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Short-term androgen suppression and radiotherapy versus intermediate-term androgen suppression and radiotherapy, with or without zoledronic acid, in men with locally advanced prostate cancer (TROG 03.04 RADAR): 10 year results from a randomised, phase 3 factorial trial

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ABSTRACT

Background

The optimal duration of androgen suppression (AS) for men with locally advanced prostate cancer (LAPC) receiving radiotherapy with curative intent is yet to be defined. Zoledronic acid is effective in preventing AS-induced bone loss but its role in preventing castration-sensitive bone metastases in LAPC is unclear. The RADAR trial determined whether the addition of 12 months adjuvant androgen suppression (Factor 1) or 18 months of zoledronic acid (Factor 2) or both improve outcomes of men with LAPC who receive 6 months of AS and prostatic radiotherapy (RT). This report presents 10 year outcomes from this trial.

Methods

Eligible men were 18 years or older with T2b-4, N0 M0 prostatic adenocarcinomas or T2a, N0 M0 tumours provided Gleason score was ≥7 and baseline PSA levels ≥10 ng/mL. Participants were randomly allocated in a 2x2 factorial design to 6 months neo-adjuvant AS using leuprorelin (22·5mg every three months, intramuscularly) and RT alone, or followed by 12 months adjuvant AS (22·5mg every three months, intramuscularly), or accompanied by 18 months of zoledronic acid (4mg every three months, intravenously) starting at randomisation, or by both. RT commenced at the end of the fifth month of AS and dosing options were 66, 70 and 74Gy in 2Gy fractions per day, or 46Gy in 2Gy fractions followed by a high dose rate brachytherapy boost dose of 19.5Gy in 6.5Gy fractions. Treatment allocation was open-label, and computer-generated randomisation was done by use of the minimisation technique, stratified by centre, baseline concentrations of PSA, clinical stage of the tumour, Gleason score, and use of a brachytherapy boost. The primary endpoint was prostate cancer-specific mortality (PCSM) and was analysed according to intention-to-treat

using competing risks methodology. The trial is closed to follow up and this is the final main endpoints report. This trial is registered with ClinicalTrials.gov, number NCT00193856.

Findings

Between 20 October 2003 and 15 August 2007 1071 men with median age 68 years were randomised. Median follow-up was 10·4 years (IQR 7·9-11·7). No interactions were observed between AS and zoledronic acid so arms were collapsed to compare treatments according to AS duration, 6AS+RT versus 18AS+RT. The total number of deaths was 375, with 143 attributable to prostate cancer. For PCSM, significant reductions favoured 18AS+RT (sHR 0·70 [95% CI 0·50-0·98], p=0·035). Adjusted cumulative incidence rates at 10 years were 13·3% (95% CI 10·3-16·0%) for 6AS+RT and 9·7% (7·3-12·0%) for 18AS+RT, representing an absolute difference of 3·7% (0·3-7·1%). Zoledronic acid did not favour any outcome significantly.

Interpretation

18 months AS+RT is a more effective option for locally advanced prostate cancer than 6 months AS+RT but zoledronic acid is not beneficial.

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RESEARCH IN CONTEXT

Evidence before this study

Before this study started on October 1st 2003 we searched Pubmed, Medline and existing international clinical trials registries between 1st January 1990 and September 30th 2003 for all studies of men with locally advanced and high risk prostate cancer using terms including “androgen suppression therapy", "zoledronic acid", "Gleason grading" and "bone metastases". This was to identify oncological outcomes and treatment-related morbidity. Up until 2003, consensus existed that 28 to 36 months of androgen suppression (AS) together with prostatic and pelvic nodal radiotherapy were regarded to be the most oncologically effective treatments. These durations of AS continue to be widely used around the world in spite of their multiple toxicities and adverse influences on patient-reported outcomes. Preventative pelvic lymph node irradiation has been used alongside prostatic irradiation in several trials but none have yet demonstrated that pelvic irradiation is beneficial. However, since 2000 radiotherapy equipment has made remarkable improvements enabling higher doses to be given to the prostate alongside lower doses to surrounding normal structures. In clinical studies zoledronic acid was shown to reverse loss of bone mineral density due to AS and to improve outcomes in men with castration resistant bone metastases. In vitro studies also found that zoledronic acid may have activity against castration sensitive prostate cancer cells but clinical studies have yet to confirm this.

Added value of the present study

The 10-year results of the TROG 03.04 RADAR trial have shown that 18 months of AS produced better oncological outcomes than 6 months of neo-adjuvant AS with limited

increases in adverse patient-reported outcomes lasting 2-3 years after randomisation. Although zoledronic acid 4mg intravenous doses every 3 months reversed the loss of bone mineral density due to 6 and 18 month durations of AS, it did not prevent bone metastases or other oncological endpoints.

Implications of all the available evidence

Less morbid treatments using intermediate durations of AS such as 18 months, alongside more limited, better shaped volumes of prostatic and pelvic nodal radiotherapy, will result in better overall outcomes and will provide a valid therapeutic option for men with locally advanced, high risk prostate cancer.

INTRODUCTION

The optimal duration of androgen suppression therapy (AS) to use alongside radiotherapy (RT) in the curative management of locally advanced prostate cancer remains unclear[1-3] after three decades of trials. However it is clear that radiotherapy to the prostate by itself to 66 Gy is ineffective in 87% of participants 10 years after treatment.[4] Since 2000, radiotherapy equipment has undergone remarkable improvements enabling, for example, higher doses to be given to the prostate alongside lower doses to surrounding normal structures. Unfortunately similar progress has not accompanied the use of AS. Neo-adjuvant androgen suppression regimens have ranged in duration between 3 and 8 months, while for men with very high risk cancers post RT adjuvant regimens that range between 6 and 36 months are often prescribed.[5,6] Up until 2009, 36 months of adjuvant AS after prostatic and pelvic nodal radiotherapy was regarded to be the most effective treatment and continues to be widely used around the world in spite of multiple toxicities and adverse influences on patient-reported outcomes. However a recently analysed French Canadian trial has reported that 18 months of AS and radiotherapy produced much reduced adverse patient-reported outcomes than 36 months.[7] The search for an optimal duration of AS for locally advanced prostate cancer and high risk diagnostic presentations, which cause only modest toxicities and small impairments in patient-reported quality of life outcomes, is therefore a priority.

In 2003 the Trans-Tasman Radiation Oncology Group (TROG) took the most efficacious treatment group of its 96.01 trial[4], 6 months of neo-adjuvant AS before and during RT (known as Short Term Androgen Suppression [STAS]), as the control group of its next trial, the Randomised Androgen Deprivation And Radiotherapy (RADAR) trial.[8] The primary objective of this trial was to determine whether an intermediate duration of adjuvant androgen suppression would be superior to STAS but without compromising quality of life

outcomes. A secondary objective was to test if bisphosphonate therapy would help to reduce some of the adverse effects of AS and prevent bone progression. Using a 2x2 factorial design the RADAR trial therefore sought to determine whether 12 months of adjuvant AS (Factor 1) or 18 months of zoledronic acid (Factor 2) or both improved the outcomes of men receiving STAS.

In our preliminary main endpoints report in Lancet Oncology 2014[8] we identified an unexpected interaction between the use of zoledronic acid and an important baseline prognostic factor, Gleason score (GS) of the primary tumour at the cutpoint ≤7/>7. This obliged us to compare our four treatment groups in a pairwise fashion, with consequent loss of power to discern differences in treatment outcomes. Unfortunately there remain no data in the literature to this day to explain the interaction. However, we now have more robust evidence that the interaction, if indeed there was one, has since dissipated as the pharmacological activity of zoledronic acid has diminished with additional follow up (appendix p10). Because no further interactions have been identified, it is therefore now reasonable to combine the treatment arms to compare 6 months AS and 18 months AS, as well as no zoledronic acid and 18 months zoledronic acid.

Taken together, the RADAR and recently reported French Canadian trials may therefore determine which of the 6, 18 and 36 month durations of neoadjuvant and adjuvant AS, when added to RT, provides the optimal balance between efficacy and adverse patient-reported outcome profiles.

METHODS

Study design and participants

The TROG 03.04 RADAR trial is a randomised, open-label, first-line phase 3 trial involving 23 centres in Australia and New Zealand. Eligible men 18 years or older with an estimated life expectancy greater than five years had histologically confirmed adenocarcinoma of the prostate without lymph node or systemic metastases, cT2b-4 stage primary tumours or cT2a stage primary tumours with Gleason score ≥7 and baseline PSA levels ≥10 ng/mL, and Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1. Tumour assessment included DRE and either TRUS biopsy or TURP. Presence of metastases was investigated by chest x-ray, CT scan of abdomen and pelvis, bone scan, and nodal sampling. Laboratory tests after diagnosis to confirm eligibility included a full blood count, urea and electrolytes, creatinine clearance, liver function tests, calcium, phosphate and vitamin D. Exclusion criteria included prior androgen suppression, prostatectomy, pelvic radiotherapy, bisphosphonate therapy, or prolonged glucocorticoid therapy (>10 mg prednisone for more than six months); malignancy within the previous five years (except for non-melanomatous skin cancer); osteoporosis resulting in spinal fracture; liver disease (ALT or AST >3 times the upper limit of normal); serum creatinine >2 times the upper limit of normal; and inability to complete self-administered quality of life assessments.

The study protocol and amendments were approved by the ethics committees of participating centres and subjects provided written informed consent. A copy of the protocol can be located at http://hdl.handle.net/1959.13/1391555.

Randomisation and masking

Computer-based randomisation was performed at the Central Trials Office, Newcastle, NSW, Australia, using minimisation with a random element and with stratification according to baseline PSA level (<10 vs. 10-20 vs. >20 ng/mL), Gleason score (≤6 vs. ≥7), T stage (T2 vs. T3/T4), and treatment centre. Centres opting to use both high-dose rate brachytherapy boost (HDRB) techniques and 3D conformal external beam techniques in different patient subgroups were classed as two different centres for the purposes of stratification. Subjects were equally assigned to one of four treatment groups in a 2x2 factorial design. Treatment was not masked to investigators or subjects.

