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A Phase III Multi-Centre Randomised Trial comparing adjuvant versus early salvage Radiotherapy following a Radical Prostatectomy: Results of the TROG 08.03 and ANZUP "RAVES" Trial

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Summary

Background:

Adjuvant radiotherapy (ART) has been shown to halve the risk of biochemical failure (BF) for patients with high risk disease after radical prostatectomy (RP). Early salvage radiation therapy (SRT) may result in similar biochemical control with lower treatment toxicity. We aimed to compare biochemical failure between patients treated with ART versus those treated with SRT.

Methods:

Patients with extraprostatic extension (EPE), seminal vesicle invasion (SVI), or positive surgical margins (PSM), ECOG performance status 0-1, and a post-operative PSA ≤0·10 ng/mL were randomised centrally 1:1 via independently generated allocation to either ART within 6 months of RP or early SRT triggered by a PSA of ≥0·20 ng/mL. Patients were stratified by radiotherapy centre, pre-operative PSA, Gleason score, and PSM and SVI status (NCT00860652). Radiation therapy in both arms was 64 Gy to the prostate bed without androgen deprivation with real time review of plan quality performed on all cases before treatment. The primary endpoint was time to biochemical failure (TTBF) with BF defined as PSA rise ≥0·40 ng/mL. SRT would be deemed non inferior to ART if BF within 10% of ART at 5 years with a hazard ratio (HR) for SRT:ART of 1·48. The primary analysis was conducted on an intention to treat basis.

Findings:

333 patients (median age 64 years, IQR 59-68) were randomised (166 ART; 167 SRT) across 32 institutions between 03/26/2009 and 12/31/2015. Median follow-up was 6·1 years (IQR 4.3, 7.5). An Independent Data Monitoring Committee recommended premature closure to enrolment because of unexpectedly low event rates. On pathological staging, 64 patients (19%) had SVI, 257 (77%) EPE, 224 (67%) PSM and 51 (15%) Gleason score 8-10. 84 SRT patients (50·3%) had RT triggered by PSA ≥0·20. The 5-year FFBF rates for the ITT population were 86% (95% CI 80-90) in the ART arm versus 87% (95% CI 82-91) in the SRT arm (hazard ratio 1·12; 95% CI 0·65-1·90; p=0·15). The grade 2+ GU toxicity rate was lower in the SRT arm (OR 0·34, 95% CI 0·17-0·68, p=0·002) whilst Grade 2+ GI toxicity was similar for both arms (OR 0·48, 95% CI 0·05-4·88, p=0·53).

Interpretation:

SRT did not meet trial specified criteria for non-inferiority. However, these data support the use of SRT as it results in similar biochemical control to ART, spares approximately half of men from pelvic radiation, and is associated with significantly lower levels of GU toxicity.

Funding:

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Research in context

Evidence before this study

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

Added value of this study

This study confirmed that men with high risk features have a more than 50% rate of a rising PSA following surgery when observed. Our results have demonstrated that early salvage therapy is similar to adjuvant radiation, with both approaches resulting in very high rates of patients being biochemically free of cancer at five years. This has been achieved with relatively modest radiation doses in the salvage group by treating relapse very early when the PSA is 0·20 ng/mL. The study has also documented an increase in genito-urinary morbidity when radiation therapy 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 radiation therapy, which would spare many men from potential RT related side effects.

Introduction

Radical prostatectomy (RP) is the most frequently employed treatment modality for men with clinically localised prostate cancer.[1] Historically, one third of patients develop recurrent disease,[2] though with better selection and contemporary surgical techniques the rate may be closer to 20%.[3] The risk of recurrence is greater among men with high risk features, including extra-prostatic extension (EPE), seminal vesicle invasion (SVI), and positive surgical margins (PSM).[4]

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

The primary aim of the RAVES trial was to test the hypothesis that for patients with pT3 disease and/or positive margins following radical prostatectomy, observation with early salvage radiation therapy is non-inferior to “standard” treatment of adjuvant radiation therapy with respect to biochemical failure.

Methods:

Study design

This phase III, multicentre, randomised controlled, non-inferiority trial was conducted in 32 radiation therapy 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 (USANZ) and the Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP). A table of participating sites and summary recruitment is available in the Appendix (Supplementary Materials), page 3. The protocol was approved by institutional ethics review boards, and is publicly available at: https://www.trog.com.au/TROG-0803-trial-documents.

Participants

Eligible patients were at least 18 years of age, had undergone a radical prostatectomy for adenocarcinoma of the prostate with pathological staging showing high risk features defined as either PSM, EPE, or SVI, as identified by local pathologists. Patients were also required to have a postoperative PSA level of ≤0·10 ng/mL, needed to be able to start radiation therapy (RT) within four months of RP (extended to permit RT within up to six months in an 8 July 2011 protocol amendment), and have an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1. Exclusion criteria included androgen deprivation (AD) before or after RP, previous pelvic RT, total hip

replacement, or evidence of nodal or distant metastases. Patients with co-morbidities that would interfere with the completion of treatment and/or five years of follow-up were also excluded. Participants were recruited in urology and radiation therapy clinics. All patients provided written informed consent before treatment. Separate consent was provided for optional translational research sub-studies.

Randomisation

Patients were randomised 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. Randomisation outcome was not masked, and subsequent arm assignments were concealed from all study staff. Stochastic dynamic minimisation (i.e. minimisation) was used to randomly assign patients 1:1 to either ART within four months (six after 2011) post RP, or to SRT within four months of PSA ≥0·20 ng/mL. Use of androgen deprivation with either adjuvant or salvage radiotherapy was not allowed. Patients were stratified by seminal vesicle involvement (pT3b: yes/no), Gleason score (continuous), pre-operative PSA (continuous), surgical margin status (positive/negataive), and radiation therapy institution. Following randomisation, TROG conducted remote source data verification of eligibility data. RP histological specimens were obtained after randomisation for central pathological review, but reporting is based on pathology results from local institutions.

Procedures

To ensure uniform RT compliance with protocol requirements, a pre-recruitment credentialing programme was implemented. Credentialing involved participating radiation oncologists and treatment centres completing a contouring and planning exercise using 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 radiation therapy plan review and re-submission prior to treatment starting if unsatisfactory. An additional credentialing process was completed at the time centres moved from 3D conformal based planning to intensity modulated radiation therapy.

Target volume specifications were based on post-prostatectomy radiation therapy consensus guidelines from the Faculty of Radiation Oncology Genito-Urinary Group (FROGG).[10] In short, the clinical target volume of the prostate bed extended from 5 to 6 mm below the anastomosis up to the level of the base of the seminal vesicles (SV) incorporating all of the surgical bed/clips unless the SVs were involved, in which case all of the residual SVs 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 radiation therapy arms was 64 Gy in 32 fractions, and the mean dose with IMRT/VMAT 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]

Prior to randomisation, pre-operative 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 co-morbid conditions)[13] were recorded. Adverse events were scored by clinicians per NCI Common Terminology Criteria for Adverse Effects (CTCAE) Version 3·0.[14] The CTCAE genito-urinary (GU) domains included cystitis, urinary incontinence, urethral stricture/stenosis, urinary frequency/urgency, urinary retention, and haemorrhage GU. Gastro-intestinal (GI) domains included diarrhoea, proctitis, haemorrhage GI (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 QLQ-PR25[16] questionnaires Version 3, the Hospital Anxiety and Depression Scale (HADS),[17] and the Sexual Health Inventory for Men.[18] Detailed analyses of patient-reported outcomes and time to hormonal treatment are the subject of a separate manuscript to enable focus on this large body of data.

