# Adjuvant or early salvage radiotherapy for the treatment of localised and locally advanced prostate cancer: a prospectively planned systematic review and meta-analysis of aggregate data

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See Comment page 1374

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## Summary

**Background** It is unclear whether adjuvant or early salvage radiotherapy following radical prostatectomy is more appropriate for men who present with localised or locally advanced prostate cancer. We aimed to prospectively plan a systematic review of randomised controlled trials (RCTs) comparing these radiotherapy approaches.

**Methods** We used a prospective framework for adaptive meta-analysis (FAME), starting the review process while eligible trials were ongoing. RCTs were eligible if they aimed to compare immediate adjuvant radiotherapy versus early salvage radiotherapy, following radical prostatectomy in men (age ≥18 years) with intermediate-risk or high-risk, localised or locally advanced prostate cancer. We searched trial registers and conference proceedings until July 8, 2020, to identify eligible RCTs. By establishing the ARTISTIC collaboration with relevant trialists, we were able to anticipate when eligible trial results would emerge, and we developed and registered a protocol with PROSPERO before knowledge of the trial results (CRD42019132669). We used a harmonised definition of event-free survival, as the time from randomisation until the first evidence of either biochemical progression (prostate-specific antigen [PSA] ≥0·4 ng/mL and rising after completion of any postoperative radiotherapy), clinical or radiological progression, initiation of a non-trial treatment, death from prostate cancer, or a PSA level of at least 2·0 ng/mL at any time after randomisation. We predicted when we would have sufficient power to assess whether adjuvant radiotherapy was superior to early salvage radiotherapy. Investigators supplied results for event-free survival, both overall and within predefined patient subgroups. Hazard ratios (HRs) for the effects of radiotherapy timing on event-free survival and subgroup interactions were combined using fixed-effect meta-analysis.

**Findings** We identified three eligible trials and were able to obtain updated results for event-free survival for 2153 patients recruited between November, 2007, and December, 2016. Median follow-up ranged from 60 months to 78 months, with a maximum follow-up of 132 months. 1075 patients were randomly assigned to receive adjuvant radiotherapy and 1078 to a policy of early salvage radiotherapy, of whom 421 (39·1%) had commenced treatment at the time of analysis. Patient characteristics were balanced within trials and overall. Median age was similar between trials at 64 or 65 years (with IQRs ranging from 59 to 68 years) across the three trials and most patients (1671 [77·6%]) had a Gleason score of 7. All trials were assessed as having low risk of bias. Based on 270 events, the meta-analysis showed no evidence that event-free survival was improved with adjuvant radiotherapy compared with early salvage radiotherapy (HR 0·95, 95% CI 0·75–1·21; p=0·70), with only a 1 percentage point (95% CI −2 to 3) change in 5-year event-free survival (89% *vs* 88%). Results were consistent across trials (heterogeneity p=0·18; $I^2$=42%).

**Interpretation** This collaborative and prospectively designed systematic review and meta-analysis suggests that adjuvant radiotherapy does not improve event-free survival in men with localised or locally advanced prostate cancer. Until data on long-term outcomes are available, early salvage treatment would seem the preferable treatment policy as it offers the opportunity to spare many men radiotherapy and its associated side-effects.

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## Introduction

It is unclear whether adjuvant or early salvage radiotherapy following radical prostatectomy is more appropriate for men who present with localised or locally advanced prostate cancer. Three published randomised controlled trials (RCTs)[1–3] showed that adjuvant radiotherapy to the prostate bed gave better biochemical control than no adjuvant radiotherapy. However, results were inconsistent regarding the longer-term outcomes of progression-free survival, metastases-free survival, and overall survival.

## Research in context

### Evidence before this study

Previous randomised trials have shown that following prostatectomy, adjuvant radiotherapy gave better biochemical control than observation policies for men with localised or locally advanced prostate cancer. However, the trials did not consistently show a benefit for long-term outcomes including survival. Consequently, uptake of adjuvant radiotherapy has been variable.

Three additional randomised trials have compared adjuvant radiotherapy with a policy of early salvage radiotherapy following prostatectomy in the same group of men. Working together with the trialists, we prospectively designed a systematic review and meta-analysis, before trial results were known, to assess whether adjuvant radiotherapy is superior to early salvage treatment.

### Added value of this study

By using the prospective FAME approach, we have reduced the potential for bias in the review and meta-analysis methods. Working collaboratively, we have been able to include up-to-date information from all patients included in eligible trials. Thus, the meta-analysis represents the totality of randomised evidence on this treatment comparison. Investigators supplied unreported results based on a harmonised definition of event-free survival, which allowed a consistent and up-to-date investigation of overall and subgroup effects.

Hence, results of the collaborative ARTISTIC meta-analysis provide greater evidence on the effects of radiotherapy timing, than any of the individual trials alone.

### Implications of all the available evidence

Our results showed no clear evidence that adjuvant radiotherapy improved event-free survival compared with early salvage radiotherapy, and thus support the use of early salvage radiotherapy following prostatectomy as the standard of care for men diagnosed with localised or locally advanced prostate cancer. Guidelines and policy should be reviewed to reflect this evidence.

Therefore, adjuvant radiotherapy was not universally recommended in these patients and uptake of adjuvant radiotherapy has been variable.[4] Easier access to more sensitive prostate-specific antigen (PSA) tests has enabled earlier detection of biochemical progression and the possibility of earlier salvage treatment. As a result, trials comparing adjuvant radiotherapy and early salvage radiotherapy strategies were initiated independently.[5–7]

The three trials focused on different primary outcomes—time free of metastases (RADICALS-RT[5]), event-free survival (GETUG-AFU 17[6]), and biochemical progression (RAVES[7])—and each was powered accordingly. Investigators acknowledged the difficulty in adequately powering these trials for longer-term, definitive outcomes due to the relatively good prognosis of the included men. Therefore, there was a clear need to synthesise the results of these trials in a systematic review to give a more reliable answer as to whether adjuvant radiotherapy or early salvage radiotherapy is most appropriate.