Procedures

All subjects received 6 months of leuprorelin (22·5mg intramuscularly 3 monthly) commencing at randomisation, 5 months before RT to the prostate and seminal vesicles. Following this they received either no further treatment (i.e. "short term" AS [the control arm: STAS]) or an additional 12 months of leuprorelin (22·5mg intramuscularly 3 monthly) (i.e. "intermediate term" AS [ITAS]). In addition to AS treatment, subjects allocated to the two bisphosphonate treatment arms received 4 mg zoledronic acid intravenously every 3 months for 18 months starting at randomisation, (STAS+Z and ITAS+Z). (See trial schema in appendix p2.)

A regulated radiation dose escalation program sub-study was achieved by requiring participating centres to select their preferred dosing options from a pre-determined range of doses and techniques. The dosing options were 66, 70 and 74Gy using 2Gy fractional increments per day to the ICRU point using external beam alone (EBRT only), and 46Gy in 2Gy fractions to the ICRU point using external beams followed by a high dose rate

brachytherapy (HDRB) boost dose of 19.5Gy in three fractions of 6.5Gy. Brachytherapy dose was prescribed to the isodose encompassing the prostate gland and any identified extracapsular extensions. Full details of the methodology employed for dose escalation, derivation of radiation target volumes, dose volume histogram constraints and set up accuracy requirements are provided in our previous reports.[8-10] The stratification scheme employed ensured that radiation dose and technique used were balanced across all four trial arms.

Adverse events were monitored every three months during androgen suppression and zoledronic acid treatments, and weekly during radiotherapy. For androgen suppression, this included clinical examinations, full blood counts, and PSA and testosterone readings. For participants receiving zoledronic acid, additional tests were performed to monitor urea and electrolytes, creatinine clearance, calcium and phosphate levels, and if participants experienced jaw pain and/or ulceration, an examination by a dentist and oral surgeon would be arranged for diagnosis and management of osteonecrosis of the mandible. To avoid the risk of osteonecrosis of the mandible, it was recommended that zoledronic acid treatment be postponed for 3 months in participants requiring an urgent invasive dental procedure, with the possibility of dose reduction or discontinuation in the event of ongoing dental issues or poor oral health. In addition, elevated creatinine levels which remained at levels more than 10% above the baseline value could necessitate delays, reductions or discontinuation of zoledronic acid to prevent renal impairment or failure. Serious adverse events (SAE's) were to be reported within 24 hours, specifying type and severity of event and if they were related to any of the study treatments.

After treatment all participants were followed up in clinic every 3 months until 30 months, then 6 monthly until 5 years post-randomisation, then annually for a further 5 years. At each

visit PSA levels were documented, clinician-assessed outcomes collected and digital rectal examination performed. Serial rising PSAs every 2 months were used to determine the possibility of prostatic recurrence and/or metastatic progression. The first indication was a rise of 2 ng/mL above the post-treatment nadir value ("Phoenix failure"). Local prostatic progression was diagnosed using serial digital rectal examinations including fine needle biopsy according to the RECIST criteria at the time of diagnosis. Investigations to diagnose metastases, including CT scans of the abdomen and pelvis, chest x-ray and isotopic whole body bone scintigraphy, were mandated if symptoms suggested a need or if the PSA reached 20 ng/mL. While the protocol did not mandate the type of secondary therapeutic intervention (STI), it recommended that STI be delayed until clinical progression was diagnosed or PSA had reached 20 ng/mL. Participants completed questionnaires for patient-reported-outcomes (PROs) at baseline, 3 months, 7 months (end of radiotherapy), 12 months, 18 months, 24 months, 36 months, 60 months, and then yearly. These included the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 (version 3) and prostate cancer module PR25. If a participant no longer wished or was unable to complete scheduled treatments and/or clinic follow-ups (eg due to transport problems or intercurrent medical conditions such as dementia), the participant (or his guardian) was offered the option of “remote follow-up” whereby consent was given to continue to collect study-related data from his GP and other medical providers, and by telephone or post if he also consented to be contacted directly. Otherwise total withdrawal from the study was at the discretion of the participant or his guardian.

Endpoints

The primary endpoint was prostate cancer-specific mortality (PCSM). Death was attributed to PC if it occurred in the context of progressive metastatic disease or recurrent primary cancer causing urinary obstruction, without reasonable alternative unrelated causes. Final attribution of cause of death was made by the Trial Endpoints Committee consisting of senior clinicians blinded to the subject's identity and treatment group. Secondary oncological endpoints were PSA, distant, bone, soft tissue and local progressions; STI; transition to castration resistance (TCR), and all-cause mortality (ACM). All time-to-event endpoints were measured from randomisation. PSA progression was calculated by the Central Trials Office using the Phoenix method (ie a PSA rise of 2 ng/mL above the post-treatment nadir). Local progression was defined as a recurrent prostatic mass diagnosed by digital rectal examination and/or by imaging techniques. Distant progression was defined as metastasis at anatomical sites outside of the prostatic region, namely bones, lymph nodes and other sites, diagnosed by bone scintigraphy, CT scanning or plain radiology. Transition to castration resistance was a post-hoc endpoint (see appendix pp5,11 for definition).

PROs presented in this updated analysis included the EORTC QLQ-C30 global health status and quality of life, and EORTC PR25 domain scores for sexual activity and hormone treatment-related, rectal and urinary symptoms[11]. All domain scores were derived as per the EORTC QLQ C-30 scoring manual.[12]

Quality control measures included radiotherapy treatment review processes[13-15] and site monitoring visits. The primary and secondary oncological endpoints were reviewed annually by the Trial Endpoints Committee, blinded to subject identity and treatment allocation, who reviewed copies of all de-identified imaging, pathology and endpoint correspondence. Random re-reviews of endpoints were conducted by the Endpoints Committee to ensure

consistency in the adjudication process. An Independent Data Monitoring Committee comprising Professors Peter Hoskin (London, England), John Symes (Sydney, Australia) and Irena Madjar (Auckland, New Zealand) was convened in 2015 primarily to investigate the increased bone progressions observed in the STAS+Z trial arm in 2014.

Statistical Analysis

The previously observed interaction reported in 2014[8] has dissipated with additional participant follow up (appendix p10). After data closeout on 31 August 2017 omnibus testing for interactions found no significant differences between the four treatment arms, hence arms could be collapsed to compare the trial factors separately. Firstly the combined 6 month neo-adjuvant AS (+/-zoledronic acid) group, abbreviated herein as 6AS+RT, was compared with the combined 18 month AS (+/-zoledronic acid) group, abbreviated herein as 18AS+RT, to determine whether Factor 1 (12 months adjuvant AS commencing after radiotherapy) was beneficial. Secondly, the combined zoledronic acid groups were compared with the two no zoledronic acid groups to determine whether Factor 2 (18 months zoledronic acid commencing at randomisation) was beneficial.

Based on 2014 main endpoint data, the power to detect reductions in the primary endpoint, PCSM, from the use of an additional 12 months AS was low. Assuming 148 prostate cancer deaths at data closeout in 2017 and two-sided type 1 (α) error of <0·05, a hazard ratio of 0·55 would be required to provide the analysis of PCSM with a power of 80%. This was because the frequency of prostate cancer deaths was lower than anticipated, probably as a result of the use of newly available tertiary drugs to treat men whose cancers had recurred but were no longer responding to conventional androgen suppression treatment measures. Under these circumstances it was decided that the use of multivariable models adjusting for

the stratification variables rather than univariable analytical models could increase the power to detect differences between the treatments groups for both primary and secondary endpoints. The trial stratification scheme used the traditional Gleason scoring system at the cutpoint <7, ≥7. When the trial was designed, it was assumed that this cutpoint would divide the trial population into approximately equal groups. However, the distribution changed rapidly during the recruitment phase. This was due to a change in grading policy by the institutional pathologists when they implemented modifications to the traditional Gleason scoring system introduced by the International Society of Urological Pathologists (ISUP)[16,17] (appendix p4). This change in policy had the effect of a large reduction in the proportion of men assigned Gleason score <7, ie modified Grade group 1, from the anticipated 50% down to 9%, and a large increase in the proportion of men assigned Gleason score ≥7 to 91%. The large substratum of men with Gleason ≥7 would therefore have effectively been distributed at random to all four treatment groups without stratification. In particular, over 50% of the men ultimately recruited in the trial had Gleason 7 (3+4 and 4+3) tumours, which are now known to have different prognostic outcomes. To improve the prognostic gradient in the Gleason ≥7 substratum, men were therefore reassigned post hoc to the modified Gleason (ISUP) Grade groups 2 to 5 after randomisation (appendix pp4-5). For these reasons, the 5-level Grade group was used in place of the stratified Gleason score (<7, ≥7).

Treatment centre was a stratification factor, however we elected not to adjust for it in our primary analyses since this is a non-trivial exercise in a competing risk model when using a shared frailty, and the assumption of a gamma distributed frailty may not be valid. We performed sensitivity analyses adjusting models for treatment centre as a shared gamma frailty to compare with our primary results.

For each endpoint, the 10 year adjusted cumulative incidence rates and 95% confidence intervals were calculated in multivariable competing risks models using the Fine and Gray[18] and direct adjustment method to derive adjusted sub hazard ratios and 95% confidence intervals for treatment factor effects. ACM hazard ratios and 95% confidence intervals were derived from a Cox regression model. All models were adjusted for the stratification factors: baseline PSA (<10, 10-20, >20 ng/mL), T stage (T2, T3/T4) and Grade group (1-5).

Competing risks for PCSM were defined as deaths due to other or unknown causes. Competing risks for local progression were defined as distant progression diagnosed more than 2 months before local progression and death due to any cause. For all other endpoints, the competing risk was death due to any cause. The proportional hazards assumption was tested in competing risks models by including each predictor variable as a time-varying covariate and ensuring no significant time variation was observed. These interactions were retained in the model if the associated variable violated the proportional hazards assumption. For Cox regression models, the proportional hazards assumption was tested by using Schoenfeld residuals. Covariates that violated the proportional hazards assumption were stratified for in these models. We used the hierarchical, "gatekeeping" strategy described by Yadav and Lewis for avoiding false positive results with many comparisons.[19]

A post-hoc, hypothesis-generating analysis was performed and presented as a forest plot to explore AS treatment effect on oncological endpoints according to NCCN risk classification (unfavourable intermediate and high risk subgroups). Unfavourable intermediate risk was defined as Gleason 4+3 (Grade group 3), percentage of positive biopsy cores ≥50%, or multiple intermediate risk factors (clinical stage T2b-c, Gleason score 7or PSA 10-20 ng/mL). High risk was defined as clinical stage T3 or T4, Gleason score 8-10 (Grade group 4 or 5) or

PSA >20 ng/mL. These models were adjusted for age at randomisation and use of high dose brachytherapy (no, yes) in addition to PSA, T stage and Grade group.