For all patients having ART or SRT, clinician-scored adverse events and the QLQ-C30, PR25, and HADS questionnaires were repeated on day one of RT, at the end of RT, six weeks after RT. Patients in both arms had clinical follow up six monthly for five years and annually thereafter. Annual assessments consisted of clinician-scored adverse events per CTCAE criteria, disease status, and all patient questionnaires.

For the ART arm, following radiotherapy PSA was measured six weeks after RT and then six monthly relative to randomisation thereafter. PSA measurement was more frequent in the SRT arm to ensure early delivery of SRT should the PSA rise to 0·20 ng/mL or higher. During the surveillance phase, PSA was measured every three months from randomisation during the first five years, and then six monthly thereafter. For patients proceeding to SRT, PSA was measured on day one of RT, six weeks after the end of RT, and then six monthly relative to randomisation thereafter.

For both arms, biochemical failure (bF) was diagnosed on the first occasion following radiotherapy that the serum PSA was $\geq$ 0.40 ng/mL and rising from the previous value. A confirmatory PSA test was performed if clinically indicated, with the date of bF considered to be the date of the first PSA level $\geq$ 0.40 ng/mL. Time to BF was measured from the date of randomisation to the date of BF. For patients randomised to SRT, a PSA result that was $\geq$ 0·40 ng/mL but less than the PSA result from day one of RT did not constitute biochemical failure. In patients who did not receive radiation therapy per randomisation, BF based on PSA was deemed to have occurred when the PSA was ≥0·40 ng/mL.

Biochemical failure (BF) was also defined as the commencement of androgen deprivation for any reason; or loco-regional or metastatic clinical progression if any of these events occurred before a PSA result of $\geq$ 0·40 ng/mL was measured. Time to local, regional, or distant failure was defined as the time from the date of randomisation to the date of documented failure. Local failure was defined as documented

palpable or biopsy-proven local failure per institutional standard of care and in later periods of the study a positive PSMA PET scan. Diagnosis of nodal failure was required to be confirmed by CT scan, 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. No patients were withdrawn due to study-related toxicities. 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 objective was to show Freedom from Biochemical Failure (FFBF) at five years with SRT was within 10% of that seen with ART. PSA measurements were done by local laboratories, and source data verification was conducted centrally for all PSA results meeting the definition for biochemical failure.

Secondary objectives comparing between the two arms CTCAE-scored genito-urinary and gastro-intestinal adverse events of grade 2 or higher, time to initiation of androgen deprivation therapy, freedom from local, regional and distant failure, and overall survival are the focus of this report. Additional secondary objectives were to compare the two treatment arms with respect to quality of life, anxiety/depression, adverse events, biochemical failure-free survival, disease specific survival, time to local and distant failure, quality adjusted life years, and cost utility. Due to the large volume of toxicity data and patient recorded outcomes, a more comprehensive toxicity analysis, including time to toxicity, will be the subject of a subsequent manuscript.

Statistical analysis

Power calculations were based on the five year FFBF rate of 74% observed in the standard arm (ART) of the EORTC trial 22911.[6] SRT would be considered to be non-inferior to ART if its five year FFBF was at most 10% lower than the five year FFBF for ART (i.e. >64%). Assuming proportional hazards, FFBF rates of 74% versus 64% at five years correspond to a hazard ratio (HR) for SRT:ART of 1·482. Given these parameters and allowing for drop-outs, it was estimated that a sample size of 470 patients accrued over 4·7 years with five years of follow-up would be required to provide 80% power to detect non-inferiority with a one-sided 5% type one error.

Time-to-event outcomes were compared between arms using Cox proportional hazards regression to estimate hazard ratios and their 95% CIs and using the log-rank test along with tests for interaction of various predictors for FFBF with regards to treatment arm. These predictors were the following stratification variables: seminal vesicle involvement (present/absent), Gleason score, pre-operative PSA, and margin positivity (present/absent).

For analysis of adverse events, odds ratios (OR) for the relationship between treatment arm and for prevalence of grade 2+ or grade 3+ toxicities of various types were derived from mixed effects logistic regression models, with treatment arm as a fixed effect and patient as a random effect. This was changed (prior to any analysis) from the pre-planned analysis of time-to-toxicity as it was considered informative. Analysis of the primary objective was conducted according to both intention-to-treat (ITT) and per-protocol (PP) methods, with the PP analysis planned to assess consistency regarding non-inferiority conclusions. The PP analysis excluded patients who received treatment outside of the protocol treatment timings. All analyses of secondary endpoints used the ITT population. The R statistical software package (Version 3.6, R Core Team, Vienna, Austria) was used for all analyses. The trial is registered on ClinicalTrials.gov: NCT00860652.

An Independent Data Monitoring Committee (IDMC) was established at study initiation to review toxicity after 200 patients and to review both toxicity and futility after 300 and 400 patients. After the first interim analysis of toxicity in March 2013, the IDMC 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 failure for SRT was significantly inferior to that of ART at the 5% one sided significance level. In March 2015 after 5.9 years of accrual with 303 patients randomised, there were only 17 biochemical failures out of 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 failure free rate at 5 years with a hazard ratio 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 demonstrating non-inferiority of the salvage RT arm, as the low event rate would result in inadequate study power. Increasing the sample size for and study duration to account for the change in assumption was deemed infeasible. The study closed to recruitment on 31 December 2015, and 30 July 2018 was the cut-off date for the primary analysis. Patients will be followed for survival and disease status until a median follow up of 10 years is reached, anticipated in 2022.

Role of the funding source

Competitive grants provided funding for this study, which was supported by the New Zealand Health Research Council, National Health Medical Research Council of Australia, Cancer Council of New South Wales, and the Cancer Council of Victoria. Additional early support was obtained from Auckland Hospital Charitable Trust, Trans-Tasman Radiation Oncology Group Seed Funding, Genesis Oncology Trust, Royal Australia and New Zealand College of Radiologists, Cancer Institute New South Wales, and the Prostate Cancer Foundation of Australia, and Cancer Australia. None of the funders had a role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study, and had final responsibility for the decision to submit for publication.

Results:

Between 27 March 2009 and 31 December 2015, 333 patients were randomised across 32 institutions in Australia and New Zealand (n=166 ART; n=167 SRT). Arm allocation, compliance, and follow up are shown in Figure 1. A total of 24 patients did not complete study follow-up as per protocol. Median follow up was 6·1 years (IQR 4.3, 7.5). Demographics and baseline features were well balanced between arms (Table 1).

Eighty-four patients in the SRT arm experienced a PSA $\geq$0·20 ng/mL to trigger radiation therapy (one of these requested SRT following a PSA of 0·17 ng/mL), (Figure 2). The number of patients treated and followed per protocol in each arm is shown in Figure 1.

