Adjuvant radiotherapy versus early salvage radiotherapy following radical prostatectomy (TROG 08.03/ANZUP RAVES): a randomised, controlled, phase 3, non-inferiority trial

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Summary

Background Adjuvant radiotherapy has been shown to halve the risk of biochemical progression for patients with high-risk disease after radical prostatectomy. Early salvage radiotherapy could result in similar biochemical control with lower treatment toxicity. We aimed to compare biochemical progression between patients given adjuvant radiotherapy and those given salvage radiotherapy.

Methods We did a phase 3, randomised, controlled, non-inferiority trial across 32 oncology centres in Australia and New Zealand. Eligible patients were aged at least 18 years and had undergone a radical prostatectomy for adenocarcinoma of the prostate with pathological staging showing high-risk features defined as positive surgical margins, extraprostatic extension, or seminal vesicle invasion; had an Eastern Cooperative Oncology Group performance status of 0–1, and had a postoperative prostate-specific antigen (PSA) concentration of 0·10 ng/mL or less. Patients were randomly assigned (1:1) using a minimisation technique via an internet-based, independently generated allocation to either adjuvant radiotherapy within 6 months of radical prostatectomy or early salvage radiotherapy triggered by a PSA of 0·20 ng/mL or more. Allocation sequence was concealed from investigators and patients, but treatment assignment for individual randomisations was not masked. Patients were stratified by radiotherapy centre, preoperative PSA, Gleason score, surgical margin status, and seminal vesicle invasion status. Radiotherapy in both groups was 64 Gy in 32 fractions to the prostate bed without androgen deprivation therapy with real-time review of plan quality on all cases before treatment. The primary endpoint was freedom from biochemical progression. Salvage radiotherapy would be deemed non-inferior to adjuvant radiotherapy if freedom from biochemical progression at 5 years was within 10% of that for adjuvant radiotherapy with a hazard ratio (HR) for salvage radiotherapy versus adjuvant radiotherapy of 1·48. The primary analysis was done on an intention-to-treat basis. This study is registered with ClinicalTrials.gov, NCT00860652.

Findings Between March 27, 2009, and Dec 31, 2015, 333 patients were randomly assigned (166 to adjuvant radiotherapy; 167 to salvage radiotherapy). Median follow-up was 6·1 years (IQR 4·3–7·5). An independent data monitoring committee recommended premature closure of enrolment because of unexpectedly low event rates. 84 (50%) patients in the salvage radiotherapy group had radiotherapy triggered by a PSA of 0·20 ng/mL or more. 5-year freedom from biochemical progression was 86% (95% CI 81–92) in the adjuvant radiotherapy group versus 87% (82–93) in the salvage radiotherapy group (stratified HR 1·12, 95% CI 0·65–1·90; $p_{\text{non-inferiority}}$=0·15). The grade 2 or worse genitourinary toxicity rate was lower in the salvage radiotherapy group (90 [54%] of 167) than in the adjuvant radiotherapy group (116 [70%] of 166). The grade 2 or worse gastrointestinal toxicity rate was similar between the salvage radiotherapy group (16 [10%]) and the adjuvant radiotherapy group (24 [14%]).

Interpretation Salvage radiotherapy did not meet trial specified criteria for non-inferiority. However, these data support the use of salvage radiotherapy as it results in similar biochemical control to adjuvant radiotherapy, spares around half of men from pelvic radiation, and is associated with significantly lower genitourinary toxicity.

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Introduction

Radical prostatectomy is the most frequently used treatment modality for men with clinically localised prostate cancer.[1] Historically, a third of patients develop recurrent disease,[2] although with better selection and contemporary surgical techniques the proportion might be closer to

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See Online for appendix

Research in context

Evidence before this study

When this study was under development in 2007, the use of adjuvant radiotherapy to the prostate bed after radical prostatectomy had been shown to halve the risk of biochemical progression when compared with observation for men with prostate cancer with high-risk features. Results of three randomised trials initiated between 1988 and 1996 supported the use of adjuvant radiotherapy (ARO 96-02/AUO AP 09/95; EORTC trial 2291; SWOG8794), with one of these studies also showing improved metastasis-free survival and overall survival. Despite this evidence, adjuvant radiotherapy has not been widely adopted due to concerns over perceived toxicity. A potential limitation of these three randomised trials is that there was no standard management for patients on observation who developed relapse. Salvage radiotherapy was given intermittently and at varying lengths of time after relapse, with some patients having documented locoregional progression before treatment. The results of the three studies were used to generate American and European guidelines, which recommend that such men be referred for consideration of adjuvant radiotherapy. Due to this broad acknowledgment of the three studies in the field of post-prostatectomy prostate cancer management, a systematic review was not done before the development of the RAVES trial. The recommendation to routinely administer adjuvant radiotherapy comes at the potential cost of increased morbidity. There is the possibility that observing these patients and delivering salvage radiotherapy when prostate-specific antigen (PSA) first starts to rise could have similar efficacy.

Added value of this study

This study confirmed that men with high-risk features have a rising PSA in more than 50% of cases following surgery when observed. Our results have shown similar high rates of disease-free survival at 5 years for both the early salvage and adjuvant radiotherapy groups. This outcome has been achieved with relatively modest radiation doses in the salvage radiotherapy group by treating relapse very early as soon as the PSA reaches 0·20 ng/mL. The study also documented an increase in genitourinary morbidity when radiotherapy is given to all patients in an adjuvant setting.

Implications of all the available evidence

These results are being released concurrently with the RADICALS and GETUG-17 trials, along with a pre-planned meta-analysis of all three trials. These trials have concordant results suggesting that adjuvant radiotherapy does not improve event-free survival in men with high-risk features following radical prostatectomy. It now appears preferable to wait until the cancer recurs, heralded by a PSA rising to 0·20 ng/mL, before commencing radiotherapy, which would spare many men from potential radiotherapy-related side-effects.

