Title: **Timing of Radiotherapy (RT) After Radical Prostatectomy (RP): First Results from RADICALS-RT Randomised Controlled Trial [NCT00541047]**

Running Head: Timing of Radiotherapy After Radical Prostatectomy: RADICALS-RT trial

Version + Date: Version 15.0; 30-Jun-2020 (updating references to figures)

Tables/Figures: 2 Tables
5 Figures

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Funding and Research Support: Funders/Grants:
Cancer Research UK/C7829/A6381
MRC Clinical Trials Unit/MC_UU_12023/28
Canadian Cancer Society/704970

This paper represents independent research part-funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at the Royal Marsden NHS Foundation Trust and the Institute of Cancer Research. The views expressed are those of the authors and not necessarily those of the NHS or the NIHR. Matthew Sydes and Mahesh Parmar are funded by the Medical Research Council.

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Competing Interests All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf. Please see the end of the manuscript for full list of author disclosures.

[1] See list at end

Transparency declaration 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

Ethical approval Appropriate ethical review was in place for each participating country. All participants gave written, informed consent.

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

Word Count:

Section	Words	Cumulative
Abstract	319	---
RIC	158	
Background	464	464
Methods	1199	1663
Results	712	2375
Discussion	1134	3509

(Word counts cover the body text of each section and excluded the headings and the ending notes; Methods excluding Funding statement)

ABSTRACT

Background

The optimal timing of radiotherapy (RT) after radical prostatectomy for prostate cancer is uncertain. The RADICALS-RT trial compared the efficacy and safety of adjuvant RT versus an observation policy with salvage RT for PSA failure.

Methods

RADICALS-RT is a randomised controlled trial enrolling patients with ≥1 risk factor (pT3/4, Gleason 7-10, positive margins or pre-op PSA≥10ng/ml) for recurrence after radical prostatectomy. Patients were randomised in a 1:1 ratio to adjuvant RT ("Adjuvant RT") or an observation policy with salvage RT for PSA failure (PSA≥0.1ng/ml or 3 consecutive rises) ("Salvage RT"). Stratification factors were Gleason score, margin status, planned RT schedule (52.5Gy/20 fractions or 66Gy/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 RT (control) to 95% at 10yr with Adjuvant RT. We report on bPFS, freedom-from-non-protocol hormone therapy, safety and patient-reported outcomes. Standard survival analysis methods were used; HR<1 favours Adjuvant RT. Trial registration: NCT00541047.

Findings

Between Oct 2007 and Dec 2016, 1396 patients from United Kingdom, Denmark, Canada and Ireland were randomised, 699 Salvage RT and 697 Adjuvant RT. Allocated groups were balanced with median age 65yr. Median follow-up is 4.9yr. 93% (649/697) Adjuvant RT reported RT within 6m; 33% (228/699) Salvage RT reported RT within 8yr after randomisation. With 169 events, 5yr bPFS was 85% for Adjuvant RT and 88% for Salvage RT: HR=1·10 (95%CI 0·81-1·49, p=0·56). Freedom-from-non-protocol hormone therapy at 5yr was 92% vs 94% (HR=1·24, 95%CI 0·76-2·01, p=0·39). Self-reported urinary incontinence was worse at 1yr for Adjuvant RT: 5·3% vs 2·7% (p=0·008). Grade 3-4 urethral stricture within 2yr was reported in 6% Adjuvant RT vs 4% Salvage RT (p=0·02).

Interpretation

First results from RADICALS-RT do not support routine administration of adjuvant RT after radical prostatectomy. Adjuvant RT increases the risk of urinary morbidity. An observation policy with salvage RT for PSA failure should be the current standard after radical prostatectomy.

RADICALS-RT TRIAL: RESEARCH IN CONTEXT

Evidence before this study

Previous randomised controlled trials of adjuvant radiotherapy after radical prostatectomy showed a reduced risk of disease recurrence, but conflicting results on longer-term outcomes. These trials are difficult to interpret in the context of current practice, due to the lack of timely salvage radiotherapy in the control arm. Clinical guidelines differed in their approach to post-operative radiotherapy timing, and surveys of clinical opinion found a lack of consensus on this issue.

Added value of the study

RADICALS-RT has compared adjuvant radiotherapy against a policy of early salvage radiotherapy in the event of PSA failure. 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

In the absence of any reliable evidence that adjuvant radiotherapy does more good than harm, observation with salvage treatment for PSA failure should be the current standard of care after radical prostatectomy.