Figure 3 outlines the ITT analysis of the primary endpoint. There were 25 failures in ART and 30 failures in the SRT arm. The five year FFBF rates were 86% (95% CI 81-92) in the ART arm compared with 87% (95% CI 82-93) in the SRT arm. The eight year rates were 80% with ART (95% CI 72-89) and 75% (95% CI 67-85) with SRT. The hazard ratio for the SRT arm on univariate analysis was 1·15 (95% CI 0·67-1·95). On multivariate analysis when incorporating stratification variables (Table 5), the hazard ratio for the SRT arm was 1·12 (95% CI 0·65-1·90*).* The proportional hazards assumption was tested and met. The one-sided test of non-inferiority had p=0·15.

An analysis of the primary end point was performed as per protocol (PP) population, which included 311 patients; 158 in the ART arm (seven were excluded for not having RT and one had ART late) and 153 in the SRT arm (four did not have SRT as per protocol and ten either did not receive RT or were lost to follow up). At five years, the FFBF rates were 86% (95% CI 81-92) in the ART arm compared with 88% (95% CI 83-94) in the SRT arm and at eight years 80% with ART (95% CI 72-89) versus 79% (95% CI 70-88) with SRT. The hazard ratio for the SRT arm on multivariate analysis when incorporating stratification variables was 0·90 (95% CI 0·50-1·61). The one-sided test of non-inferiority had p=0·047.

Analyses of time to local and time to distant failure were combined due to the low number of failure events. The 5 year Freedom from loco-regional or distant failure (FFLRDF) rates for the ITT population were 96% (95% CI 93-99) in the ART arm compared with 96% (95% CI 93-99) in the SRT arm. FFLRDF is shown in the Appendix (Supplemental Materials, page 1). The eight year rates were 91% with ART (95% CI 85-97) and 93% (95% CI 89-98) with SRT. In the ART group, there were no local failures and ten regional or distant failures. In the SRT group there were two local failures and six regional or distant failures. The five year overall survival rates were 99% (95% CI 97-100) in the ART arm compared with 98% (95% CI 96-99) in the SRT arm. The eight year rates were 92% with ART (95% CI 85-99) and 97% (95% CI 94-100) with SRT. Twelve patients had died as of 30 June 2018 (7 ART; 5 SRT), with only one death attributed to prostate cancer, occurring in the ART arm. Additional causes of death included other malignancies (ART 1; SRT 2), co-morbidities (ART 2; SRT

2), and other/unknown (ART 2; SRT 2). Disease specific survival and biochemical failure free survival were not analysed due to the very low number of events.

Figure 4 describes outcome according EPE and known risk stratification variables for the ITT population, pre-operative PSA (<10 versus ≥10 ng/mL), PSM, Gleason score (<8 versus 8–10) and EPE. There was no subgroup where five year freedom from progression favoured either arm.

Figures 5 and 6 demonstrate the prevalence of Grade 2+ GU and GI toxicities respectively. The grade 2+ GU toxicity rate was lower in the SRT arm (90/167) than in the ART arm (116/166), (OR_{mixed} 0·34, 95% CI 0·17-0·68), p=0·002. The grade 2+ GI toxicity rate was similar in the SRT arm (16/167) compared with 24/166 in the ART arm (OR_{mixed} 0·48, 95% CI 0·05-4·88), p=0·53). Erectile dysfunction was high in both arms with 160/167 in the SRT arm and 162/167 in the ART arm experiencing grade 2+ toxicity. No deaths, unexpected adverse events, or serious adverse events related to the study treatment occurred in either group. A tabulation of GU, GI, and erectile adverse events is available in the Appendix (Supplementary Materials, page 2).

Figure 8 in the Appendix (Supplementary Materials, page 2) shows time to initiation of androgen deprivation therapy (ADT). Few patients started ADT during the study (15 ART, 11 SRT). There was no difference in time to starting ADT use between arms, HR=0.70 95%CI (0.32-1.52).

Discussion

The RAVES trial demonstrates remarkably similar biochemical control rates between adjuvant and early salvage radiotherapy with five and eight year rates of 86% and 79% in the ART arm compared with 87% and 75% with SRT respectively, which supports our hypothesis that SRT does not have a FFBF rate that is more than 10% inferior to ART. With such similar rates of biochemical control, meaningful differences in clinical outcomes, such as metastatic disease or prostate cancer mortality, are unlikely to be seen with longer follow-up in this cohort. Based on the findings of the RAVES trial, it would appear that local eradication of disease in the prostate bed is equally effective for radiation therapy given in the adjuvant and salvage settings, provided SRT is given when the PSA rises to 0·20 ng/mL or soon thereafter. It is notable that in the RAVES trial, the high rates of FFBF and minimal difference between ART and SRT 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 >70Gy are most efficacious in SRT,[20] but perhaps this recommendation needs reconsidering when SRT is delivered at a PSA level of 0·20 ng/mL.

Current American (ASTRO/AUA)[2] and European (EAU-ESTRO-SIOG)[19] guidelines recommend that patients with high risk features post-prostatectomy should be offered adjuvant prostate bed radiotherapy, based on three randomised trials published 15 to 20 years ago

comparing adjuvant radiotherapy with surgery alone. [5-7] The European guidelines state that patients who have extra prostatic extension and positive surgical margins were the subgroup that sustained greatest benefit from this treatment. However, the three randomized trials have been criticized due to the fact that many patients in the surgery alone arm never received salvage radiotherapy, or if they did, it was given very late. Due to this factor and concerns about the potential toxicity of post prostatectomy radiotherapy, utilization of adjuvant 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 RT is better in an ART context (before recurrence) after RP or as SRT (after detection of recurrence)."

A point of interest is that outcomes for the adjuvant arm were significantly better than the EORTC 22911 adjuvant arm[6] (74%), despite both studies having similar rates of rising PSA (50%) in the observation arm. We suspect this is due to better patient selection for those who may benefit from prostate bed radiation therapy. Such patients are those with a higher risk of residual local disease but a lower risk for metastases. This includes having T3 disease or PSM, but also an undetectable PSA post-surgery (mandated in RAVES), Gleason 6 to 7 disease (282/333, 85% in our series), and no SV invasion (269/333, 81%). Our stratification analysis did not provide any suggestion of benefit of adjuvant radiotherapy in any of our "high risk" subgroups, although numbers of events in these subgroups are very small.

Another important question is whether we achieved the primary aim of our study and proved that early SRT is not inferior to ART. We demonstrated that the plausible range in absolute difference between SRT and ART at five years was from 6.8% inferior to 8.7% superior, which satisfied our hypothesis that SRT was not 10% worse than ART at five years. However, our hazard ratio of 1·12 had an upper one-sided 95% confidence limit of 1·90, which crossed the protocol specified 1·48 threshold of proving non inferiority. The release of the RAVES trial has been intentionally co-ordinated 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 very strong. The 5-year event free survival across all three trials was 88% with a hazard ratio of 0·98 (95% CI 0·77-1·25). We therefore feel that an approach of observation with early salvage radiotherapy does not compromise disease control endpoints compared to adjuvant treatment in this cohort of patients.