20%.[3] The risk of recurrence is greater among men with high-risk features, including extraprostatic extension, seminal vesicle invasion, and positive surgical margins.[4]

Three randomised controlled trials have reported a halving of biochemical progression with the use of adjuvant radiotherapy compared with surgery alone in patients with high-risk features following radical prostatectomy.[5–7] One of these trials also showed an improvement in metastasis-free survival and overall survival.[7] Although these trials have shown a benefit of adjuvant radiotherapy over observation, subsequent use of adjuvant radiotherapy has been uncommon,[8] in part due to clinician concerns about radiation-related toxicities and the possibility that early salvage radiotherapy to the prostate bed might provide equivalent control to adjuvant radiotherapy.[9]

The primary aim of the RAVES trial was to test the hypothesis that for patients with pT3 disease (ie, extraprostatic extension with or without seminal vesicle involvement) or positive margins following radical prostatectomy, observation with early salvage radiotherapy is non-inferior to standard treatment of adjuvant radiotherapy with respect to biochemical progression.

Methods

Study design and participants

This phase 3, randomised, controlled, non-inferiority trial (RAVES) was done in 32 oncology centres across Australia and New Zealand, and led by the Trans-Tasman Radiation Oncology Group (TROG) in collaboration with the Urological Society of Australia and New Zealand, and the Australian and New Zealand Urogenital and Prostate Cancer Trials Group (appendix p 5).

Eligible patients were aged at least 18 years and had undergone a radical prostatectomy for adenocarcinoma of the prostate with pathological staging showing high-risk features defined as either positive surgical margins, extraprostatic extension, or seminal vesicle invasion, as identified by local pathologists. Patients were also required to have a postoperative prostate-specific antigen (PSA) concentration of 0·10 ng/mL or less, to be able to start radiotherapy within 4 months of radical prostatectomy (extended to permit radiotherapy within up to 6 months in a protocol amendment as of July 8, 2011), and have an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1. Exclusion criteria included androgen deprivation therapy before or after radical prostatectomy, previous pelvic radiotherapy, total hip replacement, or evidence of nodal or distant metastases. Patients with comorbidities that would interfere with the completion of treatment or 5 years of follow-up were also excluded. Participants were recruited in urology and radiotherapy clinics. All patients provided written informed consent before treatment. Separate consent was provided for optional translational research sub-studies. The protocol was approved by institutional ethics review boards, and is publicly available.

For the **protocol** see https://www.trog.com.au/TROG-0803-trial-documents

Randomisation and masking

Patients were randomly assigned by local research staff via an independently developed and managed internet-based system, which permitted randomisations to proceed only if all eligibility criteria were met. The allocation sequence was concealed so as not to bias the randomisation but treatment assignment was not masked to investigators or patients. Stochastic dynamic programming (ie, minimisation) was used to randomly assign patients (1:1) to either adjuvant radiotherapy or salvage radiotherapy. Patients were stratified by seminal vesicle involvement (pT3b: yes *vs* no), Gleason score (continuous), preoperative PSA (continuous), surgical margin status (positive *vs* negative), and radiotherapy institution. Following randomisation, TROG did remote source data verification of eligibility data.

Procedures

Radical prostatectomy histological specimens were obtained after randomisation for central pathological review, but pathology reporting was based on pathology results from local institutions.

To ensure uniform radiotherapy compliance with protocol requirements, a pre-recruitment credentialling programme was implemented. Credentialling involved participating radiation oncologists and treatment centres completing a contouring and planning exercise with use of an identical case that was then reviewed for protocol compliance by three independent radiation oncologists. Plans with major violations were required to be resubmitted. In addition, throughout the trial, all cases underwent pre-treatment radiotherapy plan review and resubmission before treatment began if unsatisfactory. An additional credentialling process was completed at the time centres moved from 3D conformal-based planning to intensity-modulated radiotherapy.

Target volume specifications were based on post-prostatectomy radiotherapy consensus guidelines from the Faculty of Radiation Oncology Genito-Urinary Group.[10] In short, the clinical target volume of the prostate bed extended from 5–6 mm below the anastomosis up to the level of the base of the seminal vesicles incorporating all of the surgical bed or clips unless the seminal vesicles were involved, in which case all of the residual seminal vesicles were included. The planning target volume was a uniform 1-cm margin unless the volume of rectum being irradiated was deemed too large, in which case a 0·5-cm posterior margin was allowed. The dose in both the adjuvant and salvage radiotherapy groups was 64 Gy in 32 fractions, and the mean dose with intensity-modulated radiotherapy or volumetric modulated arc therapy was –1% to +2% of 64 Gy. More detailed summaries of the protocol radiotherapy guidelines and results of the quality assurance programme have been published.[11,12] Adjuvant radiotherapy was given within 6 months of radical prostatectomy; salvage radiotherapy was given within 4 months of a PSA measurement of 0·20 ng/mL or more.

Use of androgen deprivation therapy with either adjuvant radiotherapy or salvage radiotherapy was not allowed.

Before randomisation, preoperative PSA, ECOG performance status, baseline adverse events, and patient reported outcomes were collected. Additionally, prescription medication use and the Charlson Co-morbidity Index (totalling the number of comorbid conditions)[13] were recorded (appendix p 4). Adverse events were scored by clinicians per National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0.[14] The CTCAE genitourinary domains included cystitis, urinary incontinence, urethral stricture or stenosis, urinary frequency or urgency, urinary retention, and haemorrhage (genitourinary). Gastrointestinal domains included diarrhoea, proctitis, haemorrhage (rectal), and incontinence (anal).