BACKGROUND

Radical prostatectomy is a standard treatment for clinically localized prostate cancer, and is often followed by post-operative radiotherapy to the prostate bed.(1, 2) There is uncertainty about the optimal timing of radiotherapy after radical prostatectomy. Adjuvant radiotherapy may be given early, to those with no evidence of residual disease after surgery, in order to reduce the risk of subsequent recurrence. Alternatively, patients may be followed-up after surgery, with salvage radiotherapy given later only to those men who develop a rising PSA (often called "PSA failure"). It is possible that earlier treatment with adjuvant radiotherapy might be more effective than a policy of delayed salvage radiotherapy for recurrence. However, the salvage RT policy avoids unnecessary treatment of those cured by surgery alone and so may lead to less treatment-related morbidity.

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. While SWOG 8794 (3) found an overall survival benefit for adjuvant radiotherapy in a trial 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 arms did not receive timely salvage radiotherapy. Two further trials of adjuvant radiotherapy, ARO 96-02 (6) and the Finnish Radiation Oncology Group (7) trial, were not designed to report with power on long-term outcomes. Clinical guidelines differ in their approach to post-operative radiotherapy timing: For example, the European Society of Medical Oncology (ESMO) guideline states "Immediate post-operative radiotherapy after radical prostatectomy is not routinely recommended", whereas the American Society for Radiation Oncology (ASTRO) and American Urological Association (AUA) 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 a lack

of consensus regarding the timing of post-operative 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 (APCCC) 2017, faced with a range of clinical scenarios, up to 48% of the panel voted in favour of an 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 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 III, multi-centre, open-label, randomized 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 randomized shortly after radical prostatectomy between adjuvant and salvage post-operative radiotherapy (RADICALS-RT), and, in patients planned for post-operative radiotherapy, between 0 versus 6 months versus 24 months of hormone therapy (RADICALS-HD). Here, we report results from the radiotherapy timing randomization, RADICALS-RT.

Patients with non-metastatic adenocarcinoma of the prostate were eligible for RADICALS-RT if they had undergone radical prostatectomy, had post-operative PSA≤0.2ng/ml and at least one risk factor from: pathological T-stage 3 or 4; Gleason score 7 to 10; positive margins or pre-operative PSA≥10ng/ml.

Randomisation

Participants were randomised, within 22 weeks after radical prostatectomy, to receive either adjuvant RT to the prostate bed+/- pelvis, or close observation with salvage RT to the prostate bed +/- pelvis given in the event of PSA failure, defined as either: (a) two consecutive rising PSA levels with a PSA of greater than 0.1ng/ml, or (b) three consecutive rising PSA levels. Randomisation, using a 1:1 allocation, was performed centrally using minimisation with a random element which was stratified by Gleason sum score, margin status, RT schedule and study centre.

Treatment

RT to the prostate bed used a non-randomised dose-fractionation schedule of either 66Gy in 33 fractions or 52.5Gy in 20 fractions. RT was delivered once a day, five sessions a week. Treatment commenced within both 2 months after randomisation and 26 weeks of radical prostatectomy for adjuvant RT patients, and within 2 months of PSA failure for salvage RT patients. RT could be delayed

by up to 2 months if the patient was also due to receive hormone therapy. Participants could also receive RT to the pelvic lymph nodes, at the investigator's discretion. RT was planned with the patient supine, with empty rectum and comfortably full bladder. Patients could also receive up to 2 years' hormone therapy (either an LHRH analogue or bicalutamide 150mg daily) starting before and continuing during and after their post-operative radiotherapy, either according to clinical judgement, or if participating in RADICALS-HD[2] randomly allocated to receive either no, 6 months or 2 years duration of hormone therapy.

Assessment for efficacy and adverse events

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 RTOG toxicity score.(12) Data on other adverse events was collected if they 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 using standard questionnaires that included Vaizey (bowel) and ICS-Male-short form (urinary incontinence).

Outcome measures

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 (3, 5) that patient outcomes were better than previously reported. The RADICALS team instigated discussions with two other then-recruiting trials addressing radiotherapy timing, RAVES and GETUG-17, which led to the ARTISTIC meta-analysis. Given the ability of the meta-analysis to attain power for disease-specific survival, and on the observed event rate from external sources, the

[2] Results to be reported separately in due course

RADICALS team amended the primary outcome of the RADICALS-RT comparison to freedom-from-distant metastases (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.