The primary limitation of the RAVES trial was its premature closure due to the significantly better than expected control rate in both arms resulting in an unexpectedly low event rate and reduced power of the study. However, with such similar control rates between arms 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 must 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 (e.g. Gleason 9-10 with SV invasion). Another important limitation of the three trials is that they provide no information of the effectiveness of giving salvage radiotherapy at higher levels of PSA (e.g. above 0.5) which is commonly practiced.

What now should be the standard of care for high risk prostate cancer patients post prostatectomy? Based on the results of this study, we feel most clinicians would favour early salvage radiotherapy to the prostate bed when the PSA is 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 landscape has become more complicated with three randomised trials demonstrating a benefit with the addition of androgen deprivation (ADT) to salvage prostate bed radiotherapy.[24–26] The recently presented SPPORT trial[26] has also demonstrated a five year freedom from disease progression benefit with the addition of pelvic nodal treatment to prostate bed irradiation and ADT. 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 less than one year or Gleason score less than 8, with low rates of clinical progression at five to ten years. Salvage treatment approaches will therefore need to be individualised according to the pathology of the RP, the rate of recurrence, and patient wishes. Given the results of our study, a patient with a Gleason 7 and margin positive tumour recurring three to five 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 (e.g. a Gleason 8 to 10 tumour with a rapid doubling time) might best be considered for ADT plus RT to the prostate bed and nodes, whilst some low risk recurrences could probably do well with no treatment at all. In many parts of the world, PET-PSMA scanning is changing management, especially in the post prostatectomy scenario,[29] and will undoubtedly need to be incorporated into such decision making. Tumour biology and genomic analysis may also hold important answers.[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.

Conclusion

Early SRT results in similar biochemical control to ART, spares approximately half of men from pelvic radiotherapy, and is associated with significantly lower levels of GU toxicity. These data support favouring early use of salvage radiation therapy over adjuvant radiation therapy for high risk patients post prostatectomy.

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, ANZUP Cancer Trials Group, Bayer, Astellas, Janssen, the Movember Foundation, and serves as the unremunerated chair of the ANZUP Cancer Trials Group. CF reports grants from New Zealand Health Research Council, Australian National Health and Medical Research Council, the Auckland Hospital Charitable Trust, TROG Seed Funding, and the Genesis Oncology Trust 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. HW reports personal fees from Astellas, Janssen, AstraZeneca, Mundipharma, Boston Scientific, Teleflex, and Abbvi during the conduct of the study. The other authors declare no competing interests.

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Author contributions
AK: Co-Chair, Executive, Trial Management, and Technical Quality Assurance Committees, study design and management, lead Principal Investigator in Australia, patient recruitment, data collection, data interpretation, figures, writing.
CF: Trial Management Committee, project management, data review and interpretation, writing.
GMD: Executive and Trial Management Committees, study design, data interpretation, writing, local Investigator, data collection.
RF: Executive and Trial Management Committees, study design, statistics, data interpretation.
MF: Executive and Trial Management Committees, study design, patient recruitment, specialist urology advisor.
AH: Executive and Trial Management Committees, statistics, data interpretation, figures, writing.
SGW: Executive and Trial Management Committees, study design, data interpretation, writing, local Principal Investigator, data collection.
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AH: Trial Management Committee, Technical Quality Assurance Committee Chair, study design, RT quality assurance programme development and management, report review.
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JHLM: Trial Management Committee, data interpretation, local Investigator, patient recruitment, data collection, report review.
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MS: Technical Quality Assurance Committee, RT Quality Assurance reviewer, data interpretation, local Principal Investigator, patient recruitment, data collection, report review.
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CIT: Technical Quality Assurance Committee, RT Quality Assurance reviewer, data interpretation, local Principal Investigator, patient recruitment, data collection, report review.
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MP: Co-Chair, Executive, Trial Management, and Quality Assurance Committees, study design and management, lead Principal Investigator in New Zealand, patient recruitment, data collection, data interpretation, figures, writing.

Data Sharing Statement

Secondary analyses of these trial data are encouraged, subject to review by the TROG Scientific Committee. Once all planned analyses have been completed, ~~the~~ 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 by the Trans Tasman Radiation Oncology Group's policy statement on "Undertaking Secondary Analyses on TROG Trials." Approval of applications will 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.