Clinicians recorded any additional adverse events believed to be clinically important. Patient-reported outcomes were assessed via the EORTC global (QLQ-C30)[15] and EORTC prostate cancer module (QLQ-PR25)[16] questionnaires (version 3), the Hospital Anxiety and Depression Scale,[17] and the Sexual Health Inventory for Men.[18]

For all patients having adjuvant radiotherapy or salvage radiotherapy, clinician-scored adverse events and the QLQ-C30, QLQ-PR25, and Hospital Anxiety and Depression Scale questionnaires were repeated on day 1 of radiotherapy, at the end of radiotherapy, and 6 weeks after radiotherapy. Patients in both groups had clinical follow-up once every 6 months for 5 years and once a year thereafter. Annual assessments consisted of clinician-scored adverse events per CTCAE criteria, disease status, and all patient questionnaires.

For the adjuvant radiotherapy group, PSA was measured 6 weeks after radiotherapy and then once every 6 months relative to randomisation thereafter. PSA measurement was more frequent in the salvage radiotherapy group to ensure early delivery of salvage radiotherapy should the PSA rise to 0·20 ng/mL or higher. During the surveillance phase, PSA was measured every 3 months from randomisation during the first 5 years, and then once every 6 months thereafter. For patients proceeding to salvage radiotherapy, PSA was measured on day 1 of radiotherapy, 6 weeks after the end of radiotherapy, and then once every 6 months relative to randomisation thereafter.

For both groups, biochemical progression was diagnosed on the first occasion following radiotherapy that the serum PSA was 0·40 ng/mL or more and rising from the previous value. A confirmatory PSA test was done if clinically indicated, with the date of biochemical progression considered to be the date of the first PSA measurement of 0·40 ng/mL or more. For patients randomly assigned to salvage radiotherapy, a PSA result that was 0·40 ng/mL or more but less than the PSA result from day 1 of radiotherapy did not constitute biochemical progression. In patients who did not receive

radiotherapy per randomisation, biochemical progression on the basis of PSA was deemed to have occurred when the PSA was 0·40 ng/mL or more. PSA measurements were done by local laboratories, and source data verification was done centrally for all PSA results meeting the definition for biochemical progression.

Biochemical progression was also defined as the commencement of androgen deprivation therapy for any reason or locoregional or metastatic clinical progression if any of these events occurred before a PSA result of 0·40 ng/mL or more was measured. Local progression was defined as documented palpable or biopsy-proven local progression per institutional standard of care and in later periods of the study a positive prostate-specific membrane antigen (PSMA) PET scan. Diagnosis of nodal progression was required to be confirmed by CT scan of the abdomen and pelvis, MRI scan, or PSMA PET scan of the abdomen and pelvis. Patients could be removed from the study treatment for unacceptable toxicity, intercurrent illness preventing further treatment, or withdrawal of consent by the patient during treatment or follow-up. Patients who did not complete the study treatment but did not withdraw consent were invited to complete the scheduled evaluations and continue to be followed up according to the protocol.

Outcomes

The primary endpoint was freedom from biochemical progression (defined as the time from the date of randomisation to the date of biochemical progression).

Secondary endpoints included in this report were time to initiation of androgen deprivation therapy; time to local, regional, and distant progression (defined as the time from the date of randomisation to the date of documented progression); and overall survival (defined as the time from the date of randomisation to the date of death). Additional secondary endpoints not reported here are quality-of-life outcomes, anxiety and depression, adverse events, disease-specific survival, quality-adjusted life-years, and cost–utility. Due to the large volume of toxicity data, a more comprehensive toxicity analysis, including time to toxicity, will be the subject of a subsequent manuscript. Similarly, detailed analyses of patient-reported outcomes and time to initiation of androgen deprivation therapy are the subject of a separate manuscript.

Statistical analysis

Power calculations were based on the 5-year freedom from biochemical progression rate of 74% observed in the adjuvant radiotherapy group of the EORTC trial 22911.[6] Salvage radiotherapy would be considered to be non-inferior to adjuvant radiotherapy if its 5-year freedom from biochemical progression was at most 10% lower than that for adjuvant radiotherapy (ie, >64%). Assuming proportional hazards, these rates correspond to a hazard ratio (HR) for salvage radiotherapy versus adjuvant radiotherapy of 1·48. Given these parameters and allowing for dropouts, it was estimated that a sample size of 470 patients accrued over 4·7 years with 5 years of follow-up would be required to provide 80% power to detect non-inferiority with a one-sided 5% type I error. Both unstratified and stratified analyses were done.

Time-to-event outcomes were compared between groups with use of Cox proportional hazards regression to estimate HRs and their 95% CIs and the log-rank test, along with tests for interaction of various predictors for biochemical progression with regards to the treatment group. These prespecified predictors were the following stratification variables: seminal vesicle involvement, Gleason score, preoperative PSA, and surgical margin positivity. The proportional hazards assumption was tested and met.

In a post-hoc analysis of adverse events of interest (genitourinary and gastrointestinal events of grade 2 or worse), odds ratios (ORs) for the relationship between treatment groups and prevalence of grade 2 or worse toxicities of various types were derived from mixed effects logistic regression models, with treatment group as a fixed effect and patient as a random effect. This analysis of adverse events was changed (before any analysis) from the original protocol as it was felt this was the best way to statistically compare rates of adverse events between the treatment groups.

Analysis of the primary objective was done according to both intention-to-treat and per-protocol methods, with the per-protocol analysis planned to assess consistency regarding non-inferiority conclusions. The per-protocol analysis excluded patients who received treatment outside of the protocol treatment timings. All analyses of secondary endpoints used the intention-to-treat population.