Compliance with completion of PRO questionnaires was calculated for each scheduled data collection time point as the proportion of participants on study at that time point. Longitudinal changes in mean scores from baseline for each PRO[20] were also compared across treatment groups at each time point using independent t-tests. Significant findings were assessed for clinical relevance by ascertaining the proportions of men in each group who had increases or decreases of 10 or more, or intermediate changes of less than 10 in domain scores from baseline to each follow-up time.[21] These univariable proportions were compared by χ^2 testing. Because multiple tests were done, a two-sided p value of less than 0·01 was judged to be significant in PRO analyses.

Analyses were performed on an intention-to-treat basis. An adjusted two-sided p-value <0·05 was considered statistically significant for all endpoints except PROs. All analyses were done with Stata/IC Version 14·2 and SAS Version 9.4.

This trial is registered with ClinicalTrials.gov, number NCT00193856.

Role of the funding source

The sponsors of the study had no role in the study design; the collection, analysis, or interpretation of the data; or the writing of the report. Raw data were available to JWD, JA, CO and AS. The corresponding author had full access to all data in the study, and had final responsibility to submit the paper for publication.

RESULTS

Between 20 October 2003 and 15 August 2007 1071 subjects out of 2273 screened at 23 treatment centres across Australia and New Zealand were randomly allocated to the four treatment arms (Figure 1). Baseline characteristics are shown in Table 1 and were similar across the arms. These data are also presented according to duration of AS group and zoledronic acid group (appendix pp12-13). Protocol treatment compliance rates, defined as 100% of scheduled dose, were 99% (532 out of 536) for men allocated 6 months AS, 85% (456 out of 535) for 18 months AS, and 77% (409 out of 535) for zoledronic acid.

At data closeout on 31 August 2017, 10 years after the last subject was randomised, median follow-up time was 10·4 years (IQR: 7·9-11·7). The total number of deaths was 375, with 143 (38%) attributable to prostate cancer. A breakdown of cause of death by AS duration is shown in Table 2. At 10 years, the cumulative incidence of PCSM was 13·3% (95% CI 10·3-16·0%) for 6AS+RT and 9·7% (7·3-12·0%) for 18AS+RT, representing an absolute difference of 3·7% (0·3-7·1%) (sub hazard ratio (sHR) 0·70, 95% CI [0·50-0·98], adjusted p=0·035) (Figure 2A). The 10-year cumulative incidence rates for all-cause mortality were 32·3% (28·4-36·0%) for 6AS+RT and 28·0% (24·2-31·5%) for 18AS+RT (HR 0·83 [0·68-1·02], adjusted p=0·08) (Figure 2B).

To determine if an overall survival benefit could be achieved if follow up was extended beyond 10 years, we tested the endpoint metastasis-free survival, which has been shown in meta-analyses conducted by the ICECaP Working Group to be a strong surrogate endpoint for disease-specific and overall survival.[22] An exploratory post-hoc analysis showed a significant improvement in metastasis-free survival for 18AS+RT (sHR 0·77 [0·65-0·92], adjusted p-value=0·0044).

Significant reductions in cumulative incidences of distant progression and bone progression also favoured 18 months AS. Distant progressions were reported in 293 men and cumulative incidences were 27·5% (23·9-31.0%) for 6AS+RT and 20·7% (17·6-23·9%) for 18AS+RT (sHR 0·71 [0·56-0·90], adjusted p=0·004) (Figure 2C). Bone progressions were diagnosed in 229 men and cumulative incidence was 23·3% (20·0-26·7%) for 6AS+RT and 15·8% (12·9-18·7%) for 18AS+RT (sHR 0·63 [0·48-0·82], adjusted p=0·0007) (Figure 2D). Soft tissue progressions were not reduced by the longer duration of AS, with cumulative incidence rates of 16·5% (13·5-19·5%) and 14·1% (11·3-16·9%) for 6AS+RT and 18AS+RT respectively (189 events, sHR 0·84 [0·63-1·12], adjusted p=0·21). Local progression was identified in 93 patients. Cumulative incidences were 7·9% (5·7-10·1%) for 6AS+RT and 4·9% (3·0-6·8%) for 18AS+RT (sHR 0·61 [0·40-0·93], adjusted p=0·022) (Figure 2E). At 10 years PSA progression had occurred in 436 men and cumulative incidences were 45·9% (41·9-49·9%) and 34·0% (30·2-37·7%) favouring 18AS+RT (sHR 0·65 [0·54-0·79], adjusted p<0·0001). Similarly, reductions in the 366 participants requiring STI also favoured the men receiving the longer duration of AS, with cumulative incidences of 36·8% (32·9-40·6%) and 26·6% (23·1-30·1%) for 6AS+RT and 18AS+RT respectively (sHR 0·66 [0·53-0·81], adjusted p=0·0001).

Time to transition to castration resistance (TCR) was identified in 163 of 364 men who underwent androgen suppression as secondary treatment following failure of the primary treatment. Of these 364 men, 201 (55%) were diagnosed with distant progression prior to the start of secondary treatment. The cumulative incidence of TCR was significantly reduced in men receiving 18AS+RT, with a rate of 11·3% (8·7-13·9%) compared to 17·1% (14·1-20·1%) for 6AS+RT (sHR 0·63 [0·46-0·86], adjusted p=0·004). Time to TCR correlated strongly with time to prostate cancer-specific mortality (appendix p6). Median time between TCR and PCSM was 22 months (95%CI 17-25) (appendix pp5-6).

Sensitivity analyses of the primary and secondary oncological endpoints adjusting for treatment centre as a shared frailty produced almost identical outcomes (data not shown), and improvement in power was negligible.

A forest plot showed that 18AS+RT provided better outcomes than 6AS+RT in both unfavourable intermediate risk and high risk cancers (appendix p7). Distant progression was significantly reduced in both risk groups by the longer duration of AS. Subsequent reductions in PCSM did not reach statistical significance in either risk group.

None of the comparisons between the no zoledronic acid group and the zoledronic acid group significantly favoured the use of zoledronic acid for the endpoints described above. These findings are summarised in Figure 3. A total of three cases of osteonecrosis of the mandible were reported in men who received zoledronic acid, all of whom made full recoveries. The two cases identified in our 2014 report[8] were in men who received 6 months AS and the third case, reported in March 2016, occurred in a man who received 18 months AS. In an earlier report[23] we showed that zoledronic acid prevented loss of bone mineral density due to AS but did not reduce fractures.

Patient-reported outcomes have been reported in detail previously.[9,24] We have therefore updated five of the most important outcomes out to 10 years follow up for the 6AS+RT and 18AS+RT groups. These included EORTC QLQ-C30 QL2 global quality of life, and the EORTC PR25 sexual activity and hormone treatment-related, bowel and urinary symptom domains. Compliance with completion of PRO questionnaires was similar between the two treatment groups (appendix p14). Longitudinal mean change from baseline scores and longitudinal mean raw scores of each PRO according to AS duration are shown in Figure 4 and appendix p8 respectively. These plots show that separations between the two groups, favouring 6AS+RT, commence after radiotherapy (7 months) for all five outcomes. However, these

separations reach statistical and clinical significance for relatively short periods of time and by 2 years the separations between the two groups diminish considerably, and after 3 years virtually disappear out to 10 years follow up (appendix pp15-17). These findings were replicated in a post-hoc exploratory, per-protocol analysis (appendix p9).

Recovery to normal testosterone levels (≥8 nmol/L) was significantly slower in the men receiving the longer duration of hormones (median time 29·9 months for 18AS+RT compared to 12·0 months for 6AS+RT, p<0.0001) (Figure 5F). This prolonged suppression of testosterone could explain the increase in adverse PRO's in the first 3 years. However men in the 6AS+RT group were more likely to experience disease progression and receive further AS as secondary treatment (209 [39%] compared to 155 [29%] in the 18AS+RT group, p=0·0006). Long-term PRO's could therefore be impacted by testosterone levels affected by secondary treatment as well as ageing. A more detailed analysis of longitudinal changes in PRO's will be reported separately.

Serious adverse events (SAE's) have been summarised previously.[8] A third case of osteonecrosis has since been reported making a total of 12 drug-related SAE's, six of which resulted in dose discontinuations. There were no treatment-related deaths in the study, however 90 participants had dose reductions or discontinuations due to drug-related toxicity. A total of 12 men (6 in each of the ITAS and ITAS+Z arms) required dose reductions of leuprorelin, and 16 men (7 in the STAS+Z arm and 9 in the ITAS+Z arm) required reductions of zoledronic acid. The total number of discontinuations was 40 men for leuprorelin and also 40 men for zoledronic acid. In the control arm STAS, one subject stopped after the first leuprorelin injection due to depression. In the STAS+Z arm, all subjects received their full dose of leuprorelin as prescribed, however 21 men discontinued zoledronic acid. Reasons for discontinuation included 2 SAE's due to osteonecrosis, multiple

side-effects (7), bone pain (2), elevated creatinine levels (3), injection reaction (2), flu symptoms (1), skin rash (1), muscle cramps (1), painful teeth (1) and gout (1). In the ITAS arm, 22 subjects discontinued leuprorelin, of whom 14 chose to stop due to multiple hormone treatment-related side-effects. Additional reasons included 2 SAE's involving a CVA and peripheral neuropathy, fractures (2), mood disorders (2), abnormal liver function (1), and exacerbation of pre-existing diabetes (1). A total of 17 men in the ITAS+Z arm discontinued leuprorelin, with the majority of these (10) attributable to multiple hormone treatment-related side-effects. Other reasons for stopping included mood disorders (3), fatigue (1), hot flushes (1), muscle weakness (1), and sexual dysfunction (1). In addition, 19 men discontinued zoledronic acid, 2 of which were SAE-related involving syncope during drug infusion and an ischaemic toe. Other reasons were patient decision due to side-effects (8), injection reactions (5), bone pain (1), fatigue (1), flu symptoms (1) and iritis (1).