Figure 1: Consort Diagram

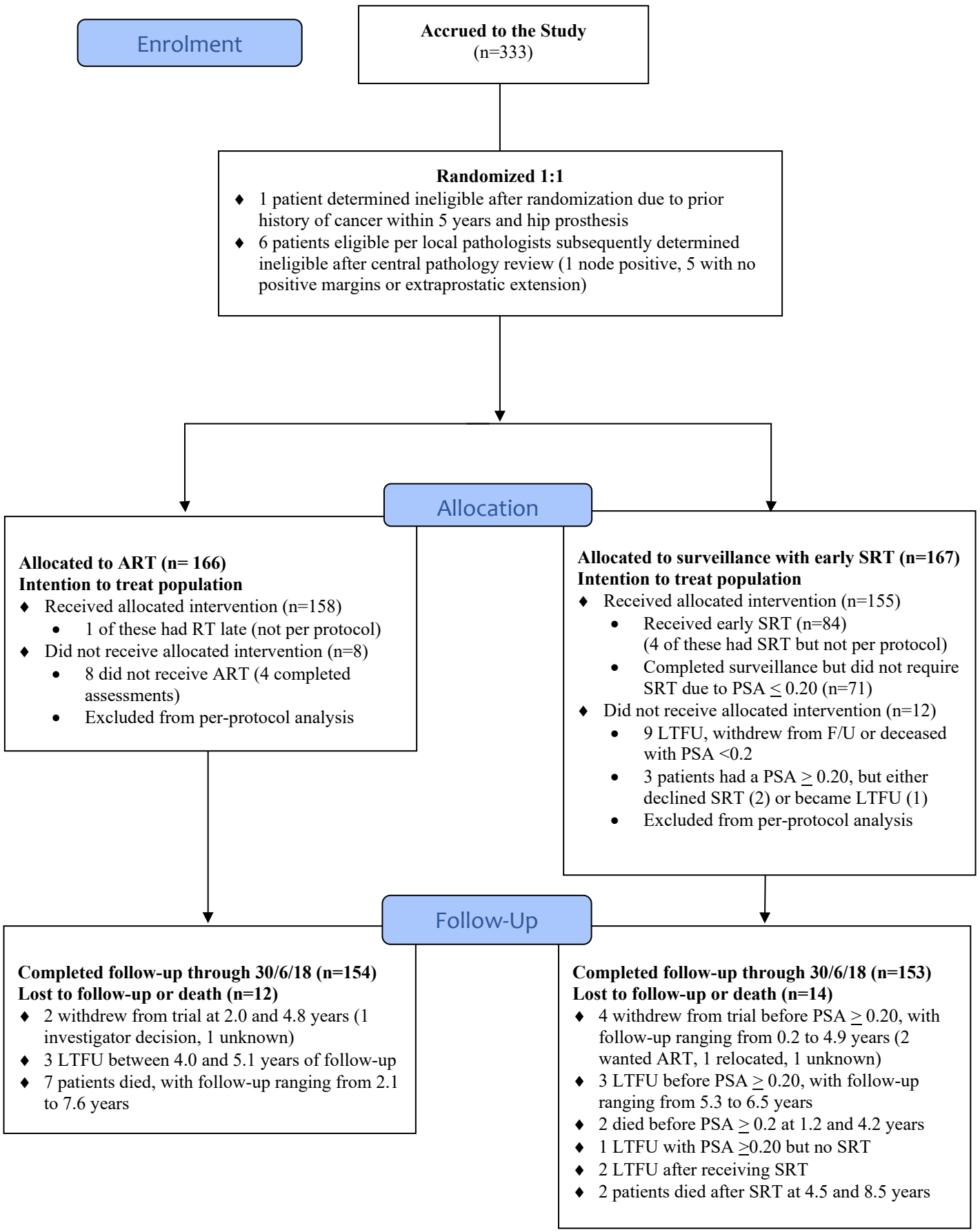


Figure 2: Time to salvage radiotherapy

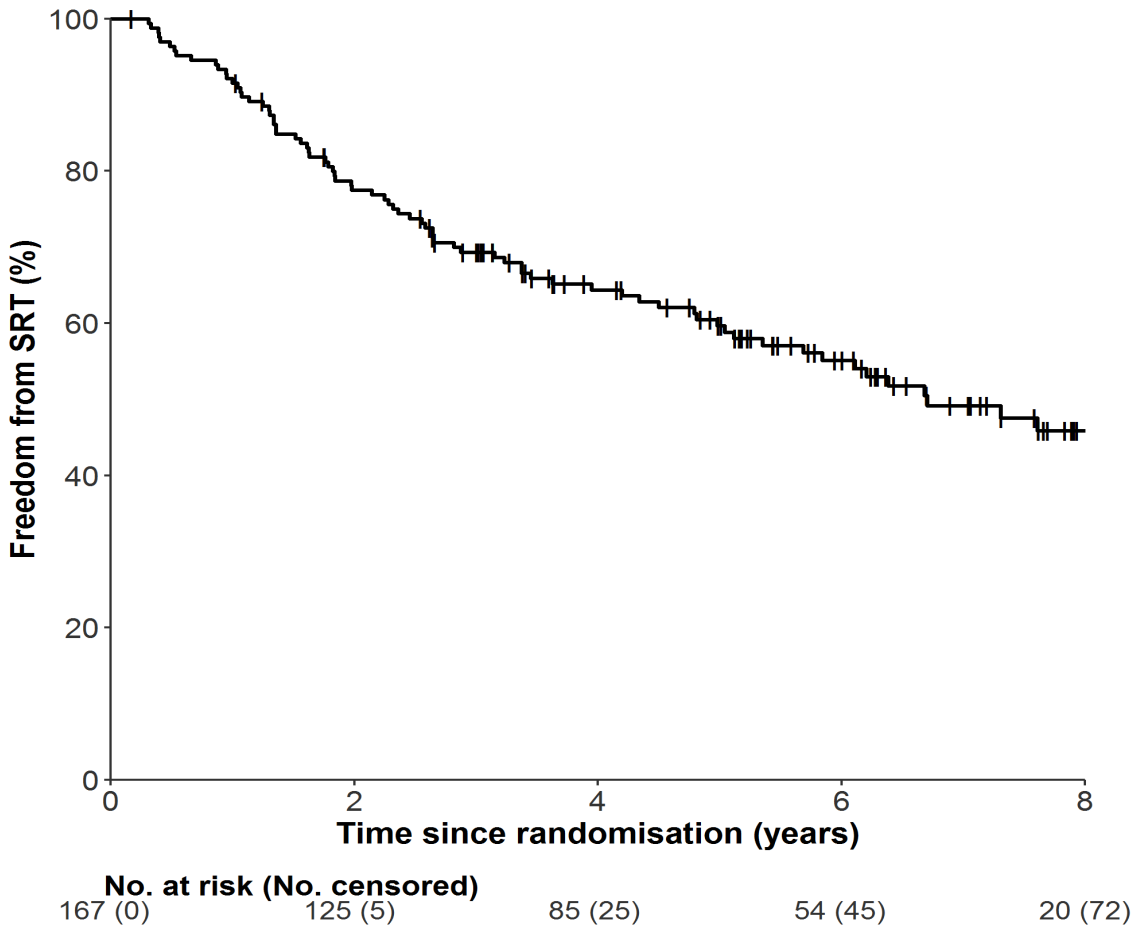
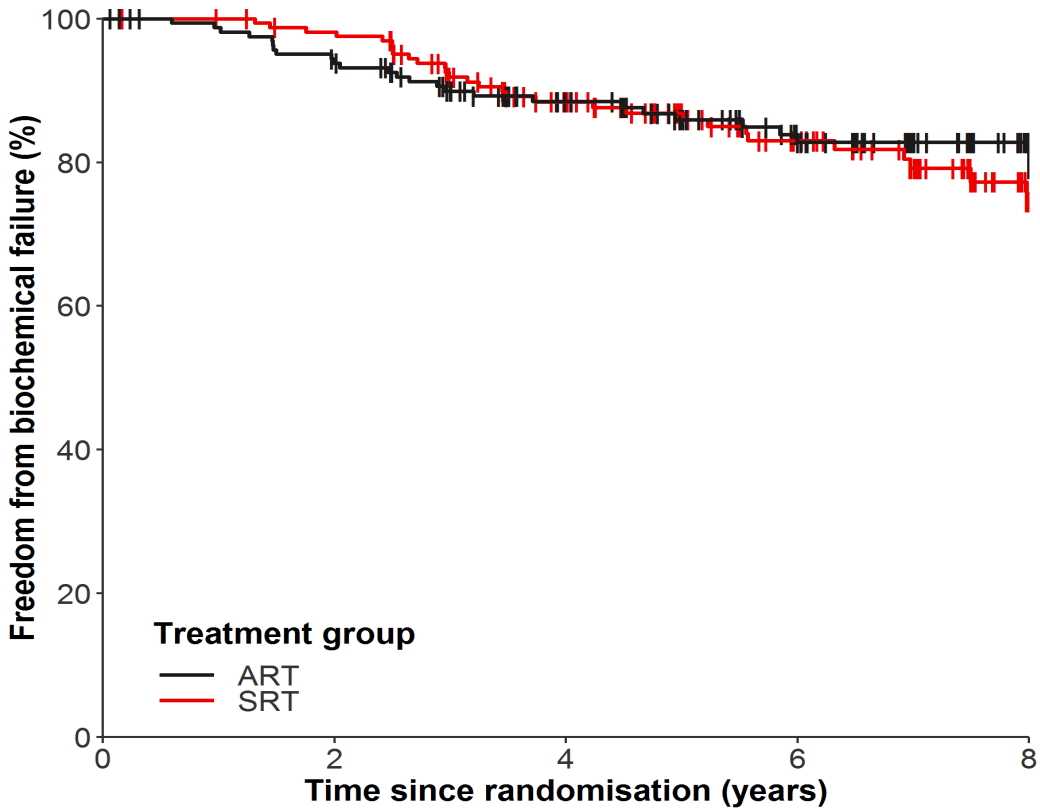


Figure 2. Kaplan-Meier curves of freedom from RT for patients in the SRT treatment arm.