An independent data monitoring committee was established at study initiation to review toxicity after 200 patients had been enrolled and to review both toxicity and futility after recruitment of 300 and 400 patients. After the first interim analysis of toxicity on March 21, 2013, the independent data monitoring committee determined that all reported toxicities were consistent with what would be expected for the patient population.

The futility analysis was planned to test whether there was evidence that the risk of biochemical progression for salvage radiotherapy was significantly inferior to that of adjuvant radiotherapy at the 5% one-sided significance level. On Feb 28, 2015, after 5·9 years of accrual with 303 patients randomly assigned, there were only 17 patients with biochemical progression compared with a predicted 113. At this time, the trial had a power of 0·31 to detect a non-inferiority margin of 0·1 in the biochemical progression-free rate at 5 years with an HR of 1·48. It was estimated it would take 18·1 years of accrual if the power of the study was to be maintained at 80% as originally planned. It was determined that further recruitment to the planned target of 470 patients would be futile in showing non-inferiority of the salvage

radiotherapy group, as the low event rate would result in inadequate study power. Increasing the sample size and study duration to account for the change in assumption was deemed infeasible. The study closed to recruitment on Dec 31, 2015, and June 30, 2018, was the cutoff date for the primary analysis. Patients will be followed up for survival and disease status until a median follow-up of 10 years is reached, anticipated in 2022.

The R statistical software package (version 3.6) was used for all analyses. This study is registered with ClinicalTrials.gov, NCT00860652.

Role of the funding source

The funders 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

Between March 27, 2009, and Dec 31, 2015, 333 patients were randomly assigned to treatment (166 to adjuvant radiotherapy; 167 to salvage radiotherapy; figure 1). 26 patients did not complete study follow-up due to withdrawal, loss to follow-up, or death. Median follow-up was 6·1 years (IQR 4·3–7·5). Demographics and baseline features are shown in the table.

84 (50%) patients in the salvage radiotherapy group had a PSA of 0·20 ng/mL or more to trigger radiotherapy (one patient requested salvage radiotherapy following a PSA of 0·17 ng/mL). The time to commencement of salvage radiotherapy is shown in figure 2.

In the intention-to-treat analysis, there were 25 biochemical progressions in the adjuvant radiotherapy group and 30 biochemical progressions in the salvage radiotherapy group. 5-year freedom from biochemical progression was 86% (95% CI 81–92) in the adjuvant radiotherapy group versus 87% (82–93) in the salvage radiotherapy group (unstratified HR 1·15 [95% CI 0·67–1·95]; stratified HR 1·12 [95% CI 0·65–1·90]; figure 3). The one-sided test of non-inferiority had a p value of 0·15. 8-year freedom from biochemical progression was 80% (95% CI 72–89) versus 75% (95% CI 67–85).

309 patients were included in the per-protocol analysis: 158 in the adjuvant radiotherapy group (seven were excluded for not having radiotherapy and one had adjuvant radiotherapy late) and 151 in the salvage radiotherapy group (four did not have salvage radiotherapy per protocol and 12 did not receive salvage radiotherapy or were lost to follow-up). 5-year freedom from biochemical progression was 86% (95% CI 81–92) in the adjuvant radiotherapy group versus 89% (84–94) in the salvage radiotherapy group (stratified HR 0·97 [95% CI 0·53–1·78]) . The one-sided test of non-inferiority had a p value of 0·086. 8-year freedom from biochemical progression was 80% (95% CI 72–89) versus 77% (68–87).

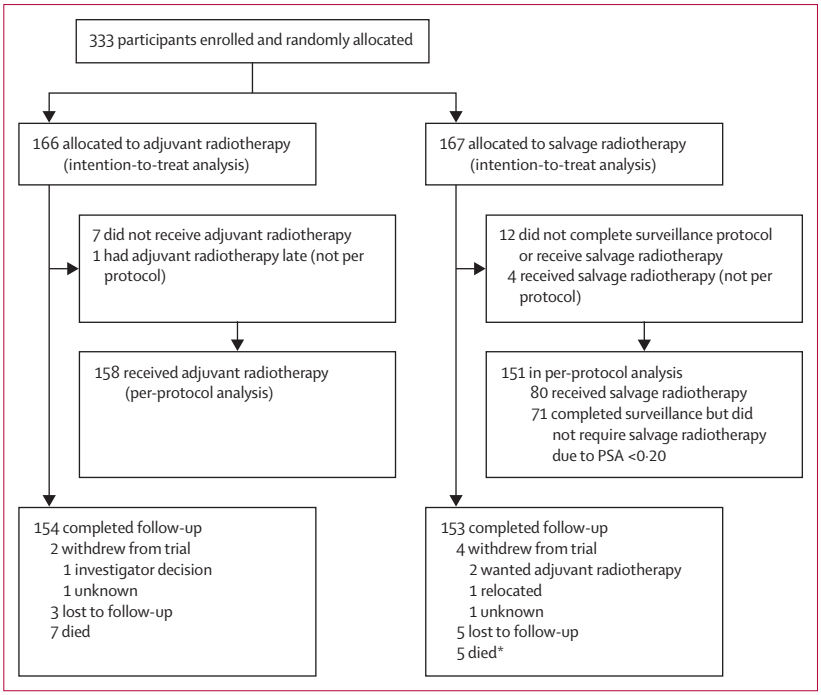

Figure 1: **Trial profile**
One patient was found to be ineligible after randomisation due to previous history of cancer within 5 years and a hip prosthesis. The patient was in the adjuvant radiotherapy group and received adjuvant radiotherapy per-protocol. Six patients eligible per local pathology were subsequently found to be ineligible after central pathology review (n=1 node positive; n=5 no positive margins or extraprostatic extension; three in the adjuvant radiotherapy group; and three in the salvage radiotherapy group). All patients were included in both per-protocol and intention-to-treat analyses. Of those patients deemed ineligible via central pathology review, all patients in the adjuvant radiotherapy group received radiotherapy, none of the patients in the salvage radiotherapy group required radiotherapy. PSA=prostate-specific antigen. *One patient did not receive radiotherapy per-protocol, withdrew, but subsequently consented to follow-up via medical records, where death was recorded.