DISCUSSION

A highly coherent set of findings has emerged from these analyses. The RADAR trial has shown that when compared to 6 months AS+RT, the use of an additional 12 months of adjuvant AS in men with locally advanced prostate cancer resulted in statistically significant reductions in the primary endpoint, PCSM, with a relative effect size of 30%. The number needed to treat is 27 men to prevent one death from prostate cancer over 10 years. Unfortunately a significant difference in all-cause mortality was not observed between the two treatment groups. All other secondary endpoints, with the exception of soft tissue progression, significantly benefitted participants receiving 18AS+RT, with relative effect sizes ranging between 29% and 39%. Similar risk reductions of 37% were achieved in the two endpoints bone progression and transition to castration resistance, which helps to explain

why the longer duration of AS was effective in preventing prostate cancer deaths. However, longer durations of AS may preferentially deplete well-differentiated, slowly evolving tumour clones. This may lead to an overgrowth of highly malignant, rapidly evolving tumour clones. Median time to PC death following TCR was short, being just under 2 years. In the earlier years of the trial, drugs which are widely used nowadays to treat castrate-resistant disease were not available or in common use, hence the poor outcome after TCR.

Although a difference in all-cause mortality was not observed between the two AS groups, our exploratory post-hoc analysis confirmed a significant increase in the surrogate endpoint metastasis-free survival for the men receiving 18 months AS, indicating that an overall survival advantage may be achieved with further follow up. However, since no further funding is available to extend our trial follow up beyond 10 years, the ICECaP project could model our final dataset to estimate when an overall survival advantage for 18 months AS might be observed.

Of major importance, the cost of the benefits of 18 months AS was restricted to a limited increase in adverse patient-reported outcomes lasting only 2 to 3 years after randomisation. In our earlier report[24] we showed that these adverse PRO effects, in particular increased hormone treatment-related symptoms and decreased sexual activity, were largely driven by prolonged testosterone suppression. Protocol compliance was good at 85% and, although lower than the 6 months AS group, this difference did not impact PRO outcomes as evidenced by the similar results produced by intention-to-treat and per-protocol analyses. Two studies which evaluated quality of life outcomes for 36 months of AS presented results according to intention-to-treat[6,7], and with treatment compliance rates of 72% and 53%, have potentially underestimated the true impact of these lengthy durations of androgen

suppression. A role in the clinic for the use of 18 months AS and radiotherapy to the prostate with its modest side-effect profile therefore seems appropriate.

Unfortunately the same cannot be said for the role of 18 months zoledronic acid which did not produce significant reductions in any oncological endpoint. The increase in bone progressions attributed in our 2014 report to the use of 18 months of zoledronic acid in men receiving 6 months of AS diminished with 3·5 years of additional follow up. Moreover the RADAR trial confirmed results from the ZEUS randomised trial[25] which found that longer duration and more dose-intense zoledronic acid than used in RADAR did not prevent the development of bone progression in men with high risk localised prostate cancers that were yet to become castration resistant.

For at least a decade there have been well-documented concerns about prolonged morbidity in men who receive long term AS.[26] However there are now three randomised controlled trials in men with high to very high risk prostate cancer that have evaluated the efficacy of 36 months of adjuvant AS after RT with the goal of cure when compared with either no AS[27], 6 months of adjuvant AS[6] and 18 months AS in total[7]. The two trials run by the EORTC, led by Bolla *et al.*, showed that 36 months adjuvant AS was statistically superior in all efficacy outcomes when compared with no adjuvant AS[27] or 6 months adjuvant AS[6]. However the trial run by the French Canadian group led by Nabid *et al.* showed that 36 month AS was not superior to 18 months AS, reporting similar overall and prostate cancer-specific survivals in both treatment arms after 10 years of follow up.[7] The respective hazard ratios and 95% CI's were 1·02 (0·81-1·29) for overall survival and 0·95 (0·58-1·55) for PCSM. Since this trial was designed to demonstrate superiority, it cannot be claimed that 36 months of AS+RT is not more efficacious than 18 months AS plus the same RT. Of importance, these trials also measured quality of life indices using the EORTC QLQ-C30 and PR25 instruments and found

that 36 months of adjuvant AS was statistically inferior in the two trials that compared 36 months with 6 and 18 months of AS. A fourth trial run by the Radiation Therapy Oncology Group (RTOG) in the USA which compared 4 months of neoadjuvant AS prior to and during radiotherapy either alone or followed by 24 months adjuvant AS also reported significant improvements in all outcomes except overall survival.[28,29] Statistically increased morbidity was not observed but quality of life outcomes were not addressed.

In regard to the serious adverse effects of radiation, increased rates of rectal and bladder cancer have been reported following prostatic radiation.[30] However, since pelvic lymph nodes were not irradiated in the RADAR trial and the median time to death for men who died of new primary abdominal cancers was only 6 years, it is unlikely that these would have been radiation-induced when the induction time of the cancer is taken into account, as well as the subsequent time from diagnosis to death.

The RADAR trial had four main limitations. Firstly, the power of the primary endpoint was compromised by the decision in 2011 to replace the original primary endpoint (PSA progression) in favour of prostate cancer-specific mortality, resulting in a considerable reduction in primary endpoint events. Another factor potentially reducing power may have been the success of new tertiary treatments for men who became castrate resistant during the trial which prolonged time to prostate cancer death. A second important limitation was that randomisation was performed using Gleason scores from the institutional pathologists. As reported in the methods and appendix, a large change in the traditional Gleason scoring system occurred after 2005 which lead many institutional pathologists to utilise the modified Gleason grades defined by ISUP in 2005. Although a central pathology review was performed, this was undertaken after randomisation due to workload constraints and logistical difficulties in getting the institutional biopsy slides transported to New Zealand and

reviewed by the trial pathologist prior to men being randomised. The revised main objective of this review, which was undertaken during the period 2010-2014 on the 996 men with evaluable slides, was to grade the biopsies according to the traditional Gleason and the modified Gleason (ISUP) scoring systems, and to compare the prognostic significance of these systems. Hence the traditional Gleason scores from the pathology review have not been presented in this report as they were not used for randomisation and 75 (7%) of men had missing scores. A separate report will be prepared to analyse 10 year clinical outcomes using data from the pathology review. A third limitation was the practical difficulty in randomly allocating participants to the RADAR dose escalation substudy. Despite this, men in the four dosing subgroups were distributed evenly across the trial's four treatment arms using stratification by minimisation and reducing the possibility that radiation dose escalation would bias any of the treatment arms. A fourth limitation was the inability to determine whether 18AS+RT, compared to 6AS+RT, would benefit high risk cancers more than unfavourable intermediate risk cancers. Although we demonstrated in post-hoc exploratory analyses a significant reduction in bone and distant metastases using 18AS+RT for both high risk and unfavourable intermediate risk cancers, the study was underpowered to determine a reduction in PCSM for either risk group (appendix p7). We have agreed with the ICECaP working party to release our metastasis-free survival data to their team to determine if 18AS+RT will provide a PCSM and overall survival benefit in these risk groups.

A question that remains unanswered is whether the adverse effects of AS can be reduced successfully without reducing its duration. In separate substudies, the RADAR trial has shown the benefits of exercise to help reduce the adverse side-effects of androgen suppression, particularly in men who have received 18 months of AS.[31,32] It has also shown that zoledronic

acid at doses used in the RADAR trial can prevent loss of bone mineral density in men receiving 18 months of AS.[23]

However when all of the trials discussed above are taken together, can it be said that an optimal duration of AS, which provides a favourable balance between efficacy and adverse patient-reported outcome profiles, has been achieved? In order to determine the optimal duration of AS for individual men, other factors will need to be taken into consideration such as pre-existing comorbidities, in particular cardiometabolic disease, and the suitability of radiation dose escalation. The RADAR trial will examine the relative efficacies of AS duration and dose escalation in a separate report. Further data are therefore required to answer these questions with accuracy, but at the present moment 18 months of AS plus radiotherapy is a valid therapeutic option for men with locally advanced and high risk prostate cancer presentations.

Author contributions:

Study concept and design: JWD, DJ, DSL, NAS, GD, JM, CA, K-HT, DC, LK, ST, NKG, TD, BD

Acquisition and quality assurance of data: AS

Manuscript writing: JWD, AS

Design and interpretation of data analyses: JWD, AS, CO, JA

Statistical analyses: AS, CO, JA

Manuscript revisions: all authors

Study supervision: JWD chaired the trial and had full access to the data

Conflict of interest statements:

"Abbvie and Novartis Pharmaceuticals provided funds for pharmaceutical supplies, investigations and data management support up until August 2007 to Professor Denham in his capacity as Director of the PCATG Inc to assist in the running of the RADAR trial. None of the other co-investigators have any conflicts of interest to declare."