Table 1. Patient characteristics

	Treatment Arm		
Characteristic	**ART (n=166)**	**SRT (n=167)**	**Total (N=333)**
Age at Randomisation, years			
Mean (SD)	63.3 (6.2)	63.4 (6.2)	63.4 (6.2)
Median [range]	63.8 [44.0 - 75.0]	63.9 [47.1 - 76.5]	63.9 [44.0 - 76.5]
Interquartile range	59.5 - 67.8	59.2 - 67.8	59.3 - 67.8
ECOG Performance Score at Randomisation			
0	148 (89.2%)	143 (85.6%)	291 (87.4%)
1	18 (10.8%)	24 (14.4%)	42 (12.6%)
Pre-operative PSA			
Mean (SD)	10.2 (12.4)	9.0 (6.2)	9.6 (9.8)
Median [range]	7.4 [1.2 - 137.0]	7.4 [0.6 - 39.7]	7.4 [0.6 - 137.0]
Interquartile range	5.5 - 10.2	5.3 - 10.4	5.4 - 10.3
Gleason Score			
6	6 (3.6%)	4(2.4%)	10 (3.0%)
7	135 (81.3%)	138 (82.6%)	273 (82.0%)
8	5 (3.0%)	6 (3.6%)	11 (3.3%)
9	20 (12.0%)	19 (11.4%)	39 (11.7%)
Positive Surgical Margins			
No	56 (33.7%)	54 (32.3%)	109 (32.7%)
Yes	110 (66.3%)	113 (67.7%)	224 (67.3%)
Seminal Vesicle Involvement			
No	135 (81.3%)	134 (80.2%)	269 (80.8%)
Yes	31 (18.7%)	33 (19.8%)	64 (19.2%)

Figure 3 Kaplan-Meier curves of freedom from biochemical failure by treatment arm



No. at risk (No. censored)

ART 166 (0)	151 (5)	111 (37)	73 (71)	21 (120)
SRT 167 (0)	160 (4)	119 (30)	76 (68)	21 (117)

Figure 4 Outcome according to known prognostic factors

		ART	SRT	
Level		**Failures / N**	**Failures / N**	
Overall		25 / 166	30 / 167	1.15 (0.67, 1.95)
Seminal vesicle invasion	No	13 / 135	22 / 134	1.66 (0.84, 3.3)
	Yes	12 / 31	8 / 33	0.56 (0.23, 1.37)
Preoperative PSA	<10	16/ 122	18 / 120	1.23 (0.52, 2.93)
	10+	9 / 44	12 / 47	1.11 (0.56, 2.17)
Positive surgical margins	No	10 / 56	14 / 54	1.46 (0.65, 3.29)
	Yes	15 / 110	16 / 113	0.97 (0.48, 1.95)
Gleason score	<8	15/ 141	20 / 143	1.28 (0.66, 2.5)
	8+	10 / 25	10 / 24	0.77 (0.31, 1.91)
Extra-prostatic Extension	No	2 / 37	2 / 39	1.2 (0.69, 2.08)
	Yes	23 / 139	28 / 128	1 (0.14, 7.17)