Secondary outcomes included initiation of non-protocol hormone therapy, treatment toxicity and patient reported outcomes. Freedom from biochemical progression was added as a secondary outcome measure, without reference to the accumulating data and with the approval of the oversight committees, in 2018 to facilitate the ARTISTIC meta-analysis; the other two trials, RAVES (NCT00860652) and GETUG-17, were both designed with a focus on biochemical failure.

Biochemical progression-free survival (bPFS) was defined as freedom from PSA≥0.4ng/ml following post-operative RT, or PSA>2.0ng/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-17 trial teams and registered in PROSPERO with the ARTISTIC meta-analysis protocol.(13)

Comparative data on long-term outcome measures remain confidential to the IDMC and are not reported here .

Statistical Analysis

The sample size target was originally approximately 2,600 patients recruited over 5½ years and followed-up for a further 7 years, in order to have 80% power to detect an improvement from 70% to 75% or 90% power to detect an improvement from 80% to 85% in DSS. 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 to10 years after randomisation. This was anticipated to require 1063 patients at an accrual rate of 30 patients per month or 1160 patients at 25 patients per month. The TMG 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-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 would be timed to coincide with the planned reporting of the other trials and to facilitate a timely meta-analysis. We calculated having at least approximately 80% power to detect a hazard ratio of 0.70 or lower if 5-year bPFS was 0.86 in the early salvage group.

All analyses are performed on an intention to treat basis. For time-to-event analysis of bPFS, patients without events are censored at the date of their most recent PSA measurement and groups are compared using the log-rank test. The hazard ratio is reported as the measure of effect, and analyses are stratified by randomisation stratification factors. Toxicity data are divided into events reported as within two years after randomisation, and subsequently. Within each period, the highest grade of event experienced by patients are compared between randomised groups using the chi-square test. For patient-reported outcomes, groups are compared at one year and five years using analysis of covariance, adjusted for baseline score.

Funding

Grant funding in the UK was provided by the Clinical Trials Advisory Award Committee on behalf of Cancer Research UK (UK/C7829/A6381). Funding in Canada is provided by the Canadian Cancer Society (704970). The trial was further support at MRC Clinical Trials Unit at UCL by a core grant from the Medical Research Council, now part of the UK Research and Innovation (MC_UU_12023/28). UK sites were supported by the National Institute of Health Research Clinical Research Network. The research funders played no directly role in the trial.

RESULTS

Patients

RADICALS-RT recruited 1396 patients over 9 years between November 2007 and December 2016, with participants being randomised to an adjuvant RT (n=697) or salvage RT policy (n=699). **Figure 1** presents the CONSORT diagram (see also **Supplementary Figure 1**). Median age was 65 years, median PSA at diagnosis 7.9 ng/ml and 37% (517/1396) had a CAPRA-S score (14) of 6+ (**Table 1, Supplementary Figure 2, Supplementary Figure 3**). Median PSA at randomisation was undetectable in both randomised groups. Median follow-up was 4.9 years at the time of data freeze (March 2019).

Treatment

Most patients allocated to the adjuvant RT policy began treatment, as planned, shortly after randomisation (**Supplementary Figure 4**). 93% (647/697) of patients allocated the adjuvant RT policy reported starting RT within 6 months at a median of 4.9 months (IQR 4.1, 5.7 months) after prostatectomy. At the time of analysis, 227 patients allocated to the salvage RT policy had started treatment following PSA failure; 32% (223/699) of patients allocated to the salvage RT policy started RT within 5 years after randomisation. The median PSA level at the time of starting salvage radiotherapy was 0.2ng/ml (IQR 0.1, 0.3) . Among patients allocated to the salvage RT policy, 8% (58/699) met the protocol definition of PSA failure during follow-up but did not yet report starting RT. Most patients who had RT received 66Gy in 30 fractions (61%, n=536) or 52.5 Gy in 20 fractions (29%, n=258), with similar proportions in both randomised groups. Most patients received RT to the prostate bed only, with RT additionally to pelvic lymph nodes in only 3% (21/649) of salvage RT policy patients and 7% (15/228) adjuvant RT policy patients.