In 2014, while recruitment to all three trials was ongoing, representatives from the RADICALS-RT, GETUG-AFU 17, and RAVES trial teams and the Meta-analysis Group of the MRC Clinical trials Unit at University College London met to discuss the feasibility and value of a prospectively designed individual participant data (IPD) meta-analysis of the three trials.[8] However, recognising that IPD would not be available from the trials until long-term follow-up is completed, we planned an aggregate data systematic review in the first instance. Such systematic reviews are usually planned retrospectively, with existing knowledge of some or all trial results, which can introduce potential bias into the review and meta-analysis methods. Instead, under the auspices of the ARTISTIC collaboration, we prospectively planned a systematic review and series of meta-analyses before trial results were known,[9] to assess the effects of adjuvant radiotherapy versus early salvage radiotherapy in this patient population.

## Methods

### Study design

For this prospective systematic review and meta-analysis of aggregate data,[8,9] we used a prospective framework for adaptive meta-analysis (FAME[9]), which reduces the likelihood of bias in the selection of studies, assessment of risk of bias, outcome definition, and in the timing and conduct of planned analyses. The approach has been used in six precious systematic reviews in prostate cancer.[10–12] We applied the following FAME key principles: (1) starting the systematic review process while all trials were ongoing or yet to report; (2) searching comprehensively for all published, unpublished, and eligible trials; (3) liaising with trial teams to develop and maintain a detailed picture of how information and results are likely to accumulate; (4) predicting the feasibility and timing of reliable meta-analysis; and (5) interpreting results taking account of available and unavailable data, and assessing the value of updating the systematic review and meta-analysis. All methods were prespecified in a protocol, which was submitted for registration in PROSPERO in April, 2019, before data collection or analysis (CRD42019132669).

### Search strategy and selection criteria

We included ongoing trials that were still recruiting patients. All eligible trials included men (age ≥18 years) with intermediate-risk or high-risk, localised or locally advanced prostate cancer, with no evidence of distant metastases, and who had a radical prostatectomy before enrolment into the trial. Trials should have aimed to compare adjuvant radiotherapy versus a policy of deferred,

early salvage radiotherapy following radical prostatectomy. Patients had to be randomly assigned to adjuvant radiotherapy or early salvage radiotherapy more than 4 weeks but no longer than 22 weeks after radical prostatectomy. Inclusion criteria for patients were postoperative PSA no greater than 0·2 ng/mL and one or more high-risk features including pT stage 3 or 4, Gleason score 7–10, preoperative PSA of at least 10 ng/mL, or positive surgical margins. Exclusion criteria for patients were previous radiotherapy or androgen deprivation therapy (either before or after prostatectomy).

Eligible trials were identified (by CLV) through searches of ClinicalTrials.gov and the WHO trials registry platform. We used "prostate cancer" and "radiotherapy" as keywords, to be as inclusive as possible, and limited the search results to randomised controlled trials published in any language. We also searched the online archive of conference abstracts from the American Society of Clinical Oncology (ASCO) and ASCO Genitourinary Cancer Symposium using the terms "prostate", "radiotherapy", and "random" and reviewed all submitted abstracts in the genitourinary and prostate cancer sessions of the European Society of Medical Oncology annual meeting (2016–19) to identify reports of any additional eligible trials, limiting the search using the term "radiotherapy". Searches were carried out initially in May, 2014, and updated periodically until final submission of the manuscript in July 8, 2020.

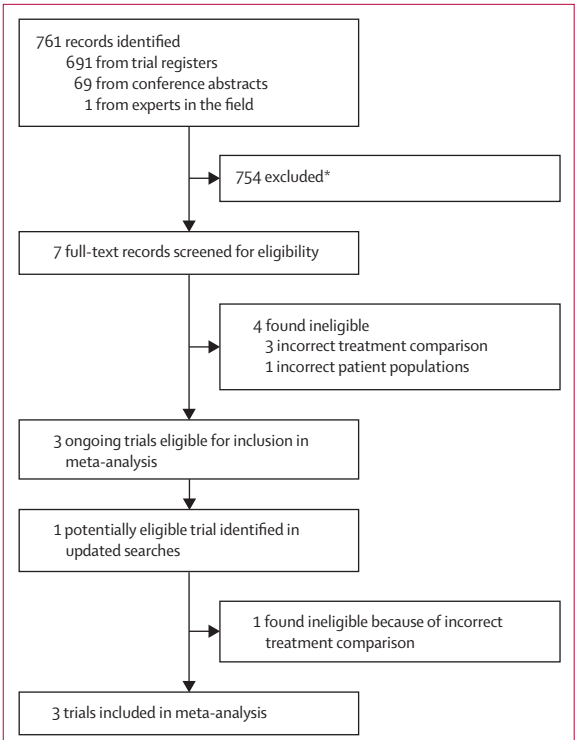


***Figure 1:*** **Study selection**
*Reasons for exclusion: ineligble study types, incorrect treatment comparison, different patient populations, and duplicate records.