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Table 1. Baseline characteristics by treatment arm

	STAS (n=268)	STAS+Z (n=268)	ITAS (n=268)	ITAS+Z (n=267)	Total (n=1071)
Randomised	268	268	268	267	1071
Age (years)					
Median (IQR)	69 (64-73)	69 (64-73)	68 (63-73)	68 (63-72)	68 (63-73)
T stage					
T2*	170 (63)	171 (64)	170 (63)	169 (63)	680 (64)
T3,4	98 (37)	97 (36)	98 (37)	98 (37)	391 (37)
Gleason Score (GS)					
≤6	26 (10)	25 (9)	25 (9)	25 (9)	101 (9)
7	155 (58)	155 (58)	138 (52)	151 (57)	599 (56)
8	48 (18)	44 (16)	40 (15)	51 (19)	183 (17)
9	36 (13)	41 (15)	61 (23)	38 (14)	176 (16)
10	3 (1)	3 (1)	4 (1)	2 (1)	12 (1)
Grade group					
1 (GS ≤6)	26 (10)	25 (9)	25 (9)	25 (9)	101 (9)
2 (GS 3+4)	88 (33)	86 (32)	85 (32)	88 (33)	347 (32)
3 (GS 4+3)	67 (25)	69 (26)	53 (20)	63 (24)	252 (24)
4 (GS 8)	48 (18)	44 (16)	40 (15)	51 (19)	183 (17)
5 (GS 9,10)	39 (14)	44 (16)	65 (24)	40 (15)	188 (18)
PSA group (ng/mL)					
<10	74 (28)	74 (28)	72 (27)	73 (27)	293 (27)
10-20	110 (41)	109 (40)	110 (41)	110 (41)	439 (41)
>20	84 (31)	87 (32)	86 (32)	84 (32)	339 (32)
NCCN risk group					
Intermediate	92 (34)	98 (37)	81 (30)	89 (33)	360 (34)
High	176 (66)	170 (63)	187 (70)	178 (67)	711 (66)
Radiation dose					
66Gy	30 (11)	30 (11)	32 (12)	33 (12)	125 (12)
70Gy	111 (41)	108 (40)	106 (40)	102 (38)	427 (40)
74Gy	68 (25)	65 (24)	64 (24)	65 (24)	262 (24)
High dose rate brachytherapy	57 (21)	57 (21)	61 (23)	62 (23)	237 (22)
Not Given	2 (1)	8 (3)	5 (2)	5 (2)	20 (2)

* T2a tumours were eligible provided Gleason score ≥7 and baseline PSA levels ≥10 ng/mL

Data are n (%) unless otherwise stated

Abbreviations: STAS, short term (6 months) androgen suppression; ITAS, intermediate term (18 months) androgen suppression; Z, zoledronic acid; IQR, interquartile range; GS, Gleason score; PSA, prostate-specific antigen; NCCN, National Comprehensive Cancer Network; Gy, Gray

Table 2. Cause of death by duration of androgen suppression group

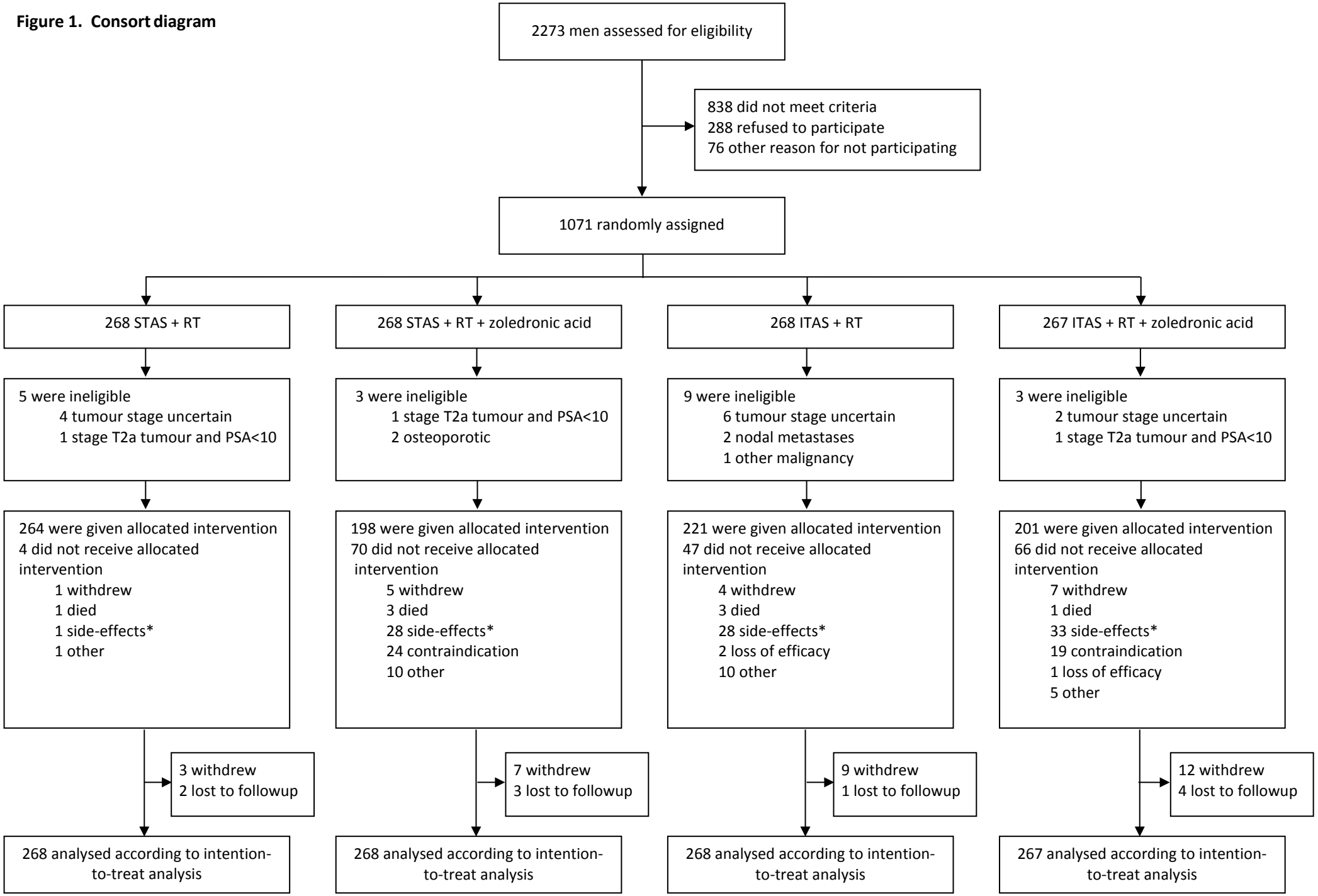
Cause of death	**6AS+RT** (n=536)	**18AS+RT** (n=535)	**Total**
Prostate cancer	81	62	143
New primary cancer	43	47	90
Abdominal	*16*	*16*	
Lung	*8*	*12*	
Other	*19*	*19*	
Cardiac	29	23	52
Cerebrovascular	8	7	15
Respiratory	20	15	35
Renal	1	5	6
Trauma	2	2	4
Dementia	6	4	10
Other known	5	8	13
Other unknown	5	2	7
Total deaths	**200**	**175**	**375**

Data are numbers

Abbreviations: 6AS+RT, 6 months of androgen suppression plus radiotherapy; 18AS+RT, 18 months of androgen suppression plus radiotherapy

List of Figure Legends

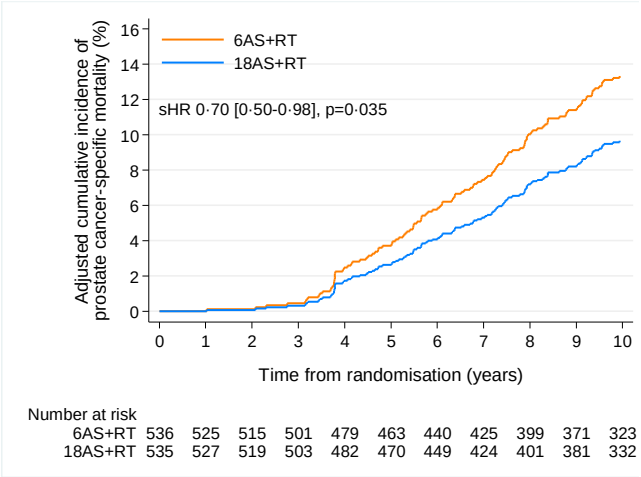
Figure 1. Consort diagram



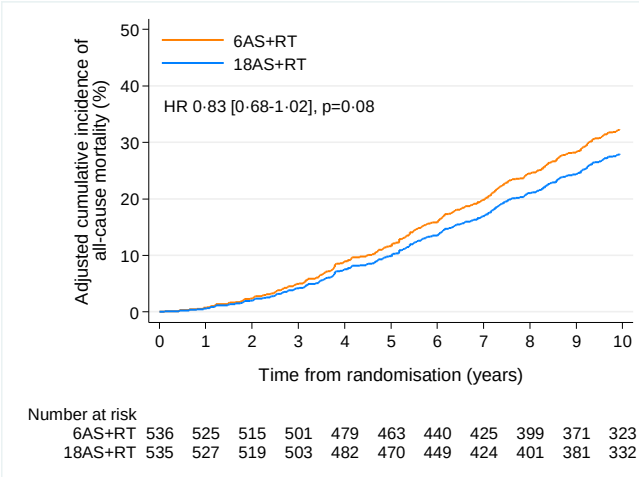
* In STAS+Z+RT all 28 side-effects were attributable to Z and there were no side-effects due to STAS (ie 6 months AS). ITAS+RT had many more side-effects than STAS+RT because they received an additional 12 months of AS. ITAS+RT+Z had the highest number of side effects because they received both experimental treatments (an extra 12 months of AS + 18 months Z).
Abbreviations: STAS, short-term (6 months) androgen suppression and radiotherapy; ITAS, intermediate-term (18 months) androgen suppression; RT, radiotherapy

Figure 2. Adjusted cumulative incidence by duration of androgen suppression group*