Of the 649 adjuvant RT patients who began RT, 24% (154/649) also reported receiving (neo-) adjuvant hormone therapy, 90 and 45 randomised to 6 months and 2 years treatment respectively in RADICALS-HD, and a further 19 reported hormone therapy outside of RADICALS-HD. Of the 228 salvage RT patients who began RT, 27% (61/228) reported receiving (neo-) adjuvant hormone therapy,

33 and 13 to 6 months and 2 years treatment respectively in RADICALS-HD, and 15 non-randomised.

Early efficacy outcome measures

A total of 169 biochemical progression events were reported, 87 events in the adjuvant RT policy and 82 in patients randomized to the salvage RT policy (**Figure 2A**). There was no evidence of a difference between the adjuvant and salvage groups in terms of bPFS: hazard ratio for adjuvant RT=1.10 (95% CI 0.81-1.49, p=0.56). Among patients with a bPFS event, 91 reported initiation of non-protocol hormone therapy (42 adjuvant, 49 salvage). At 5 years, 7% of adjuvant patients and 8% of salvage patients had initiated non-protocol HT, hazard ratio for adjuvant group=0.88 (95% CI 0.58-1.33, p=0.53) (**Figure 2A**).

Long-term efficacy outcome measures

At the time of analysis, data on the primary outcome measure of FFDM were not sufficiently mature for comparison of randomized groups. Patients randomized to the control group (salvage RT policy) were noted to have 91% freedom-from-distant metastases (95% CI 83-95%) at 9 years. Data on overall survival are similarly immature, with 26 deaths among control group (salvage RT policy) patients, 8 attributed by site investigators to prostate cancer.

Adverse events

RTOG toxicity events were more commonly reported in the group randomised to adjuvant RT in comparison with the salvage RT policy (**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 3% of adjuvant patients and less than 1% of salvage patients . Beyond 2 years after randomisation, Grade 3-4 haematuria was reported for 4% of adjuvant patients and less than 1% of salvage patients. Grade 3-4 urethral stricture was also more commonly reported among adjuvant patients within 2 years post-randomisation (6% of adjuvant patients and 4% of salvage patients). Events meeting the serious adverse event criteria were uncommon, with 46 events reported in total (33 adjuvant, 13 salvage),

(**Supplementary Table 1**) only 3 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 (**Supplementary Table 2**, **Supplementary Table 3**), a small but statistically significant worsening of symptoms with adjuvant RT 1 year after randomization (**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. While 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 arm to date suggests limited 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 saved for use only in patients with PSA failure. Most men 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 failure in the observation arm, and when it was given, it was typically given late. For example, in the SWOG trial, only 39/211 (18%) patients received salvage RT for PSA failure, and the median PSA at the time of salvage radiotherapy was 0.75ng/ml. By contrast, the median PSA level in RADICALS-RT at the time of salvage treatment was 0.2ng/ml. It is possible that the lack of timely salvage radiotherapy may 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 post-operative radiotherapy.

The ARO 96-02 trial (6) and the Finnish Radiation Oncology Group trial (7) did include timely salvage radiotherapy in the control arm, 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 recurrence *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 demonstrates that radiotherapy has activity, but does not shed any light on its optimum timing. Indeed, this point is well illustrated by the EORTC 22911 trial, which showed a substantial benefit for adjuvant radiotherapy in bPFS (HR 0.48; 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 arms, by focusing on PSA recurrence *after* radiotherapy. In RADICALS-RT, a small initial PSA rise in patients on the salvage RT arm was regarded, not as biochemical failure, but rather only as an indication for salvage radiotherapy. A subsequent PSA rise, after radiotherapy, or a rise to >2ng/ml at any time, was regarded as biochemical failure.

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 T3/4 or margin positive disease. RADICALS-RT included 984/1396 (70%) patients with these features, and a further 412/1396 (30%) patients where the clinical team was uncertain about the use of post-operative radiotherapy in the absence of these features (**Supplement**). The prospective ARTISTIC meta-analysis collaboration has been developed to include all the relevant randomized trials of post-operative 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 post-operative radiotherapy timing on longer-term outcomes such as freedom from distant metastases. The ARO 96-02 trial (n=307) had only 47 metastatic events at the time of the latest update, with 22 in the control arm and 25 in the adjuvant radiotherapy arm (p=0.53).(6) The Finnish Radiation Oncology Group trial (n=250) had just 6 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. For example, in the MRC PR07