## Outcomes

The primary outcome measure for this first stage of the meta-analysis is event-free survival. We agreed a harmonised definition of event-free survival as the time from randomisation until the first evidence of either biochemical progression (PSA ≥0·4 ng/mL and rising after completion of any postoperative radiotherapy), clinical or radiological progression, initiation of a non-trial treatment, death from prostate cancer, or a PSA level of at least 2·0 ng/mL at any time after randomisation. Patients last reported as alive with no recorded clinical or biochemical event or non-trial treatment initiated were censored on the date of most recent follow-up. Patients not experiencing one of these events who died from causes other than prostate cancer were censored on the date of death.

We also planned to assess the effects of radiotherapy timing on time free of metastases, prostate-cancer specific survival and overall survival in subsequent staged meta-analyses, to be conducted when we have sufficient statistical power.

## Data analysis

Data relating to the trial designs, in particular in relation to the methods of randomisation, were extracted from trial protocols and supplemented by trialists. We also sought summaries of patient baseline characteristics (age, PSA, performance status, tumour stage, Gleason score, surgical margins, seminal vesicle involvement, extracapsular extension, and lymph node involvement) and interventions, and results for the outcome of event-free survival overall and within predefined patient subgroups directly from the trial teams. There was no risk of duplicate data.

Risk of bias assessments were carried out for each of the trials for the outcome of event-free survival, using the Cochrane risk of bias 2 tool.[13,14] This amendment of the protocol was to reflect the recent release of the revised tool. A low risk of bias was desirable for all domains.

When prospectively planning the meta-analysis, we assumed baseline survival of 88% at 5 years, and anticipated that at least 120 events would have occurred in the early salvage radiotherapy arm across the three trials[5–7] by September, 2019. This would give more than 90% power to detect a 5% difference in event-free survival between immediate and early salvage radiotherapy and more than 99% power for a 10% difference. This provided a firm basis for planning a reliable meta-analysis of trial results.

As events for the longer-term outcomes are accumulating slowly, there is insufficient power to assess the effects on these. Therefore, we will review control arm event rates for these outcomes regularly, and will carry out further planned meta-analyses following a similar process.

For the primary analysis, we combined the hazard ratios (HRs) across trials using the fixed-effect model[15] to give a pooled HR representing the overall risk of an event on adjuvant radiotherapy compared with early salvage

radiotherapy. $\chi^2$ heterogeneity tests and the $I^2$ statistic[16] were used to assess statistical heterogeneity and a DerSimonian and Laird random-effects model[17] was also used to assess the robustness of the results to the choice of model.

Provided there were sufficient data available, we aimed to assess whether the treatment effect varied according to whether or not the trials included planned use of hormone therapy. We also planned to investigate whether the treatment effect was consistent across patient subgroups. Subgroups were defined by pre-surgical PSA (≤10 ng/mL *vs* >10 ng/mL); Gleason score (≤6, 7, or ≥8); involvement of seminal vesicles (involved *vs* not involved); surgical margins (positive *vs* negative); and Cancer of the Prostate Risk Assessment post-surgical score (CAPRA-S) risk group (low [0–2] *vs* intermediate [3–5] or high [≥6]), which takes into account several patient and disease characteristics at baseline in order to predict risk.[18] Individual interaction HRs for each trial were calculated from the ratio of the estimated HRs for each subgroup (eg, the HR for CAPRA-S low risk divided by the HR for intermediate or high risk), and these were combined across trials using a fixed-effect meta-analysis.[19,20] All p values were two sided. Analyses were done in Stata (version 16.0).

### Role of the funding source

The funding body for ARTISTIC 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 results included in the study, although not to the underlying trial data, and had final responsibility for the decision to submit for publication.

## Results

Our initial searches of clinical trial registers and conference abstract searches retrieved 760 records. One additional trial was identified through discussion with the RADICALS-RT trial investigators. After removing duplicates and clearly ineligible records, we screened seven potentially eligible trials (figure 1). Four trials were excluded either because they made a different treatment comparison or because they were conducted in patients with more advanced disease. Three trials—RADICALS-RT,[5] GETUG-AFU 17,[6] and RAVES[7]—were retained as being eligible for inclusion. Updated searches done in February, 2016, identified a further potentially eligible trial; however, this was subsequently excluded because it compared adjuvant radiotherapy with no radiotherapy, rather than with an early salvage policy.[21]

RADICALS-RT recruited 1396 patients in the UK, Denmark, Canada, and Ireland from November, 2007, until December, 2016; GETUG-AFU 17 recruited 424 patients in France between April, 2008, and June, 2016; and RAVES recruited 333 patients in Australia and New Zealand between March, 2009, and December, 2015 (table 1). Median follow-up ranged from 60 months (range 2–132) to 78 months (1–122). Although the GETUG-AFU 17 and RADICALS-RT trials were designed to assess whether adjuvant radiotherapy was superior to early salvage radiotherapy, the RAVES trial was designed to assess whether early salvage