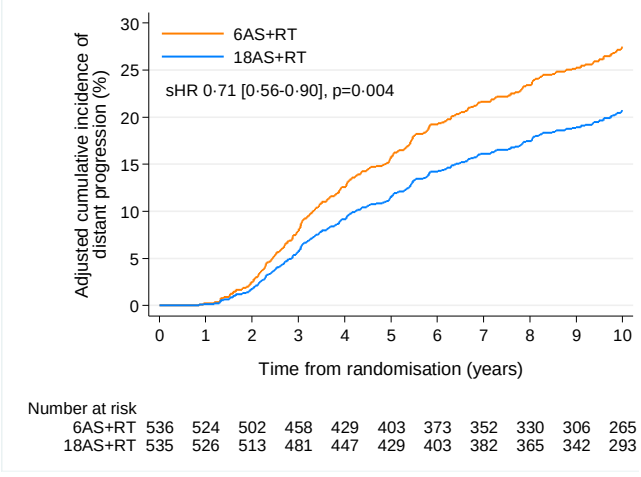
A. Prostate cancer-specific mortality



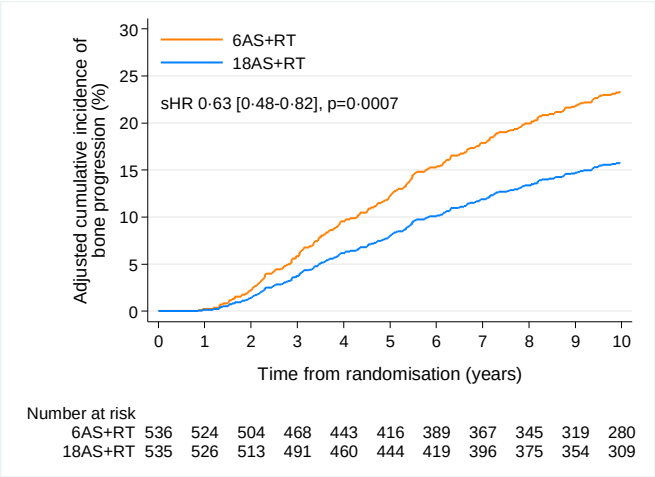
B. All-cause mortality



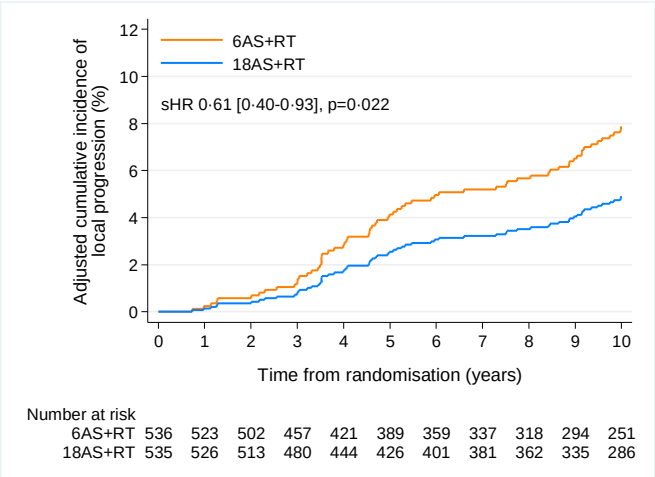
C. Distant progression



D. Bone progression



E. Local progression

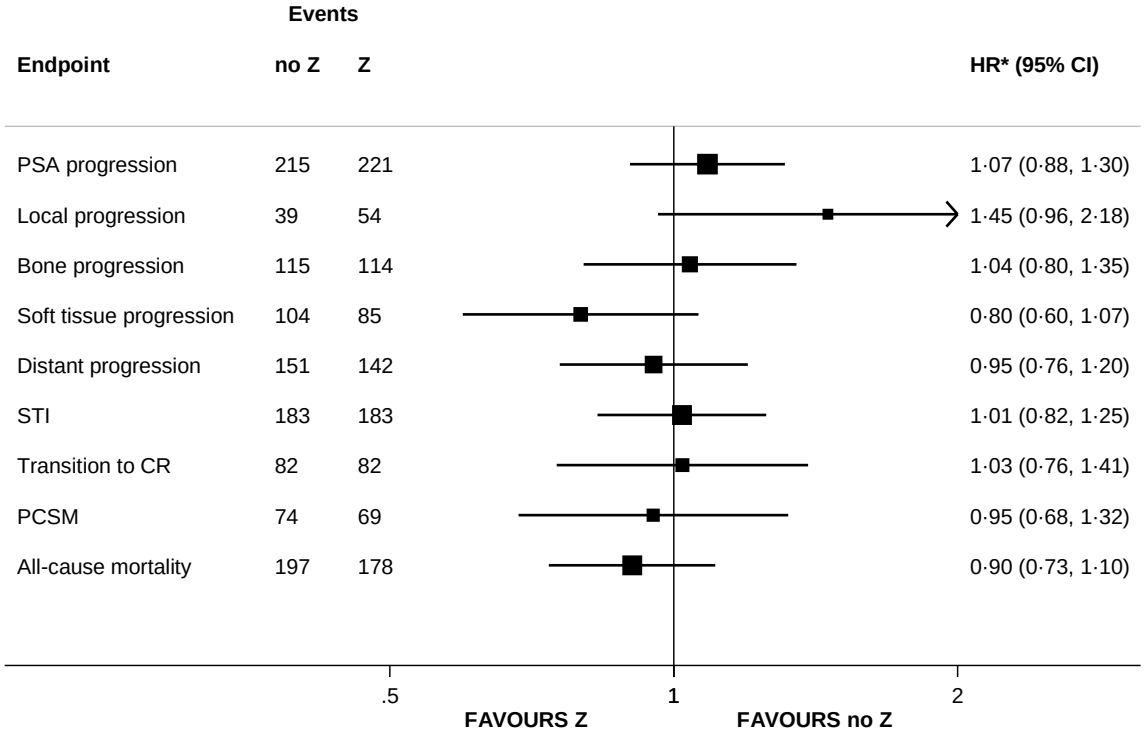


Crude numbers at risk shown

* Models adjusted for baseline PSA (<10, 10-20, >20 ng/mL), T stage (T2, T3/T4), Grade group (1 = Gleason score (GS) ≤6; 2=3+4; 3=4+3, 4= GS8, 5=GS9/10), and use of zoledronic acid (no, yes)

Abbreviations: 6AS+RT, 6 months of androgen suppression plus radiotherapy; 18AS+RT, 18 months of androgen suppression plus radiotherapy

Figure 3. Summary of treatment effects by zoledronic acid group for oncological outcomes

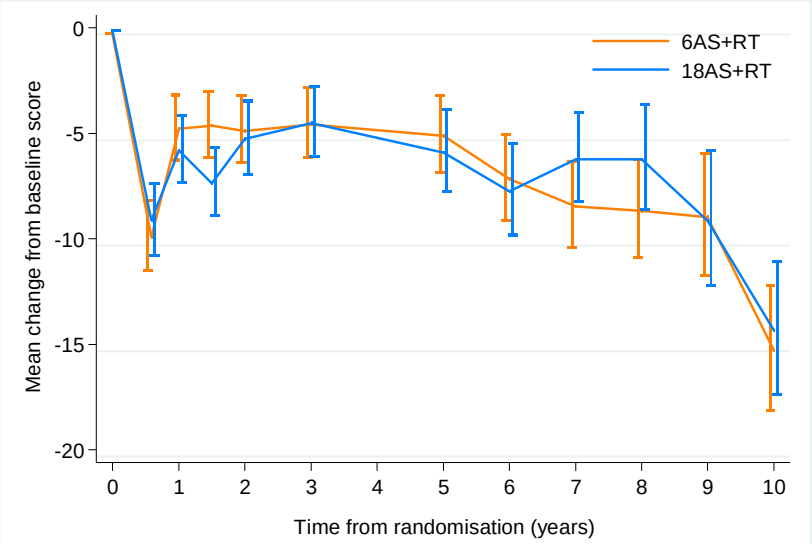


* Adjusted hazard ratio is presented for all-cause mortality and adjusted sub hazard ratios for all other outcomes. Models are adjusted for baseline PSA (<10, 10-20, >20 ng/mL), T stage (T2, T3/T4), Grade group (1 = Gleason score (GS) ≤6; 2=3+4; 3=4+3, 4= GS8, 5=GS9/10), and duration of androgen suppression (6 months, 18 months)

Abbreviations: Z, zoledronic acid; STI, secondary therapeutic intervention; CR, castration resistance; PCSM, prostate cancer-specific mortality; HR, hazard ratio; CI, confidence interval

Figure 4. Mean change from baseline score for patient-reported outcomes* and time to normal testosterone recovery by duration of androgen suppression group

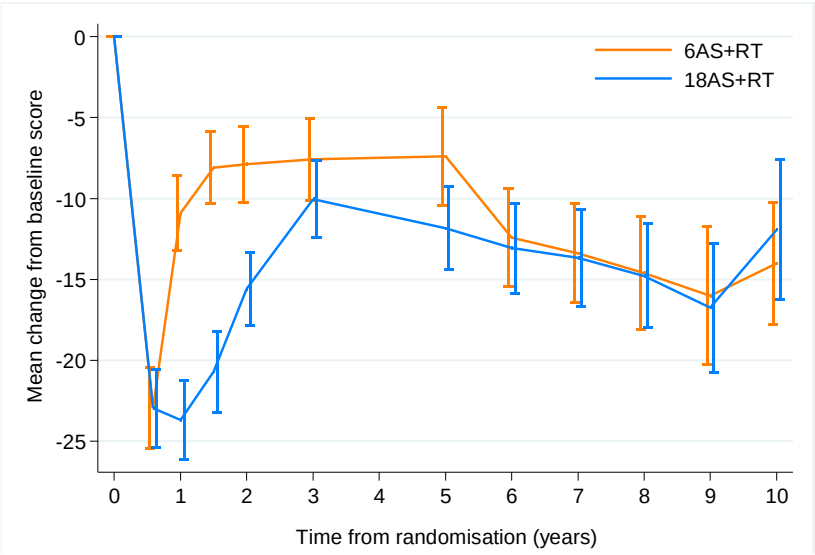
A. Global health status and quality of life†