trial, the point estimate of the hazard ratio for radiotherapy effect was 0.31 for bPFS, and 0.70 for OS .(15) In RADICALS-RT, if we had observed a statistically significant bPFS benefit, it would not have been safe to conclude that there will be a FFDM benefit. However, the observed lack of benefit in terms of bPFS makes it unlikely that a benefit in FFDM will emerge. Taken together with the lack 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 randomized controlled trial of adjuvant radiotherapy after radical prostatectomy, it mandates salvage radiotherapy in the control arm, and is powered to study, in due course, the long-term outcome measure of freedom-from-distant metastases. The patient population, recruited primarily from the UK, Denmark and Canada, is representative of men undergoing radical prostatectomy internationally. Compliance with allocated treatment and follow-up was high and was consistent across both arms. Outcome measures include 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 currently insufficient to report reliably 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 (16) and GETUG-16 showed an advantage for 6 months of goserelin in progression-free survival (17, 18). Around 30% of patients in RADICALS-RT reported receiving hormone therapy with their post-operative radiotherapy. While greater use of hormone therapy may have improved outcomes, there is no evidence that this would have had a differential effect on the two arms of the trial. Similarly, recent evidence from the RTOG SPPORT trial (19) 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 over 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 may receive salvage radiotherapy years after their prostatectomy, they may benefit from new knowledge not available in the immediate post-operative period.

The prospective ARTISTIC meta-analysis collaboration has been developed to include all the relevant randomized trials of post-operative 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 failure; but 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 failure should be the current standard of care after radical prostatectomy.

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ACKNOWLEDGEMENTS

We recognise the efforts of all trial team members at the trials units and hospitals who have supported and engaged with RADICALS. A list of investigators and oversight committee members is listed below. We thank Tim Morris for putting the time-to-event graphs into KMunicate format. [3]

[3] Morris TP, Jarvis CI, Cragg W, Phillips PPJ, Choodari-Oskooei B, Sydes MR. Proposals on Kaplan-Meier plots in medical research and a survey of stakeholder views: KMunicate. BMJ Open. 2019;9(9):e030215. doi:10.1136/bmjopen-2019-030215

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London: Charing Cross Hospital (PI: Alison Falconer; Invg: A Falconer, S Harinarayanan, M Stancliffe, S Stewart)

London: Croydon University Hospital (PI: Miguel Ferreira; Invg: N Arsanious, C Crowley, M Ferreira, R Huddart, B John, P Patel, M Perry)

London: Guy's Hospital (PI: Stephen Morris; Invg: R Beaney, T Guerrero-Urbano, S Harris, S Hughes, S Morris, K Nathan)

London: Hammersmith Hospital (PI: Stephen Mangar; Invg: S Mangar, S Stewart)

London: Hillingdon Hospital (PI: Jane Maher; Invg: J Maher, K Ng, A Pope)

London: Mount Vernon Hospital [Middlesex] (PI: Peter Hoskin; Invg: R Alonzi, N Anyamene, J Dickson, P Hoskin, R Hughes, P Ostler)

London: North Middlesex Hospital (PI: Jackie Newby; Invg: N Gupta, S Karp, L Melcher, F Neave, J Newby)

London: Royal Free Hospital (PI: Sarah Needleman; Invg: S Needleman, K Pigott, N Rosenfelder, M Vilarino-Varela)

London: Royal Marsden Hospital (PI: Nicholas Van As; Invg: V Khoo, A Tree, N Van As, L Welsh)

London: St Bartholomews Hospital (PI: Alexandre Kaliski; Invg: A Kaliski, K Tipples, P Wells)

London: St Georges Hospital (PI: Chris Anderson; Invg: C Anderson, R Issa, V Khoo, M Perry)

London: St Marys Hospital (PI: Simon Stewart; Invg: S Stewart)

London: St Thomas's Hospital (PI: Teresa Guerrero-Urbano; Invg: T Guerrero-Urbano)

London: University College Hospital (PI: Ajay Aggarwal; Invg: A Aggarwal, J Hall, R Khong, A Mitra, H Payne, J Teh, D Woolf)

London: Whipps Cross University Hospital (PI: John Hines; Invg: J Green, J Hines, S Holden, J Peters, T Philp, P Wells, D Woolf)

London: Whittington Hospital (PI: Maria Vilarino-Varela; Invg: M Vilarino-Varela)

Macclesfield: Macclesfield District General Hospital (PI: Adebanji Adeyoju; Invg: A Adeyoju, R Brough, S Brown, G Collins, M Kujawa, W Zafar)