The one-sided test of non-inferiority had a p value of 0·047. 8-year freedom from biochemical progression was 80% (95% CI 72–89) versus 79% (70–88).

Analyses of time to locoregional and time to distant progression were combined due to the low number of events. In the adjuvant radiotherapy group, there were no local progressions and ten regional or distant progressions. In the salvage radiotherapy group, there were two local progressions and six regional or distant progressions. 5-year freedom from locoregional or distant progression in the intention-to-treat population was 96% (95% CI 92–98) in the salvage radiotherapy group versus 96% (91–98) in the adjuvant radiotherapy group (appendix p 1). 8-year freedom from locoregional or distant progression was 93% (95% CI 89–98) versus 91% (85–97). 5-year overall survival was 98% (95% CI 96–99) with salvage radiotherapy versus 99% (97–100) with adjuvant radiotherapy. 8-year overall survival was 97% (95% CI 94–100) with salvage radiotherapy and 92% (85–99) with adjuvant radiotherapy. 12 patients had died as of June 30, 2018 (seven in the adjuvant radiotherapy group; five in the salvage radiotherapy group), with only one death attributed to prostate cancer, which occurred in the adjuvant radiotherapy group. Additional causes of

	Adjuvant radiotherapy (n=166)	Salvage radiotherapy (n=167)
Age at randomisation, years		
Mean, SD	63·3 (6·2)	63·4 (6·2)
Median, range	63·8 (44·0–75·0)	63·9 (47·1–76·5)
ECOG performance status score		
0	148 (89%)	143 (86%)
1	18 (11%)	24 (14%)
Preoperative PSA (ng/mL)		
Mean, SD	10·2 (12·4)	9·0 (6·2)
Median, range	7·4 (1·2–137·0)	7·4 (0·6–39·7)
Gleason score		
6	6 (4%)	4 (2%)
7	135 (81%)	138 (83%)
8	5 (3%)	6 (4%)
9	20 (12%)	19 (11%)
Positive surgical margins		
No	56 (34%)	54 (32%)
Yes	110 (66%)	113 (68%)
Seminal vesicle involvement		
No	135 (81%)	134 (80%)
Yes	31 (19%)	33 (20%)

Data are mean (SD), median (range), or n (%). ECOG=Eastern Cooperative Oncology Group. PSA=prostate-specific antigen.

Table: **Baseline characteristics**

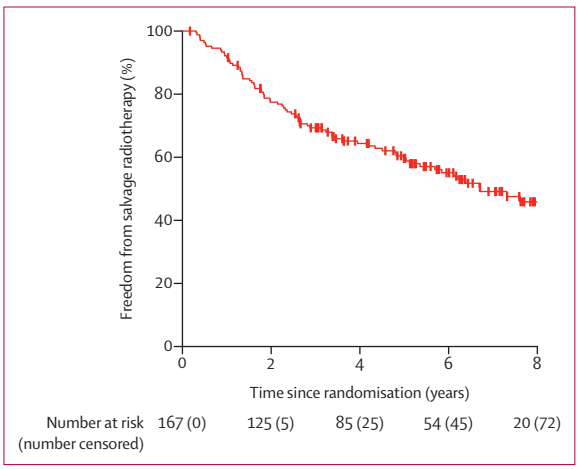

Figure 2: **Freedom from radiotherapy for patients in the salvage radiotherapy group**

death included other malignancies (adjuvant radiotherapy n=1; salvage radiotherapy n=2), comorbidities (adjuvant radiotherapy n=2; salvage radiotherapy n=2), and other or unknown (adjuvant radiotherapy n=3; salvage radiotherapy n=1). Disease-specific survival and biochemical progression-free survival were not analysed because of the very low number of events.

Subgroup analyses of freedom from biochemical progression in the intention-to-treat population according to the risk stratification variables (preoperative PSA, positive surgical margins, Gleason score, extraprostatic extension, and seminal vesicle involvement) identified no subgroup that appeared to obtain particular benefit from adjuvant radiotherapy (figure 4).

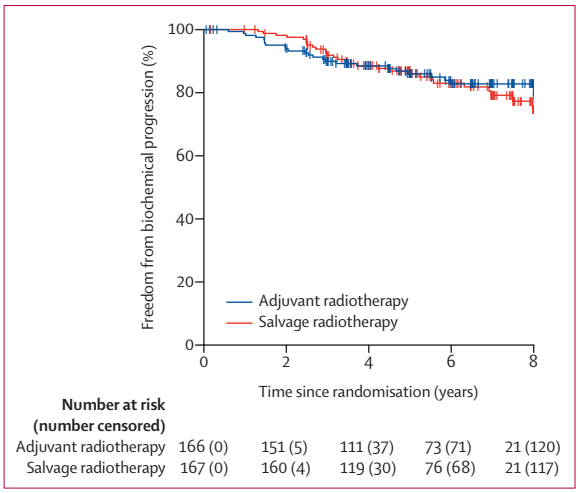

Figure 3: **Freedom from biochemical progression by treatment group**

The grade 2 or worse genitourinary toxicity rate was lower in the salvage radiotherapy group (90 [54%] of 167) than in the adjuvant radiotherapy group (116 [70%] of 166; OR_{mixed} 0·34, 95% CI 0·17–0·68; p=0·0022; figure 5). The grade 2 or worse gastrointestinal toxicity rate was similar in the salvage radiotherapy group (16 [10%] of 167) and in the adjuvant radiotherapy group (24 [14%] of 166; OR_{mixed} 0·48, 95% CI 0·05–4·88; p=0·53; figure 6). Erectile dysfunction was high in both groups: 160 (96%) of 167 in the salvage radiotherapy group and 162 (98%) of 166 in the adjuvant radiotherapy group had grade 2 or worse toxicity. No deaths, unexpected adverse events, or serious adverse events related to the study treatment occurred in either group. Genitourinary, gastrointestinal, and erectile adverse events are shown in the appendix (p 2). No patients withdrew from the trial because of study-related toxicities.