Number at risk

6AS+RT	534	507	482	461		388	357	334	277	182	217
18AS+RT	528	514	481	462		404	371	328	289	187	211

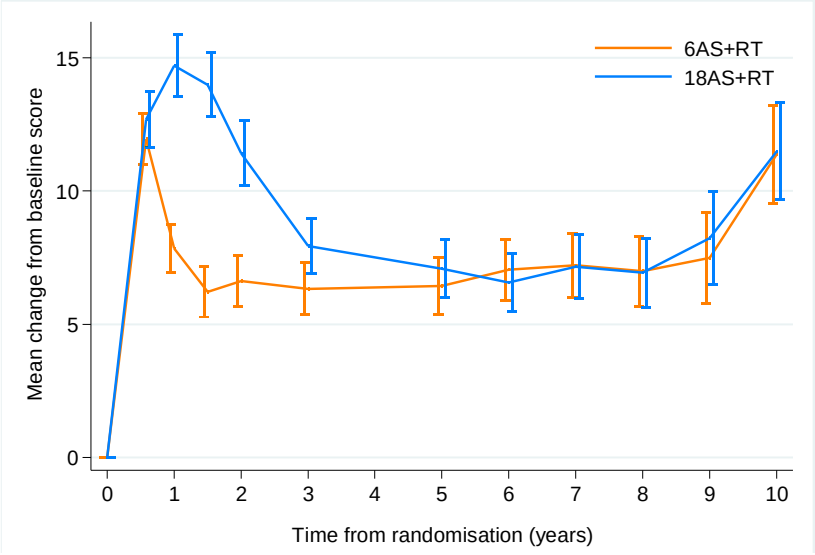
B. Sexual activity†



Number at risk

6AS+RT	530	511	489	463		390	361	338	279	178	214
18AS+RT	531	515	481	464		403	374	336	285	186	209

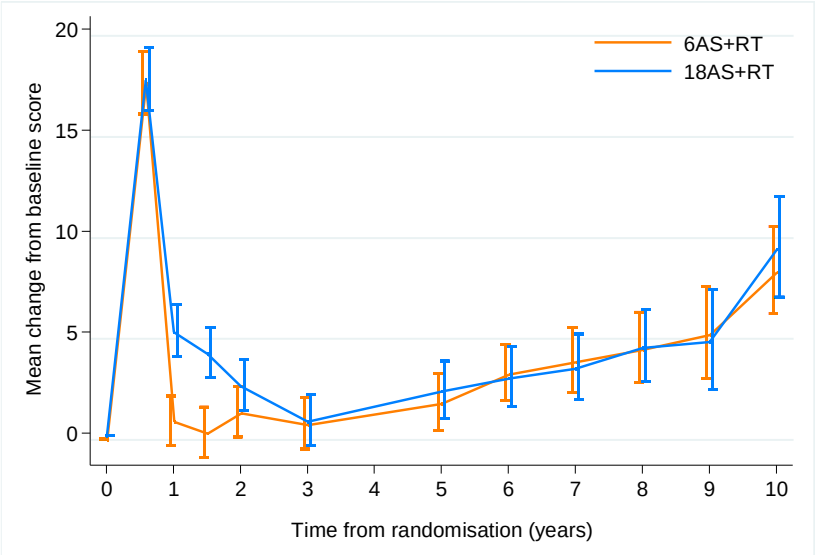
C. Hormone treatment-related symptoms‡



Number at risk

6AS+RT	533	509	491	465	391	362	338	281	182	218
18AS+RT	532	517	484	463	410	377	338	293	188	211

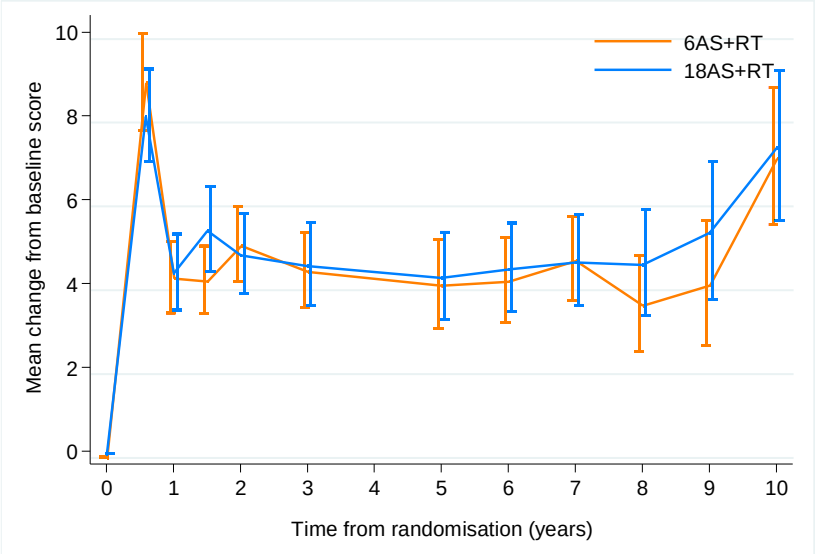
D. Urinary symptoms‡



Number at risk

6AS+RT	533	514	492	467	395	364	341	282	184	218
18AS+RT	533	518	486	468	410	382	341	296	192	212

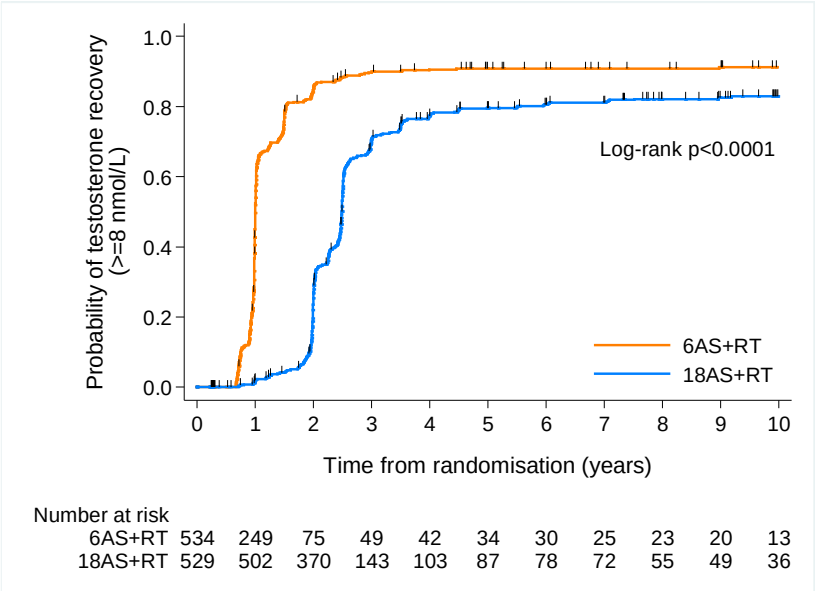
E. Bowel symptoms‡



Number at risk

6AS+RT	533	512	492	466	391	363	339	281	182	219
18AS+RT	532	518	484	463	410	379	338	294	189	211

F. Time to normal testosterone recovery



Number at risk

6AS+RT	534	249	75	49	42	34	30	25	23	20	13
18AS+RT	529	502	370	143	103	87	78	72	55	49	36

* Data are mean change scores from baseline and 95% confidence intervals

† Negative score means worse level of functioning

‡ Higher score means worse level of symptoms

Abbreviations: 6AS+RT, 6 months of androgen suppression plus radiotherapy; 18AS+RT, 18 months of androgen suppression plus radiotherapy

Supplementary Appendix
Short-term androgen suppression and radiotherapy versus intermediate-term androgen suppression and radiotherapy, with or without zoledronic acid, in men with locally advanced prostate cancer (TROG 03.04 RADAR): 10 year results from a randomised, phase 3 factorial trial

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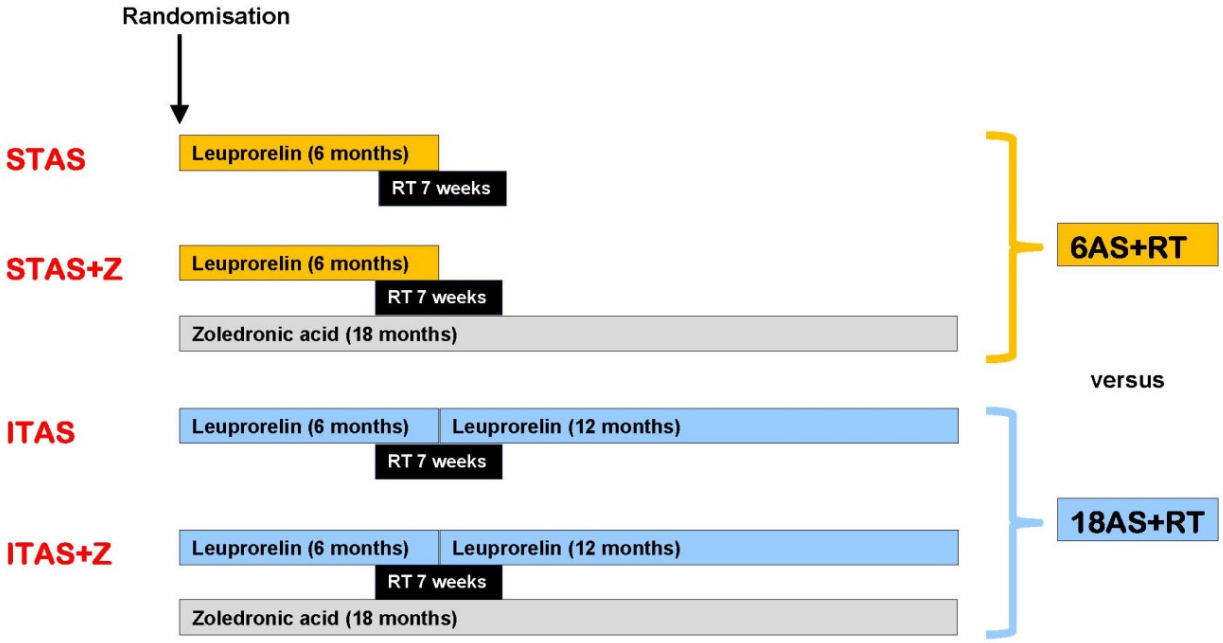
Figure S1. Trial Schema



Leuprorelin: 22.5mg im every 3 months
Zoledronic acid: 4mg iv every 3 months
STAS: short-term androgen suppression
ITAS: intermediate-term androgen suppression
Z: 18 months of zoledronic acid
RT: dose escalated radiotherapy