Maidstone: Maidstone Hospital (PI: Patryk Brulinski; Invg: S Beesley, P Brulinski, C Mikropoulos, H Taylor, C Thomas)

Manchester: Christie Hospital (PI: Jacqueline Livsey; Invg: A Choudhury, N Clarke, R Conroy, R Cowan, T Elliott, J Livsey, J Logue, J Wylie)

Manchester: Withington Hospital (PI: James Wylie; Invg: V Ramani, V Sangar, J Wylie)

Middlesbrough: James Cook University Hospital (PI: Clive Peedell; Invg: D Chadwick, J Hardman, J McBride, C Peedell, D Shakespeare, H Van der Voet, D Wilson)

Newcastle: Freeman Hospital (PI: Trevor Roberts; Invg: J Frew, R McMenemin, I Pedley, T Roberts)

Newcastle: Newcastle General Hospital (PI: Ian Pedley; Invg: I Pedley)

Newcastle: Royal Victoria Hospital (PI: Christiaan Stevens; Invg: C Stevens)

Newport: Royal Gwent Hospital (PI: Adam Carter; Invg: A Carter, A Cox, S Rahman, J Wilson)

Northampton: Northampton General Hospital (PI: Dorai Ramanathan; Invg: J Branagan, P Camilleri, C Elwell, D Ramanathan)

Norwich: Norfolk and Norwich University Hospital (PI: Rob Wade; Invg: A Cooper, K Heasley, G Kapur, J Nobes, J Ostrowski, R Wade, S Walker)

Nottingham: Nottingham University Hospitals (PI: Georgina Walker; Invg: J Mills, I Sayers, S Sundar, G Walker)

Nuneaton: George Eliot Hospital (PI: Denise Hrouda; Invg: D Hrouda, J Worlding)

Oldham: Royal Oldham Hospital (PI: Jacqueline Livsey; Invg: A Choudhury, R Conroy, J Livsey)

Oxford: Churchill Hospital (PI: Hiba Al-Chamali; Invg: D Ajzensztejn, H Al-Chamali, G Andrade, G Bhatnagar, S Brewster, P Camilleri, D Cole, K Hyde, R Jampana, A Kiltie, R Owens, N Panakis, A Sabbagh, A Sabharwal, M Skwarski, R Stuart)

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Peterborough: Peterborough City Hospital (PI: Charlotte Ingle; Invg: E Barter, R Benson, D Gregory, A Hollingdale, C Ingle)

Peterborough: Peterborough District Hospital (PI: Charlotte Ingle; Invg: E Barter, R Benson, D Gregory, C Ingle)

Plymouth: Derriford Hospital (PI: Paul McInerney; Invg: J Hammonds, P McInerney, E McLarty, S Natale, S Pascoe, H Sells)

Poole: Poole Hospital (PI: Joe Davies; Invg: S Brock, P Crellin, J Davies, S Harinarayanan)

Portsmouth: Queen Alexandra Hospital (PI: Azarel Virgo; Invg: G Khoury, K Madhava, Y Nagar, A Virgo)

Portsmouth: St Mary's Hospital (PI: Yoodhvir Nagar; Invg: Y Nagar)

Preston: Royal Preston Hospital (PI: Omi Parikh; Invg: A Birtle, O Parikh, M Wise)

Redditch: Alexandra Hospital (PI: Joanna Hamilton; Invg: L Capaldi, J Hamilton)

Romford: Queen's Hospital (PI: Ramachandran Subramaniam; Invg: S Gibbs, S Gujral, A Kelkar, R Subramaniam, M Vandal)

Rotherham: Rotherham District General Hospital (PI: Catherine Ferguson; Invg: C Ferguson)

Salford: Salford Royal Hospital (PI: Anna Tran; Invg: C Betts, N Clarke, R Cowan, T Elliott, M Lau, K O'Flynn, D Shackley, A Tran)

Salisbury: Salisbury District Hospital (PI: Gregor Mcintosh; Invg: A Bhatnagar, A Campbell, M El-Saghir, P Guy, G Mcintosh)

Scunthorpe: Scunthorpe General Hospital (PI: Sanjay Dixit; Invg: S Dixit)

Sheffield: Weston Park Hospital (PI: Catherine Ferguson; Invg: K Bowen, C Ferguson, P Kirkbride, J Martin)