| | Accrual period | Key eligibility criteria | Use of hormone therapy | Radiotherapy field | Radiotherapy schedule | Adjuvant radiotherapy timing | Early salvage radiotherapy timing | Trigger for early salvage radiotherapy | Primary outcome measure | Trial design |
|---|---|---|---|---|---|---|---|---|---|---|
| RADICALS-RT[5] | November, 2007–December, 2016 | One or more of positive margins; pT3a, pT3b, or pT4; or Gleason 7–10 | Participants could choose to enter a second randomisation to no hormones or hormones for 6 or 24 months' duration; participants not randomised could receive hormone therapy off protocol | Radiotherapy to prostate bed | 66 Gy in 33 fractions or 52·5 Gy in 20 fractions | ≤6 months of radical prostatectomy | ≤2 months of trigger PSA | PSA >0·1 ng/mL and rising, or three consecutive rising PSA levels still below 0·1 ng/mL | Freedom from distant metastases | Superiority |
| GETUG-AFU 17[6] | April, 2008–June, 2016 | pT3a, pT3b, or pT4a (with bladder neck invasion); positive margins; and extracapsular extension | All participants received hormone therapy alongside radiotherapy both in the adjuvant or early salvage setting | Radiotherapy to prostate bed | 66 Gy in 33 fractions | ≤6 months of radical prostatectomy | As soon as possible after PSA relapse and before PSA of 1 ng/mL | PSA ≥0·20 ng/mL and rising | Event-free survival | Superiority |
| RAVES[7] | March, 2009–December, 2015 | pT2, pT3a, or pT3b; and either positive margins or extracapsular extension | No use of hormone therapy | Radiotherapy to prostate bed | 64 Gy in 32 fractions | ≤6 months of radical prostatectomy | ≤4 months of trigger PSA | PSA ≥0·20 ng/mL | Freedom from biochemical progression | Non-inferiority |

PSA=prostate-specific antigen.

***Table 1:*** **Trial characteristics**

radiotherapy was non-inferior to adjuvant radiotherapy in terms of biochemical progression. The radiotherapy schedule was similar in all trials: 64 Gy in 32 fractions or 66 Gy in 33 fractions; RADICALS-RT also permitted 52·5 Gy in 20 fractions. For all trials, patients randomly assigned to adjuvant radiotherapy should have commenced it within 6 months after surgery. Early salvage radiotherapy was triggered at a level of 0·2 ng/mL PSA for RAVES, at 0·2 ng/mL and rising for GETUG-AFU 17, and at 0·1 ng/mL or three consecutive rises still below 0·1 ng/mL for RADICALS-RT. Initiation of early salvage radiotherapy following these triggers varied across the trials, as did intended use of hormone therapy (table 1). All of the included trials were judged to have low risk of bias (table 2).

All three trials aimed to recruit patients with localised or locally advanced prostate cancer, with similar, but non-identical, definitions: RADICALS-RT allowed patients with pT3 and pT4 disease, GETUG-AFU 17 was restricted to patients with pT3 or pT4a (with bladder neck invasion) and positive surgical margins (R1) only, and RAVES included patients with at least one of

| | RADICALS-RT[5] | GETUG-AFU 17[6] | RAVES[7] |
|---|---|---|---|
| Risk of bias arising from the randomisation process | Low risk | Low risk | Low risk |
| Was the allocation sequence random? | Yes: minimisation with stratification by Gleason score, margin status, radiotherapy schedule, and study centre | Yes: minimisation with stratification by study centre, pT stage, and Gleason grade to avoid significant imbalances between the arms | Yes: minimisation algorithm; patients are stratified by preoperative PSA, Gleason score; margin positivity; seminal vesicle involvement; and radiotherapy institution |
| Was the allocation sequence concealed? | Yes: central randomisation at the MRC Clinical Trials Unit at University College London using a computer-implemented algorithm | YES: central randomisation using an internet-based service, or via central randomisation at the Institut Bergonié | Yes: internet-based randomisation system |
| Did baseline differences suggest a problem? | No: arms are well balanced | No: arms are well balanced | No: arms are well balanced |
| Risk of bias due to deviations from the intended interventions | Low risk | Low risk | Low risk |
| Were participants aware of their assigned intervention during the trial? | Yes: masking is not possible in a radiotherapy trial | Yes: masking is not possible in a radiotherapy trial | Yes: masking is not possible in a radiotherapy trial |
| Were carers and people delivering the interventions aware of participants' assigned intervention during the trial? | Yes: masking is not possible in a radiotherapy trial | Yes: masking is not possible in a radiotherapy trial | Yes: masking is not possible in a radiotherapy trial |
| Were there deviations from the intended intervention that arose because of the trial context? | No: the trial context did not cause changes to intervention | No: the trial context did not cause changes to intervention | No: the trial context did not cause changes to intervention |
| Was an appropriate analysis used to estimate the effect of assignment to intervention? | Yes: full ITT analysis was provided for the meta-analysis outcome of event-free survival | Yes: full ITT analysis was provided for the meta-analysis outcome of event-free survival | Yes: full ITT analysis was provided for the meta-analysis outcome of event-free survival |
| Risk of bias due to missing outcome data | Low risk | Low risk | Low risk |
| Were data available for all, or nearly all, participants randomised? | Yes: results for event-free survival were provided for all participants randomised | Yes: results for event-free survival were provided for all participants randomised | Yes: results for event-free survival were provided for all participants randomised |
| Risk of bias in measurement of the outcome | Low risk | Low risk | Low risk |
| Was method of measuring the outcome inappropriate? | No: we used an agreed meta-analysis definition of event-free survival that was suitable across different trial designs | No: we used an agreed meta-analysis definition of event-free survival that was suitable across different trial designs | No: we used an agreed meta-analysis definition of event-free survival that was suitable across different trial designs |
| Could measurement of the outcome have differed between intervention groups? | No: we used an agreed definition of event-free survival that was suitable for the different intervention groups, and before results were known | No: we used an agreed definition of event-free survival that was suitable for the different intervention groups, and before results were known | No: we used an agreed definition of event-free survival that was suitable for the different intervention groups, and before results were known |
| Outcome assessor aware of intervention received? | Yes: this was unlikely to influence PSA-based biochemical progression (the dominant event in the composite outcome); relatively few clinical and radiological progressions or deaths were reported and unlikely to be affected by outcome assessor | Yes: this was unlikely to influence PSA-based biochemical progression (the dominant event in the composite outcome); relatively few clinical and radiological progressions or deaths were reported and unlikely to be affected by outcome assessor | Yes: this was unlikely to influence PSA-based biochemical progression (the dominant event in the composite outcome); relatively few clinical and radiological progressions or deaths were reported and unlikely to be affected by outcome assessor |
| Risk of bias in selection of the reported result | Low risk | Low risk | Low risk |
| Were the data that produced this result analysed in accordance with a prespecified analysis plan finalised before unblinded outcome data were available for analysis? | Yes: data were analysed and supplied in accordance with the meta-analysis protocol that was registered before trial results were known; this is distinct from the trial analysis | Yes: data were analysed and supplied in accordance with the meta-analysis protocol that was registered before trial results were known; this is distinct from the trial analysis | Yes: data were analysed and supplied in accordance with the meta-analysis protocol that was registered before trial results were known; this is distinct from the trial analysis |
| Overall judgment | Low risk | Low risk | Low risk |