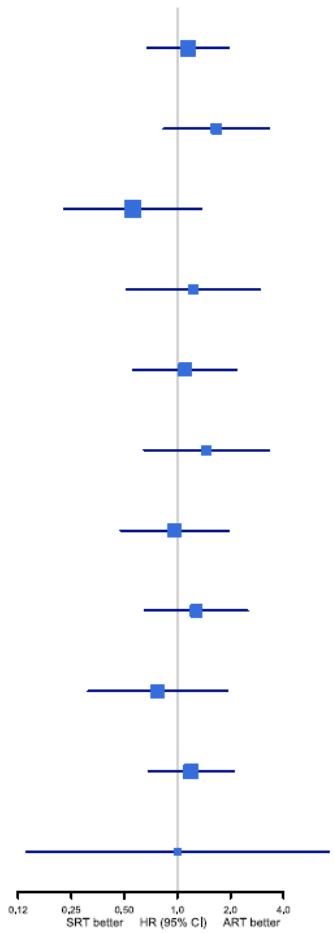


Figure 5 Prevalence of Grade 2+ GU toxicity

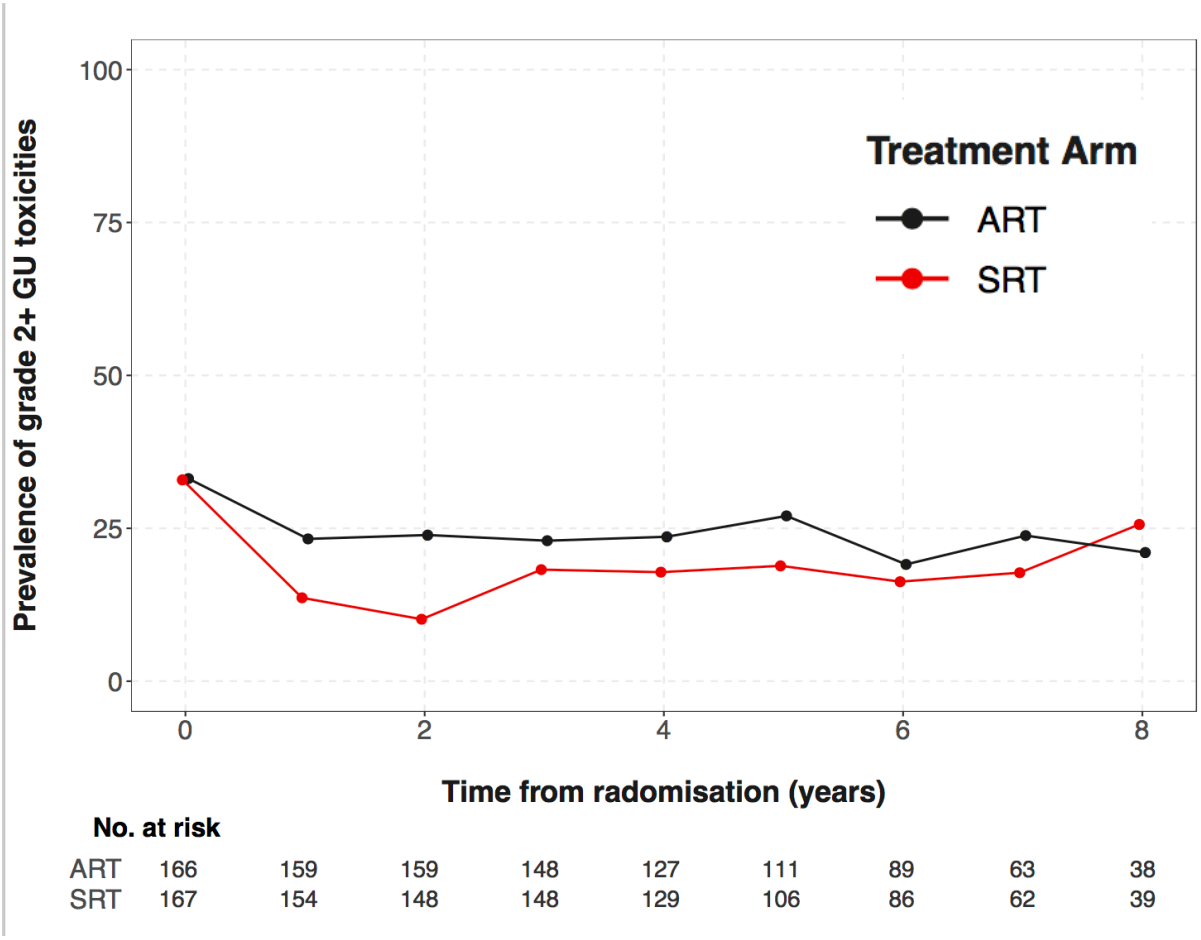
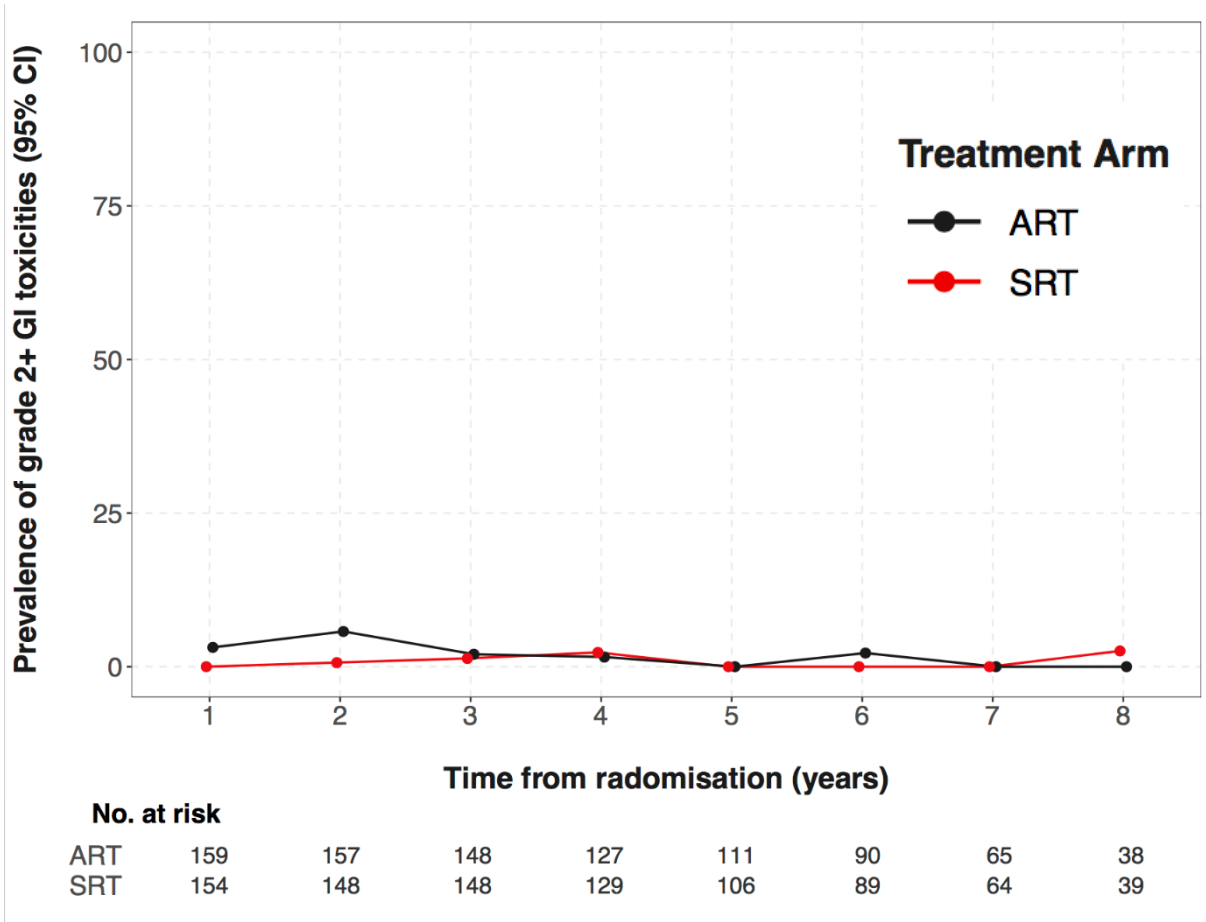


Figure 6. Prevalence of Grade 2+ Gastro-Intestinal Toxicity



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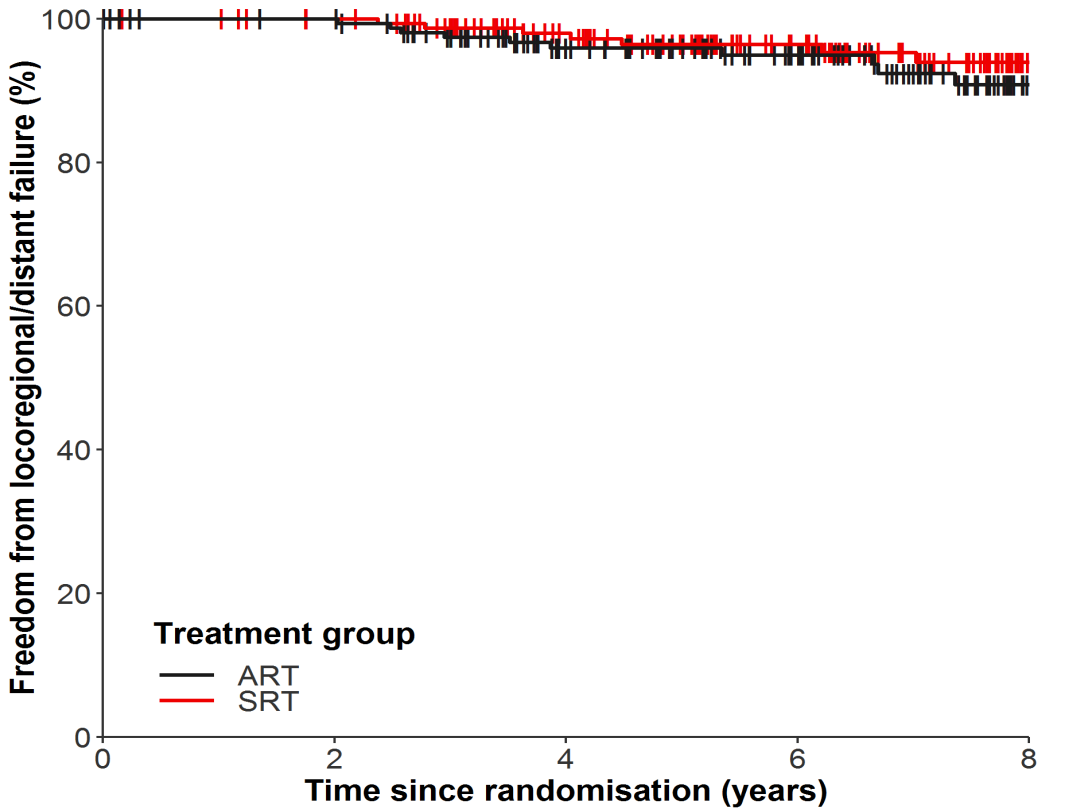
Appendix: Supplementary materials

