 (<1%)	3 (<1%)	0	..

Data are n (%). p values represent adjuvant versus salvage, χ^2 test. No grade 5 events reported.

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

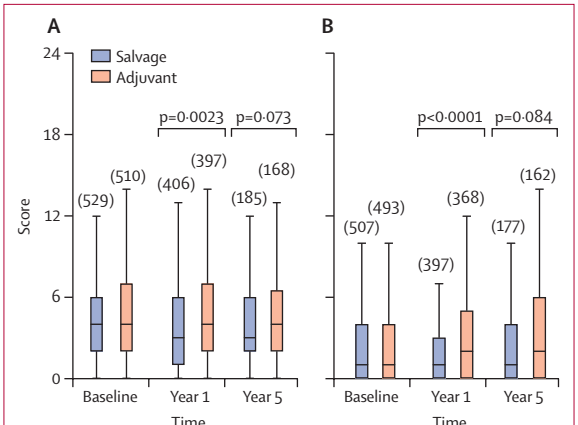

Figure 3: **Patient-reported outcome measures for urinary and bowel function**
Urinary (A) and faecal incontinence (B). A score of 0 is the best score and 24 is the worst. Box plots show median, IQR, and range (excluding outliers).

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 showed similar results 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.

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[3] and EORTC 22911[4,5] 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[6] and the Finnish Radiation Oncology Group trial[7] did 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.[15] 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).[6] The Finnish Radiation Oncology Group trial (n=250) had just six metastatic events.[7] 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.[19] 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[20] and GETUG-16 showed an advantage for 6 months of goserelin in progression-free survival.[21,22] 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[23] 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 AstraZeneca, and personal fees from AbbVie, Janssen, and Astellas, outside the submitted work. HPa reports personal fees from Janssen, Astellas, AstraZeneca, 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 Phama, 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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