PSA=prostate specific antigen. MRC=Medical Research Council. ITT=intention to treat.

***Table 2:*** **Risk of bias assessment**

| | RADICALS-RT[5] | | GETUG-AFU 17[6] | | RAVES[7] | |
|---|---|---|---|---|---|---|
| | Adjuvant radiotherapy | Early salvage radiotherapy | Adjuvant radiotherapy | Early salvage radiotherapy | Adjuvant radiotherapy | Early salvage radiotherapy |
| Patients randomised | 697 | 699 | 212 | 212 | 166 | 167 |
| Median follow-up, months* | 60 (range 2–132) | .. | 75 (range 0–130) | .. | 78 (range 1–122) | .. |
| Median age, years | 65 (60–68) | 65 (60–68) | 64 (60–68) | 64 (59–68) | 64 (60–68) | 64 (59–68) |
| Median preoperative PSA | 7·8 (5·8–11·4) | 8·0 (5·6–11·6) | Not available | Not available | 7·4 (5·5–10·2) | 7·4 (5·3–10·4) |
| Stage | | | | | | |
| pT2 | 163 (23%) | 176 (25%) | 0 | 0 | 37 (22%) | 39 (23%) |
| pT stage 3a/b | 529 (76%) | 519 (74%) | 208 (99%) | 206 (98%) | 129 (78%) | 128 (77%) |
| pT4 | 5 (1%) | 4 (1%) | 3 (1%) | 5 (2%) | 0 | 0 |
| Gleason score | | | | | | |
| ≤6 | 48 (7%) | 48 (7%) | 21 (10%) | 22 (10%) | 8 (5%) | 8 (5%) |
| 7 | 537 (77%) | 528 (76%) | 173 (82%) | 167 (78%) | 132 (80%) | 134 (80%) |
| ≥8 | 112 (16%) | 123 (17%) | 17 (8%) | 23 (11%) | 26 (16%) | 25 (15%) |
| Positive margins | 439 (63%) | 443 (63%) | 211 (100%) | 210 (100%) | 110 (66%) | 113 (68%) |
| Seminal vesicle involvement | | | | | | |
| Yes | 129 (19%) | 132 (19%) | 44 (21%) | 46 (22%) | 31 (19%) | 33 (20%) |
| No | 568 (81%) | 567 (81%) | 167 (79%) | 165 (78%) | 135 (81%) | 134 (80%) |
| Unknown | 0 | 0 | 1 (<1%) | 1 (<1%) | 0 | 0 |
| Extracapsular extension | | | | | | |
| Yes | 492 (71%) | 483 (69%) | 212 (100%) | 212 (100%) | 129 (78%) | 128 (77%) |
| No | 205 (29%) | 215 (31%) | 0 | 0 | 37 (22%) | 39 (23%) |
| Unknown | 0 | 1 (<1%) | 0 | 0 | 0 | 0 |
| Lymph node involvement | | | | | | |
| Involved | 38 (5%) | 28 (4%) | 0 | 0 | 1 (1%) | 0 |
| Not involved | 335 (48%) | 374 (54%) | 212 (100%) | 212 (100%) | 165 (99%) | 167 (100%) |
| Nx | 324 (47%) | 297 (43%) | 0 | 0 | 0 | 0 |
| CAPRA-S risk group† | | | | | | |
| Low (0–2) | 58 (8%) | 55 (8%) | .. | .. | 22 (13%) | 21 (13%) |
| Intermediate (3–5) | 382 (55%) | 384 (55%) | .. | .. | 100 (60%) | 98 (59%) |
| High (≥6) | 257 (37%) | 260 (37%) | .. | .. | 44 (27%) | 48 (29%) |

PSA=prostate-specific antigen. Nx=no information or not assessable. CAPRA-S=Cancer of the Prostate Risk Assessment post-surgical score. *Median follow-up is for both adjuvant radiotherapy and early salvage radiotherapy groups combined. †The GETUG AFU-17 trial did not record preoperative PSA levels and therefore CAPRA-S scores,[18] which comprise scores based on a number of patient and disease characteristics at baseline, including preoperative PSA levels, cannot be calculated for the trial.

***Table 3:*** **Patient characteristics**

positive margins (pT2 or pT3) or extracapsular extension (pT3). Furthermore, patients without extracapsular extension were excluded from the GETUG AFU-17 trial, but not from the RAVES or RADICALS-RT trials.

The baseline characteristics of the 2153 included patients largely represent the eligibility criteria of the three trials (table 3). Median age was similar between trials at 64 or 65 years (table 3), with patients ranging in age from 37 years to 79 years. The majority of patients had either stage pT3a or b disease (1719 [79·8%]), positive surgical margins (1526 [70·9%]), and extracapsular extension (1656 [76·9%]; table 3).