There was no difference in time to starting androgen deprivation therapy use between groups (HR 0·70, 95% CI 0·32–1·52; appendix p 3). Few patients started androgen deprivation therapy during the study (15 adjuvant radiotherapy, 11 salvage radiotherapy).

Discussion

The RAVES trial shows similar biochemical control rates between adjuvant radiotherapy and early salvage radiotherapy with 5-year freedom from biochemical progression of 86% in the adjuvant radiotherapy group compared with 87% in the salvage radiotherapy group. Although the study was underpowered for non-inferiority, these findings support our hypothesis that salvage radiotherapy does not have a freedom from biochemical progression rate that is more than 10% inferior to adjuvant radiotherapy. With such similar rates of biochemical control, meaningful differences in clinical

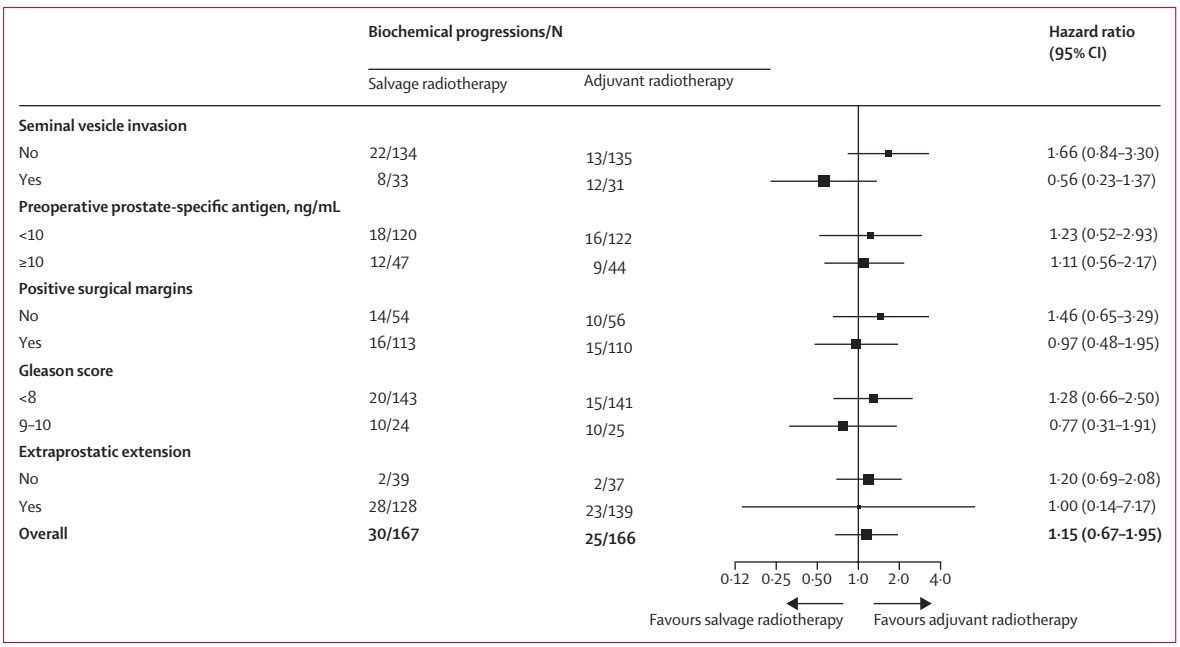

Figure 4: **Freedom from biochemical progression according to known prognostic factors**

outcomes (eg, metastatic disease or prostate cancer mortality) are unlikely to be seen with longer follow-up in this cohort. On the basis of the findings of our trial, it would appear that local eradication of disease in the prostate bed is equally effective for radiotherapy given in the adjuvant setting and salvage setting, provided salvage radiotherapy is given when the PSA rises to 0·20 ng/mL, or soon thereafter.

It is notable that in our trial, the high rates of freedom from biochemical progression and minimal difference between adjuvant radiotherapy and salvage radiotherapy were achieved using 64 Gy, which might be considered a relatively modest dose in the salvage setting. A previous meta-analysis has suggested that salvage doses of more than 70 Gy are most efficacious in salvage radiotherapy,[19] but perhaps this recommendation needs reconsidering if salvage radiotherapy is delivered when the PSA concentration is 0·20 ng/mL.