Figure 7: Kaplan-Meier curves of freedom from loco-regional or distant failure by treatment arm



No. at risk (No. censored)

ART 166 (0)	160 (6)	121 (39)	88 (71)	36 (120)
SRT 167 (0)	161 (6)	129 (35)	91 (71)	35 (125)

Table 2: Tabulation of adverse events

Worst grade	GU		GI		Erectile	
	SRT	ART	SRT	ART	SRT	ART
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
0	11 (7%)	4 (2%)	93 (56%)	57 (34%)	0 (0%)	2 (1%)
1	66 (40%)	46 (28%)	58 (35%)	85 (51%)	5 (3%)	4 (2%)
2	70 (42%)	82 (49%)	15 (9%)	20 (12%)	34 (20%)	30 (18%)
3	18 (11%)	26 (16%)	1 (1%)	4 (2%)	126 (75%)	132 (80%)
4	2 (1%)	8 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
5	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Figure 8: Time to initiation of androgen deprivation therapy

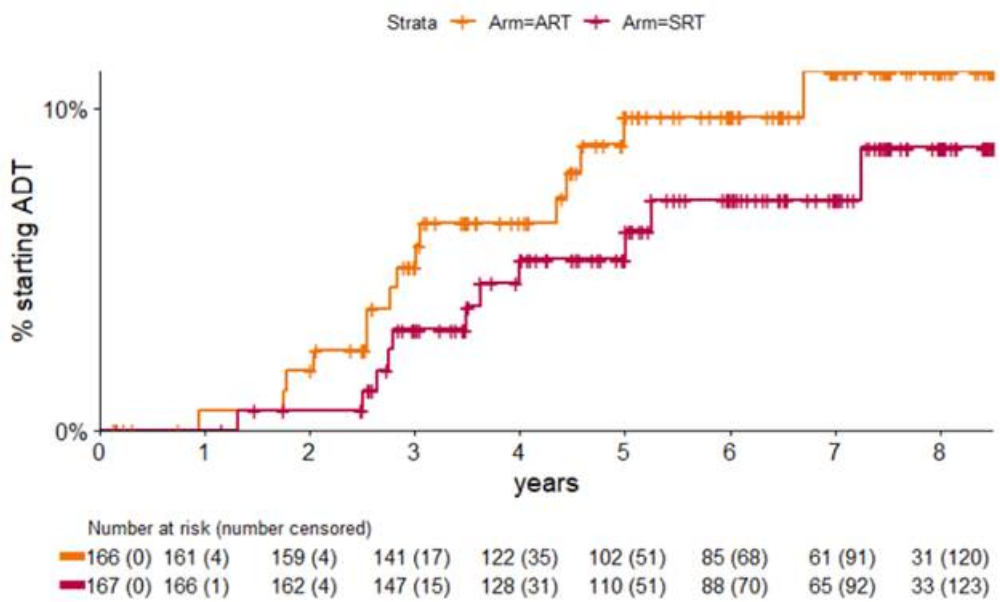


Table 3: Tabulation of co-morbidities.

Variable	SRT		ART	
	No (%)	**Yes (%)**	No (%)	Yes (%)
Myocardial Infarction	154 (93%)	11 (7%)	155 (94%)	10 (6%)
Heart Failure	162 (98%)	3 (2%)	163 (99%)	2 (1%)
Angina	159 (96%)	6 (4%)	157 (95%)	8 (5%)
Other Malignancies	77 (95%)	4 (5%)	73 (89%)	9 (11%)
Peptic Ulcer	159 (96%)	6 (4%)	161 (98%)	4 (2%)
Stroke	153 (93%)	12 (7%)	162 (98%)	3 (2%)
Diabetes	145 (88%)	20 (12%)	153 (93%)	12 (7%)
COP	159 (96%)	6 (4%)	160 (97%)	5 (3%)
Dementia	164 (99%)	1 (1%)	163 (99%)	1 (1%)
Connective Tissue	162 (98%)	3 (2%)	161 (98%)	4 (2%)
Liver Disease	160 (97%)	5 (3%)	163 (99%)	2 (1%)
Kidney Disease	162 (98%)	3 (2%)	163 (99%)	2 (1%)
Bowel Disease	162 (98%)	3 (2%)	162 (98%)	3 (2%)
Hypertension	40 (51%)	38 (49%)	44 (54%)	37 (46%)
Hypercholesterolaemia	53 (68%)	25 (32%)	53 (65%)	28 (35%)

Table 4: TROG 08.03 RAVES participating sites and recruitment summary

Site	Principal Investigator	Recruitment
Calvary Mater Newcastle Hospital	Dr Colin Tang Prof Jarad Martin	42
Auckland Hospital	Dr Maria Pearse	36
Royal North Shore Hospital	Prof Andrew Kneebone	29
Westmead Hospital	Dr Sandra Turner	28
St George Hospital	Dr Joseph Bucci	18
Campbelltown/Liverppool Hospital	Dr Mark Sidhom	16
Royal Prince Alfred Hospital	Dr George Hruby Dr Nitya Patanjali	16
Sir Charles Gairdner Hospital	Prof David Joseph Dr Rohan White	15
Waikato Hospital	Dr Leanne Tyrie Dr Ziad Tholathatil	15
Peter MacCallum Cancer Centre	Prof Scott Williams Dr Suki Gill Dr Mark Shaw	14
Perth Radiation Oncology	Dr Serena Sia	13
Royal Perth Hospital	Dr Serena Sia	13
Dunedin Hospital	Dr John North	12
The Alfred/William Buckland Radiotherapy Centre	Dr Bronwyn Matheson	8
Austin Health	Dr Daryl Lim Joon	5
Christchurch Hospital	Dr Chris Atkinson Dr Stephen Williams Dr Scott Babington	5
Radiation Oncology Mater Centre	Dr Kumar Gogna	5
Nambour Hospital	Dr Marcel Knesl	4
Nepean Hospital	Dr Viet Do	4
Palmerston North Hospital	Dr Donald Chan Dr Claire Hardie	4
Princess Alexandra Hospital	Dr Margot Lehman	4
Royal Brisbane and Women's Hospital	Dr Liz Kenny Dr Charles Lin	4
Toowoomba Cancer Research Centre	Prof Jarad Martin Dr Eric Khoo Dr Samuel Leung	4
Central West Cancer Centre	Dr Kandeepan Thuraisingam	3
Fiona Stanley Hospital	Dr Serena Sia	3
St Vincent's Clinic	Dr Raj Jagavkar	3
Townsville Hospital	Dr Alex Tan	3
Radiation Oncology Queensland Gold Coast	Dr Renee Finnigan	2
Wellington Hospital	Dr John Violet Dr Douglas Iupati	2
Auckland Radiation Oncology	Dr Maria Pearse	1
Riverina Cancer Care Centre	Dr Kandeepan Thuraisingam Dr Anupam Chaudhuri Dr Noel Aherne	1
Sydney Adventist Hospital	Dr Amy Teh	1
	Total	**333**