We were able to include updated event-free survival results for 2053 patients, representing 100% of those randomised in the three trials, and at data cutoff (April 22, 2020), 270 events had been recorded. 1075 patients were randomly assigned to receive

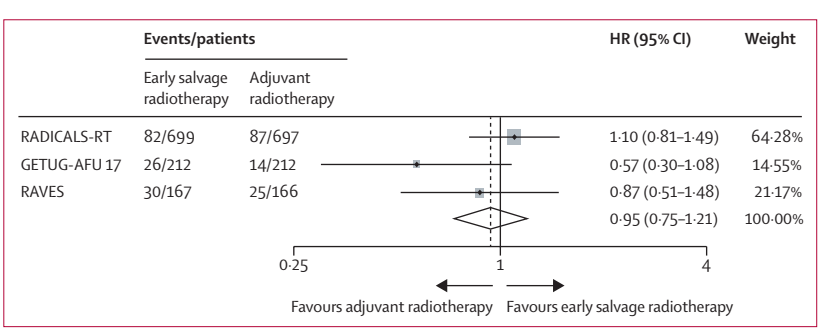


***Figure 2:*** **Effect of radiotherapy timing on event-free survival**
Each filled square denotes the HR for that trial comparison, with the horizontal lines showing the 95% CI. The size of the square is directly proportional to the amount of information contributed by a trial. The diamond represents a (fixed-effect) meta-analysis of the trial HRs, with the centre of this diamond indicating the HR and the extremities the 95% CI. HR=hazard ratio.