American (ASTRO or AUA)[2] and European (EUA-ESTRO-SIOG)[20] guidelines recommend that patients with high-risk features post-prostatectomy should be offered adjuvant prostate bed radiotherapy, based on three randomised trials first published between 2005 and 2007 comparing adjuvant radiotherapy with surgery alone.[5–7] The European guidelines state that patients who have extraprostatic extension and positive surgical margins were the subgroup that sustained greatest benefit from this treatment. However, the three randomised trials have been criticised as many patients in the surgery alone group never received salvage radiotherapy or, if they did, it was given very late. Because of this factor and concerns about the potential toxicity of post-prostatectomy radiotherapy, use of adjuvant

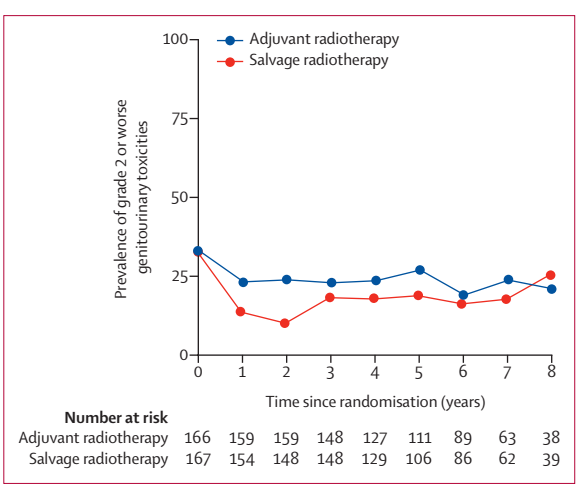

Figure 5: **Prevalence of grade 2 or worse genitourinary toxicities**

radiotherapy was as low as 10% in one series.[8] This controversy is reflected in the American guidelines which state that "a pressing clinical question is whether the administration of radiotherapy is better in an adjuvant radiotherapy context (before recurrence) after radical prostatectomy or as salvage radiotherapy (after detection of recurrence)".

A point of interest is that 5-year freedom from biochemical progression for the adjuvant group in our trial (86%) was significantly better than for those in the EORTC 22911 adjuvant group[6] (74%), despite both studies having similar rates of rising PSA (50%) in the observation group. We suspect this finding is due to better patient selection for those who might benefit from

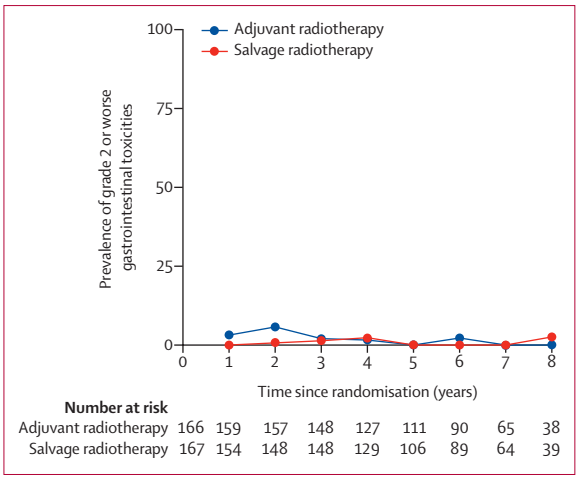

Figure 6: **Prevalence of grade 2 or worse gastrointestinal toxicities**

prostate bed radiotherapy. Such patients are those with a higher risk of residual local disease but a lower risk for metastases, which includes having T3 disease or positive surgical margins, but also an undetectable PSA post-surgery (mandated in our trial), Gleason score 6–7 disease (283 [85%] of 333 in our study), and no seminal vesicle invasion (269 [81%] of 333). Our subgroup analysis did not provide any suggestion of benefit of adjuvant radiotherapy in any of our subgroups considered high risk, although numbers of events in these subgroups were very small.

Another important question is whether we achieved the primary aim of our study and provided support that early salvage radiotherapy is not inferior to adjuvant radiotherapy. We showed that the plausible range in absolute difference between salvage radiotherapy and adjuvant radiotherapy at 5 years was from 6·8% inferior to 8·7% superior, which satisfied our hypothesis that salvage radiotherapy was not 10% worse than adjuvant radiotherapy at 5 years. However, our stratified HR of 1·12 had an upper one-sided 95% confidence limit of 1·90, which crossed the protocol specified 1·48 threshold of supporting non-inferiority.

The publication of the RAVES trial has been intentionally coordinated with the RADICALS[21] and GETUG-17[22] trials with a pre-planned meta-analysis[23] totalling 2153 patients. The concordance between these trials is strong and is consistent with the conclusions of the RAVES trial. We therefore feel that an approach of observation with early salvage radiotherapy does not compromise disease control endpoints compared with adjuvant treatment in this cohort of patients.

The primary limitation of our trial was its premature closure due to the substantially better than expected control rate in both groups resulting in an unexpectedly low event rate and reduced power of the study. However, with such similar control rates between groups and the concordance of findings with the larger RADICALS and GETUG-17 trials, the likelihood that early salvage radiotherapy is clinically inferior to the adjuvant approach in this cohort becomes very small. Caution should be taken extrapolating these findings to higher risk populations including those with residual PSA readings post-prostatectomy, node-positive patients, or those with a combination of very high-risk features (eg, Gleason score 9–10 with seminal vesicle invasion). Another important limitation of all three trials is that they provide no information for the effectiveness of giving salvage radiotherapy at higher PSA concentrations (eg, >0·5 ng/mL), which is commonly practised.

What now should be the standard of care for patients with prostate cancer at high risk post-prostatectomy? On the basis of the results of this study, we feel most clinicians would favour early salvage radiotherapy to the prostate bed when the PSA has reached 0·20 ng/mL over adjuvant radiotherapy for a T3 or margin-positive prostate cancer to spare those men who were not likely to relapse the added morbidity of an unnecessary treatment. However, the treatment landscape has become more complicated with three randomised trials showing a benefit with the addition of androgen deprivation therapy to salvage prostate bed radiotherapy.[24–26] The SPPORT trial[26] has also shown a 5-year freedom from disease progression benefit with the addition of pelvic nodal treatment to prostate bed irradiation and androgen deprivation therapy. In contrast to these trials suggesting a benefit of treatment intensification, the EUA have produced guidelines[27,28] describing a low-risk relapse group post-prostatectomy, such as those with doubling time greater than 1 year or Gleason score less than 8, with low rates of clinical progression at 5–10 years. Salvage treatment approaches will therefore need to be individualised according to the pathology of the radical prostatectomy, the rate of recurrence, and patient wishes. Given the results of our study, a patient with a Gleason score of 7 and margin-positive tumour recurring 3–5 years after surgery is likely to do very well with radiotherapy to the prostate bed alone when the PSA is not more than 0·20 ng/mL. A high-risk recurrence (eg, a Gleason 8–10 tumour with a rapid doubling time) might best be considered for androgen deprivation therapy plus radiotherapy to the prostate bed and nodes, while patients at low risk of recurrence could probably do well with no treatment at all. More recently, PET-PSMA scanning is changing prostate cancer management, especially in the post-prostatectomy scenario,[29] and will undoubtedly need to be incorporated into treatment decision making. Tumour biology and genomic analysis might also hold important answers to the question of who needs to be treated and how.[30] More than 200 patients in the RAVES trial have consented to our genetic sub-studies and this work will help contribute to our understanding on this subject.