Shrewsbury: Royal Shrewsbury Hospital (PI: Narayanan Srihari; Invg: R Prashant, N Srihari)

Slough: Wexham Park Hospital (PI: Nicola Dallas; Invg: R Brown, N Dallas, O Karim, M Laniado, H O'Donnell, S Sharif)

Southampton: Southampton General Hospital (PI: Alec Paschalis; Invg: C Heath, V McFarlane, M Noble, A Paschalis)

Southend: Southend University Hospital (PI: Abby Cyriac; Invg: I Ahmed, O Chan, A Cyriac, J Prejbisz, D Tsang)

Southport: Southport and Formby District General Hospital (PI: Neeraj Bhalla; Invg: N Bhalla, C Eswar, A Sivapalasuntharam)

Stevenage: Lister Hospital (PI: Nikhil Oommen; Invg: N Oommen)

Stockport: Stepping Hill Hospital (PI: John Logue; Invg: W Brough, R Brough, G Collins, J Logue)

Stoke: Royal Stoke University Hospital (PI: Kathirvelu Dhinakaran; Invg: F Adab, R Bhana, K Dhinakaran)

Sunderland: Sunderland Royal Hospital (PI: Damian Greene; Invg: D Green, D Greene, I Pedley)

Sutton: Royal Marsden Hospital (PI: Chris Parker; Invg: D Dearnaley, A Horwich, R Huddart, C Parker, R Venkitaraman)

Sutton Coldfield: Good Hope Hospital (PI: Daniel Ford; Invg: D Ford, J Glaholm)

Sutton-in-Ashfield: King's Mill Hospital (PI: Alastair McCabe; Invg: E Chadwick, J Lim, A McCabe, D Saunders, S Sundar, G Walker)

Swansea: Morriston Hospital (PI: Pradeep Bose; Invg: P Bose)

Swansea: Singleton Hospital (PI: Delia Pudney; Invg: M Phan, D Pudney)

Swindon: Great Western Hospital (PI: David J Cole; Invg: D Cole, S De Silva-Minor, O Khan)

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Truro: Royal Cornwall Hospital (PI: Alastair H Thomson; Invg: A Gould, A Thomson, D Wheatley)

Wakefield: Pinderfields Hospital (PI: Ann Henry; Invg: J Anderson, N Casanova, R Chahal, C Coyle, P Dickinson, C Fosker, A Henry, S Kanaga-Sundaram, S Rodda, S Sundaram, P Weston)

Walsall: Manor Hospital (PI: Anula Chetiyawardana; Invg: A Chetiyawardana)

Warwick: Warwick Hospital (PI: Andrew Chan; Invg: A Chan, A Stockdale)

Weston-super-Mare: Weston General Hospital (PI: Symeon Eleftheriadis; Invg:)

Winchester: Royal Hampshire County Hospital (PI: Sangeeta Paisey; Invg: S Paisey, R Shaffer)

Wirral: Clatterbridge Centre for Oncology (PI: Helen Innes; Invg: H Innes, J Littler, I Syndikus, S Tolan)

Wishaw: Wishaw General Hospital (PI: Azmat Sadozye; Invg: J De Souza, D Dodds, A Sadozye)

Wolverhampton: New Cross Hospital (PI: Peter Cooke; Invg: M Churn, P Cooke, P Keng-Koh, A Samanci, I Sayers)

Worcester: Worcestershire Royal Hospital (PI: Jo Bowen; Invg: J Bowen, L Capaldi, K Gupta)

Worthing: Worthing Hospital (PI: Ashok Nikapota; Invg: D Bloomfield, A Nikapota, G Plataniotis)

Wrexham: Wrexham Maelor Hospital (PI: Aileen Flavin; Invg: A Al-Samarraie, Z Ali, A Flavin)

Wycombe: Wycombe Hospital (PI: Ami Sabharwal; Invg: J Brady, P Camilleri, N Panakis, A Protheroe, T Pwint, A Sabharwal, A Weaver)

Yeovil: Yeovil District Hospital (PI: Emma Gray; Invg: E Beaumont, E Gray, T Porter, G Sparrow)

York: York District Hospital (PI: David Bottomley; Invg: D Bottomley, J Joseph, H Musunuru, M Stower, R Wilson)

And all of the research staff who worked with these investigators and each site

Finally, and most importantly, we recognise and thank all of the participants of the trial and the families and friends who supported them. Clinical trials only happen because people choose to join them.