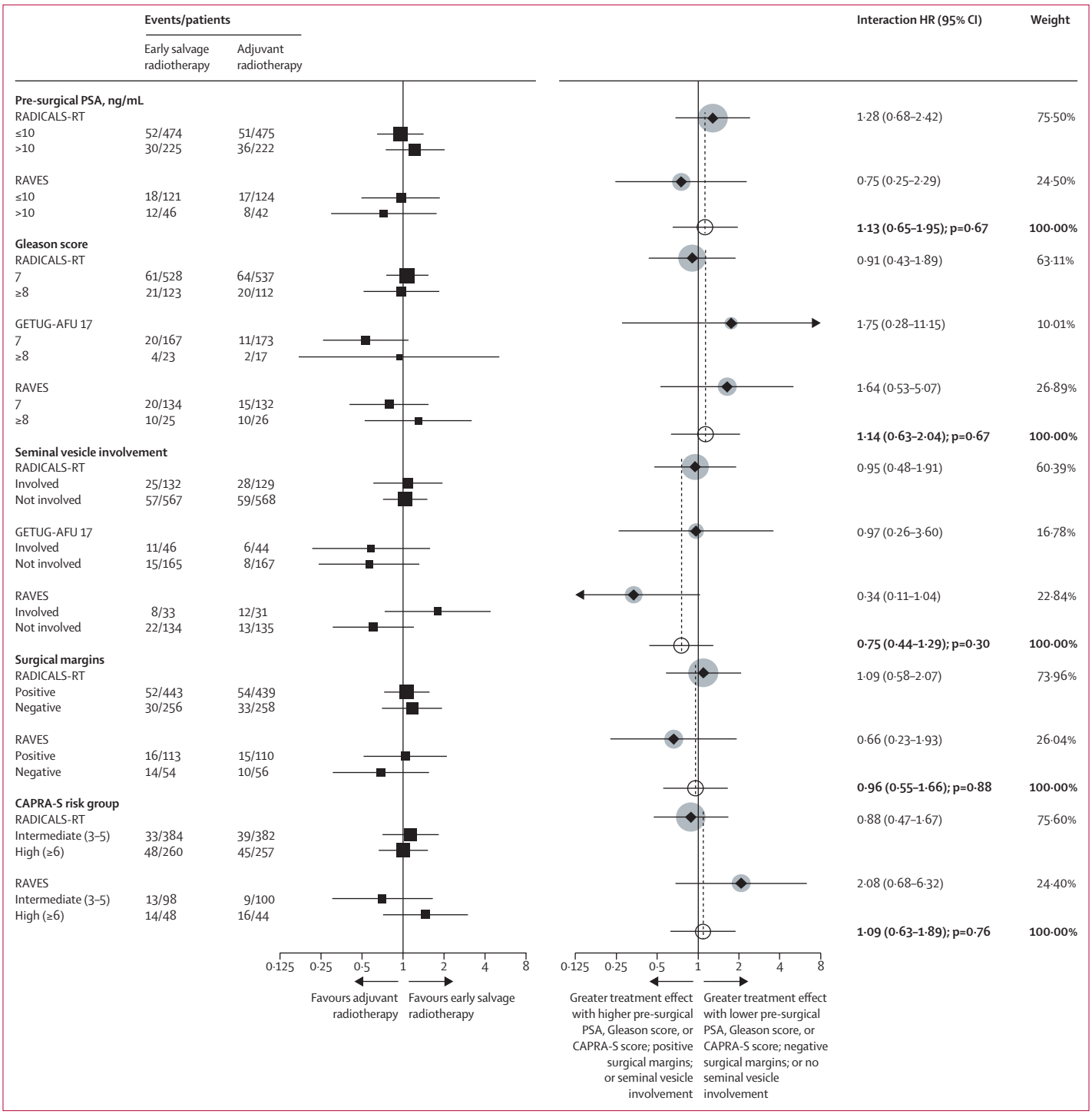


*Figure 3:* **Effect of radiotherapy timing on event-free survival by pre-surgical PSA, Gleason score, seminal vesicle involvement, surgical margins, and CAPRA-S risk group**
Each filled square denotes the HR for each subgroup of patients defined by pre-surgical PSA, Gleason score, seminal vesicle involvement, surgical margins, and CAPRA-S risk group within each trial, with the horizontal lines showing the 95% CI. The size of the square is directly proportional to the amount of information contributed by a subgroup. Each filled circle denotes the HR for the interaction between the effect of radiotherapy and these subgroups for each trial, with the horizontal lines showing the 95% CI. The size of each circle is directly proportional to the amount of information contributed by a trial. The open circle represents a (fixed-effect) meta-analysis of the interaction HRs, with the horizontal line showing the 95% CI. HR=hazard ratio. CAPRA-S=Cancer of the Prostate Risk Assessment post-surgical score.

adjuvant radiotherapy and 1078 to a policy of early salvage radiotherapy. At the time of these analyses, only 421 (39·1%) patients randomly assigned to early salvage radiotherapy had received postoperative radiotherapy. Although event-free survival events were dominated by biochemical progressions, as expected, the proportion of patients free of biochemical progression at 5 years was high (87% in RAVES, 88% in RADICALS-RT, and 94% in GETUG-AFU 17).[5–7]

Pooling the event-free survival results of the three trials in a meta-analysis gives an overall fixed-effect HR of 0·95 (95% CI 0·75 to 1·21; p=0·70; figure 2). With a baseline event-free survival rate of 88% at 5 years, this translated to a 1% absolute difference (95% CI −2 to 3) between early salvage radiotherapy and adjuvant radiotherapy at 5 years. Although RADICALS-RT is the largest trial, the other two trials contribute more than 35% of the total weight to the meta-analysis (figure 2). Results were broadly consistent across trials (heterogeneity p=0·18; inconsistency $I^2$=42%) and the results from a random-effects model were very similar (HR 0·89, 95% CI 0·62 to 1·27; p=0·52).

Results were supplied for the effect of radiotherapy timing on event-free survival by all prespecified subgroups for the RADICALS-RT and RAVES trials. However, the GETUG-AFU 17 trial did not record preoperative PSA, and all patients had positive surgical margins and extracapsular extension. Therefore, GETUG-AFU 17 has not been included in the analysis of event-free survival by preoperative PSA, surgical margins, or CAPRA-S risk group. Furthermore, due to the very low numbers of events reported in patients with a Gleason score of 6 or less or categorised as low CAPRA-S risk for both the RAVES and RADICALS-RT trials, it was not possible to estimate a HR within these groups. Therefore, the interaction analysis of Gleason score compares event-free survival in patients with scores of 7 with those who have a score of 8 or more and the analysis of CAPRA-S risk group compares event-free survival in patients with intermediate (score 3–5) and high (score ≥5) risk.

Based on the available data, there was no good evidence that the effect on event-free survival of adjuvant radiotherapy varied according to any of our predefined subgroups: pre-surgical PSA, Gleason score, seminal vesicle involvement, surgical margins, or CAPRA-S risk group (figure 3).

## Discussion

Based on our findings, the systematic use of adjuvant radiotherapy following prostatectomy does not improve PSA-driven event-free survival in men with localised or locally advanced prostate cancer. We found that event-free survival rates were high, at around 88% after 5 years in both groups, despite around 60% of patients randomly assigned to receive early salvage radiotherapy not having initiated treatment by the time of this analysis. There was no evidence to suggest that the effect of adjuvant radiotherapy on event-free survival varied according to pre-surgical PSA, Gleason score, seminal vesicle involvement, surgical margins, or CAPRA-S risk group.

By using the prospective FAME approach, and working collaboratively with trialists, we have been able to overcome some of the limitations associated with a standard aggregate data meta-analysis. First, we reduced the potential for bias in the selection of studies by specifying eligibility criteria and conducting searches for eligible trials while they were ongoing or unreported. We also limited the potential for bias in the analysis by harmonising the event-free survival outcome definition and planning all analyses (including subgroup analyses) in advance of the trial results being known. This is further reflected in a low risk of bias assessment for each domain for each trial. Furthermore, working with the trialists we were able to include up-to-date event-free survival results from 100% of patients randomised in all eligible trials, and the timing of this analysis was determined on the basis of having sufficient power. Therefore, the meta-analysis represents the totality of randomised evidence about the effects of radiotherapy timing in men with localised or locally advanced prostate cancer, and our prospective and collaborative approach has allowed a more consistent, thorough, and timely investigation of effects than is typically possible with aggregate data meta-analysis. The results provide context for the individual trials and maximise their usefulness and impact on clinicians, patients, and policy makers.

For the trial teams involved in the ARTISTIC collaboration, prospectively planning the systematic review and meta-analysis has helped the trialists to reassure patients and funders that there was value in continuing with the trial, and an independent data monitoring committee for one of the trials that the primary outcome should be amended. It has also provided an opportunity to discuss and resolve issues and ultimately to address the clinical questions the trials set out to answer. In this way, the ARTISTIC collaboration has functioned similarly to an IPD meta-analysis and prospective IPD meta-analysis.[9,22]

Prospective meta-analysis typically uses IPD, and the advantages of obtaining IPD for meta-analysis are well documented,[22,23] but IPD for these trials will not be available for many years. Therefore, to obtain an early signal regarding the effect of radiotherapy timing on the intermediate outcome of event-free survival, we adopted a prospective and collaborative aggregate data approach. Despite exceeding the anticipated number of events needed to detect an absolute improvement of 5% with adjuvant radiotherapy with 90% power, we had insufficient power to detect a very small (<5%) benefit. That said, we found no evidence of an absolute effect of adjuvant radiotherapy on 5-year event-free survival (1% absolute difference, 95% CI −2 to 3). Given that large benefits of radiotherapy on early biochemical outcomes in men with prostate cancer both in the localised or locally advanced[1–3] and metastatic settings[12]

have failed to translate into clear long-term benefits, a clinically meaningful benefit of adjuvant radiotherapy would seem unlikely. However, as there is no evidence currently that biochemical progression is a reliable surrogate of survival or other clinically driven outcomes in the localised prostate cancer setting,[24] the ARTISTIC collaboration will continue to work together to monitor accumulating events across the trials and plan meta-analyses of the long-term outcomes.