In conclusion, early salvage radiotherapy results in similar biochemical control to adjuvant radiotherapy,

spares approximately half of men from pelvic radiotherapy, and is associated with significantly lower amounts of genitourinary toxicity. These data support favouring early use of salvage radiotherapy over adjuvant radiotherapy for patients at high risk post-prostatectomy.

Contributors

AK was co-chair and part of the executive, trial management, and technical quality assurance committees, was responsible for study design and management, and was the lead principal investigator in Australia responsible for patient recruitment, data collection, data interpretation, figures, and writing. CF-B was responsible for the trial management committee, project management, data review, and interpretation and writing. GMD was part of executive and trial management committees, and was responsible for study design, data interpretation, writing, and data collection as a local investigator. RF was part of the executive and trial management committees, and responsible for study design, statistics, and data interpretation. MF was part of the executive and trial management committees, and responsible for study design, patient recruitment, and was a specialist urology advisor. AHe was part of the executive and trial management committees and responsible for statistics, data interpretation, figures, and writing. SGW was part of the executive and trial management committees, and responsible for study design, data interpretation, writing, and data collection as a local principal investigator. WD was part of the trial management committee, and was responsible for central pathology review programme development and implementation, study design, data collection, and report review. AHa was part of the trial management committee, was the technical quality assurance committee chair, and responsible for study design, radiotherapy quality assurance programme development and management, and report review. DJJ was part of the trial management committee, and responsible for data interpretation, patient recruitment, data collection, and report review as a local principal investigator. JMM was part of the trial management committee, and responsible for data interpretation, patient recruitment, data collection, and report review as a local principal investigator. JHLM was part of the trial management committee, and responsible for data interpretation, patient recruitment, data collection, and report review as a local investigator. JLM was part of the trial management committee, and responsible for patient recruitment, data collection, and report review as a local investigator. MS was part of the technical quality assurance committee, was a radiotherapy quality assurance reviewer, and was responsible for data interpretation, patient recruitment, data collection, and report review as a local principal investigator. NS was part of the trial management committee, and responsible for data interpretation, patient recruitment, data collection, and report review as a local investigator. CIT was part of the technical quality assurance committee, was a radiotherapy quality assurance reviewer, and was responsible for data interpretation, patient recruitment, data collection, and report review as a local principal investigator. ST was part of the trial management committee, and responsible for data interpretation, patient recruitment, data collection, and report review as a local principal investigator. KLW was part of the trial management committee and the technical quality assurance committee, was a radiotherapy quality assurance reviewer, and was responsible for radiotherapy quality assurance programme development, data interpretation, patient recruitment, data collection, and report review as a local investigator. HHW was part of the trial management committee, and responsible for study design, patient recruitment, and report review, and was a specialist urology adviser. IDD was responsible for study management and outreach, data interpretation, and report review. TSL was a local principal investigator, and responsible for patient recruitment, data collection, and report review. MP was co-chair and part of the executive, trial management, and quality assurance committees, was responsible for study design and management, and as lead principal investigator in New Zealand was responsible for patient recruitment, data collection, data interpretation, figures, and writing. CB was responsible for statistics, data interpretation, figures, and writing.

Declaration of interests

IDD reports grants from Cancer Australia and the National Health and Medical Research Council during the conduct of the study; institutional payments to support prostate cancer research outside the submitted work from Pfizer, Australian and New Zealand Urogenital and Prostate (ANZUP) Cancer Trials Group, Bayer, Astellas, Janssen, the Movember Foundation, AstraZeneca, Merck Sharp & Dohme, Roche/Genentech, Tokai, and Bristol Myers Squibb and serves as the unremunerated chair of the ANZUP Cancer Trials Group. CF-B reports grants from New Zealand Health Research Council, Australian National Health and Medical Research Council, the Auckland Hospital Charitable Trust, Trans-Tasman Radiation Oncology Group (TROG) Seed Funding, and the Cancer Research Trust New Zealand during the conduct of the study. JMM reports a grant from Mundipharma and personal fees from Ferring Pharmaceuticals, Janssen, and Sanofi outside the submitted work. HHW reports personal fees from Astellas, Janssen, AstraZeneca, Mundipharma, Boston Scientific, Teleflex, and AbbVie during the conduct of the study. All other authors declare no competing interests.

Data sharing

Secondary analyses of these trial data are encouraged, subject to review by the TROG scientific committee. Once all planned analyses have been completed, de-identified individual participant data and a data dictionary will be made available to the scientific community upon formal application once publication of primary and secondary analyses are complete. All applications will be reviewed per the Trans-Tasman Radiation Oncology Group's policy statement on Undertaking Secondary Analyses on TROG Trials. Approval of applications will be granted by the TROG secondary analysis committee in collaboration with the trial management committee for the RAVES trial. Please contact trog@trog.com.au for further details on application procedure or to receive a copy of the study protocol.

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