Although the three trials have results that are broadly consistent, we were unable to explore the effect of giving hormone therapy alongside radiotherapy on event-free survival as we had planned. GETUG-AFU 17 gave concomitant radiotherapy and hormone therapy, RAVES used radiotherapy alone, and RADICALS-RT included an optional second randomisation to either long (24 months) or short (6 months) duration hormones or to no hormones. Patients who did not opt for this randomisation could receive hormones off protocol. While it might be tempting to speculate that concomitant hormone treatment might modify the effect of radiotherapy timing on event-free survival on the basis of results from the GETUG-AFU 17 trial, until the results of the RADICALS hormone duration randomisation are available, the overall HR of 0·95 for event-free survival remains the most reliable.

The power of our patient subgroup analyses is limited by the low event rate overall. Nevertheless, we do not see any indication of a benefit of adjuvant radiotherapy in any of the subgroups assessed. Therefore, based on the evidence available, our main conclusion holds true across all patients included in the meta-analysis. As very few patients across all three trials had node-positive disease, we were unable to assess the effect of radiotherapy timing in this population.

Previous RCTs assessing the effects of adjuvant radiotherapy in localised and locally advanced prostate cancer have not compared the approach with a policy of early salvage treatment. Indeed, a criticism of the earlier trials[1,2] was that relatively few patients randomly assigned to observation received salvage radiotherapy at all, and those who did had relatively high PSA levels before salvage radiotherapy was initiated. In a more recent Finnish trial,[21] although 86% of men randomly assigned to the observation arm were reported to have received salvage radiotherapy, median PSA levels were 0·7 ng/mL at the time it was initiated. Thus, the salvage radiotherapy policy cannot be considered to be truly early, as it was in the three trials included in this meta-analysis. Like the earlier trials, the Finnish trial concluded that there was a large improvement in biochemical recurrence with adjuvant radiotherapy compared to observation,[21] but evidence of a clear benefit on longer-term clinical outcomes is lacking. When making treatment choices, the lack of evidence of a benefit of adjuvant radiotherapy must be considered alongside adverse effects of this treatment. All three trials included here have reported increases in specific side-effects with adjuvant radiotherapy, including increased urinary morbidity (RADICALS-RT), grade 2 or greater genito-urinary toxicity (RAVES), and grade 2 or greater late genito-urinary toxicity and erectile dysfunction (GETUG-AFU 17).[5–7]

Based on this prospectively designed meta-analysis, adjuvant radiotherapy following prostatectomy does not improve PSA-driven event-free survival compared with policies of early salvage radiotherapy in men with localised or locally advanced prostate cancer. Early salvage radiotherapy policies therefore seem to offer the opportunity to avoid, or at least postpone, radiotherapy and its associated adverse effects for many men with no obvious disadvantage to event-free survival. Most men included in these trials have done well, with around 88% remaining event free 5 years after prostatectomy. Based on these findings, the likelihood that delaying radiotherapy would have a deleterious effect on longer-term outcomes is low, but we will complete further meta-analyses on these clinically important outcomes as data from the included trials mature.

In conclusion, we believe early salvage radiotherapy should be considered as the standard of care. Guidelines and policy should be reviewed to reflect this.

#### Contributors

All authors were involved in devising and agreeing the final protocol for this work. CLV and DF carried out the analyses. CLV drafted the manuscript with substantive input from JFT. All authors reviewed and commented on the draft manuscript and agreed the final version for submission. ublication results from the trials were supplied with the permission of the trial teams and sponsors and were prepared and supplied for the analyses by CBra, AC, CF-B, CBro, and SC.

#### Declaration of interests

CLV, DF, AK, MP, PR, AC, CBra, MB, SC, SF, CBro, and JFT declare no competing interests. CP reports grants from Bayer, personal fees from Bayer and Janssen, and other support (including speaker fees, advisory board membership, and honoraria) from Bayer, AAA Pharmaceuticals, and Janssen, outside of the submitted work. PS reports honoraria, speaker fees, and advisory board fees from Ipsen, Astellas, Bouchara, Takeda, and Ferring, during the conduct of the study, as well as other relationships and activities from Janssen, Bayer, and Sanofi, outside of the submitted work. CF-B reports grants from New Zealand Health Research Council, Australian National Health and Medical Research Council, Auckland Hospital Charitable Trust, TROG Seed Funding, and Genesis Oncology Trust, during the conduct of the study. MRS reports grants and non-financial support from Astellas, Clovis Oncology, Janssen, Novartis, Pfizer, and Sanofi; and personal fees from Eli Lilly and Janssen, outside of the submitted work. IL reports other financial relationships from Sanofi, Ipsen, and Astellas, outside of the submitted work. MKBP reports grants and non-financial support from Astellas, Clovis Oncology, Novartis, Pfizer, and Sanofi, outside of the submitted work.

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