List of Investigators

Sites listed in order of number of subjects recruited, largest first

Site	Country	Principal Investigator	Number of subjects recruited
Sir Charles Gairdner Hospital	Australia	Prof David Joseph	328
Newcastle Mater Hospital	Australia	Prof Jim Denham	129
Wellington Hospital	New Zealand	Prof David Lamb	87
Christchurch Hospital	New Zealand	Assoc Prof Chris Atkinson	65
Auckland Hospital	New Zealand	Dr John Matthews	55
Westmead Hospital	Australia	Assoc Prof Sandra Turner	46
Geelong Hospital	Australia	Dr Rod Lynch	44
Royal Brisbane Hospital	Australia	Dr Liz Kenny	40
Peter MacCallum Cancer Centre	Australia	Prof Gillian Duchesne	38
Brisbane Mater Hospital	Australia	Dr Kumar Gogna	36
Genesiscare	Australia	Prof David Christie	31
Riverina Cancer Centre	Australia	Dr Anupam Chaudhuri	27
Illawarra Cancer Care Centre	Australia	Dr Elias Nasser	22
Princess Alexandra Hospital	Australia	Dr Margot Lehman	22
Launceston General Hospital	Australia	Dr David Byram	17
St George Hospital	Australia	Dr Joseph Bucci	14
Campbelltown Hospital	Australia	Dr Mark Sidhom	13
Liverpool Hospital	Australia	Dr Mark Sidhom	13
Royal North Shore Hospital	Australia	Dr Thomas Eade	13
Dunedin Hospital	New Zealand	Dr John North	11
Nepean Hospital	Australia	Dr Viet Do	10
Palmerston North Hospital	New Zealand	Dr Johan Nel	8
Waikato Hospital	New Zealand	Dr Leanne Tyrie	2
		Total	**1071**

* formerly known as East Coast Cancer Centre – Gold Coast

Supplementary Notes

a) Interactions between Gleason score and zoledronic acid

An interaction between the use of zoledronic acid (Z) and Gleason score (GS) was reported in the preliminary main endpoints analyses in Lancet Oncology in 2014. In those analyses the interaction was strongest for the bone progression endpoint. At that point, there were significant multiplicative interactions between the use of Z and GS score for bone and distant progression, with similar sub hazard ratios of 0.51 and 0.50 respectively. The total number of bone progression events increased from 176 in 2014 to 229 in 2017 and distant progression events from 218 in 2014 to 293 in 2017. The tests for interaction between Z and GS were repeated in 2017 for the 10 year data (Table S1). We found that sub hazard ratios (sHR) moved closer to 1 and p values no longer reached significance confirming dissipations of the interactions involving these two endpoints.

b) The impact of the modified Gleason score in ISUP 2005 on RADAR trial stratification

When the RADAR trial protocol was finalised in 2003 it was estimated that Gleason score (GS) ≤6 tumours would occur in approximately one half of subjects randomly allocated in the trial. To control the number of strata used in the minimisation randomisation process, it seemed reasonable to stratify GS histology at the ≤6 cut point. In 2005 after the trial had been recruiting subjects for approximately 2 years, it became obvious that the great majority of pathologists across Australia and New Zealand would adopt the recommendation of the 2005 International Society of Urological Pathologists (ISUP). In doing so it was felt by the RADAR trial management committee (which includes an ISUP participant, Professor Brett Delahunt, as the trial's pathologist) that the proportion of newly diagnosed men with GS ≤6 tumours could fall in the remaining years of recruitment. However, the magnitude of the fall was not fully anticipated. There were several reasons for the substantial upgrading that was ultimately seen:

1. Upgrading the previously pattern 3 components of poorly formed fused glands and cribriform glands to pattern 4.
2. The introduction of a tertiary pattern into the scoring scheme. Men who had tertiary patterns that were higher than the secondary would have the tertiary pattern replace the secondary in the scoring system. For example, a man with a GS 4+3 tumour with a very small volume of pattern 5 tumour would have his tumour upgraded from GS 4+3=7 to GS 4+5=9, a very different scenario.
3. GS patterns 1 and 2 are not diagnosed in thin core biopsies according to the recommendations of the 2005 Modified Gleason classification. As a result most men who had hitherto been diagnosed with total GS tumour <6 were removed from the scheme.

The overall impact of these three sets of changes in scoring criteria was to produce a large reduction in the proportion of men diagnosed with total GS ≤6 tumours. When the final subject was enrolled in August 2007, the proportion of men with GS ≤6 tumours had dropped from an anticipated 50% to 9%. (Only 7 men had GS<6, all of which were total score 5.) This led to an increase in the proportion of men with GS ≥7 tumours to 91%. The five tier 2014 ISUP grading scale designates ≤6 tumours as Grade 1 and divides GS ≥7 tumours into four grades (Grade 2 = GS 3+4; Grade 3 = GS 4+3; Grade 4 = GS 4+4, 3+5 and 5+3; Grade 5 = GS 4+5, 5+4 or 5+5) that resulted in a sizeable prognostic gradient across these four grades (as shown in the tabulation below) or to no gradient at all for men in the GS ≤6 tumours trial stratum.

Using 2014 RADAR distant progression (DP) data:

2014 ISUP Grade	**Number of subjects**	**Number of DP events**
2	347 (35.8%)	38/347 (10.95%)
3	252 (26.0%)	54/252 (21.43%)
4	183 (18.9%)	42/183 (22.95%)
5	188 (19.4%)	79/188 (42.02%)
Totals	970 (100%)	213/970 (21.96%)

This gradient is to be compared with the DP gradient associated with the RADAR two tier stratification covariable:

GS ≤6 5/101 (4.95%)
GS ≥7 213/970 (21.96%)

The five-tier 2014 ISUP grading system is associated with a more precise and larger prognostic gradient than the dichotomous RADAR stratification scheme. Therefore the use of ISUP grade as a five tier categorical variable rather than the dichotomous RADAR stratification variable, alongside the other trial stratification variables (T stage and PSA), will increase the power of the models used to discriminate differences between the treatment groups.

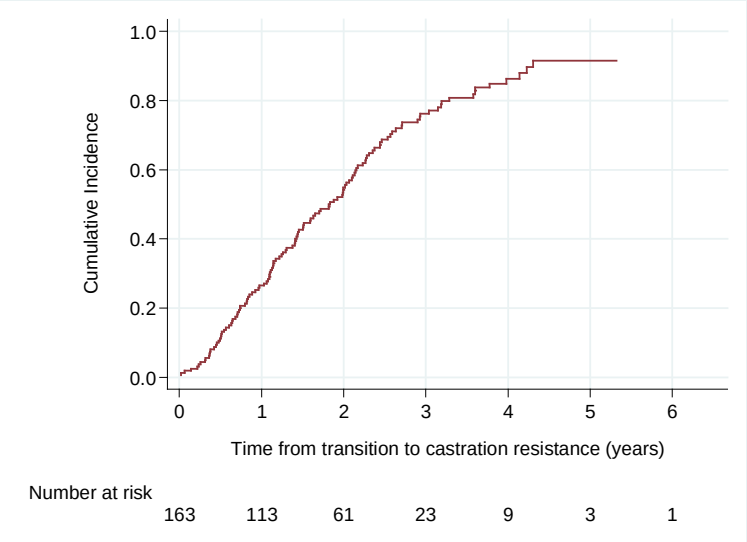
c) Transition to castration resistance and prostate cancer-specific mortality

Transition to the castration resistant form of prostate cancer (CRPC) is a fatal event that renders the tumour incurable by any known means. We found that a reasonable estimate of the timing of the earliest signs of transition to castration resistance (TCR) can be obtained using the approach defined in the guidelines shown in Table S2, even in subjects who do not have serial testosterone measures.[1-3]

Figure S2A shows the cumulative incidence of PCSM from the time of TCR. Median time to PCSM was 22 months (95% CI 17-25) and at 5 years >90% had died of prostate cancer (PC). In the 126 men who developed TCR and subsequently died of PC, the correlation between times from randomisation to TCR and PCSM is very strong (Pearson correlation $\rho=0.92$, $p<0.001$) as shown in Figure S2B. This suggests that time to TCR from randomisation could be a very good intermediate endpoint which could predict time to PCSM reasonably accurately. In 2014 PC deaths were less frequent than expected and it was realised at the time that at the end of 2017, it would be highly likely for funding to cease and for participant follow-up to be curtailed at 10 years. There were therefore very real fears in 2014 that the primary endpoint of the trial (PCSM) would be underpowered and the results of the trial would be inconclusive. It was thought that the powerful correlation between times to TCR and PCSM, shown in Figure S2B, could be helpful in predicting survival outcomes by deriving the composite endpoint of TCR and PCSM.

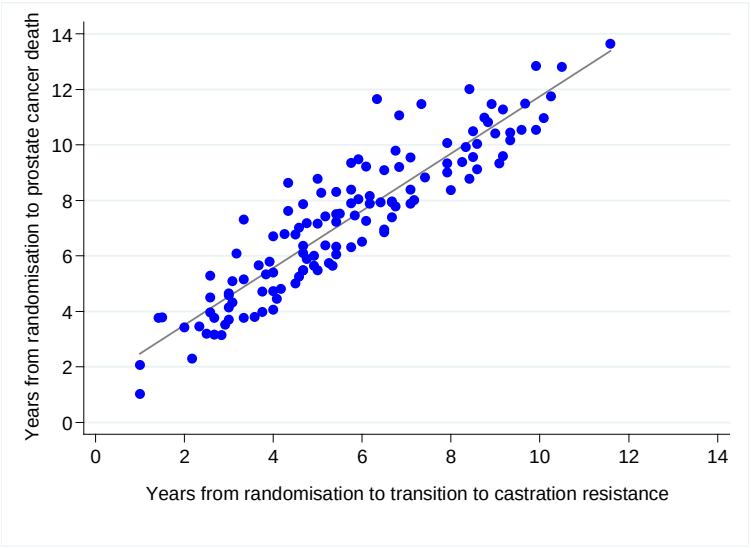
A sensitivity analysis using the composite endpoint TCR/PCSM was planned if trial factor or trial arm differences for the primary endpoint PCSM could not be resolved in the 10 year analysis due to lack of power. However, since the trial did produce a significant result for PCSM, this sensitivity analysis was not necessary.

Figure S2A. Cumulative incidence of PCSM after transition to castration resistance



Number of subjects (total =1071)	
Developed TCR	163
TCR + PC death	126
TCR + other death	7
TCR + alive	30
PC death without TCR	17
Time (months) – median, 95% CI	
TCR to PC death	22 (17-25)

Figure S2B. Correlation between time to transition to castration resistance and time to PC death measured from randomisation

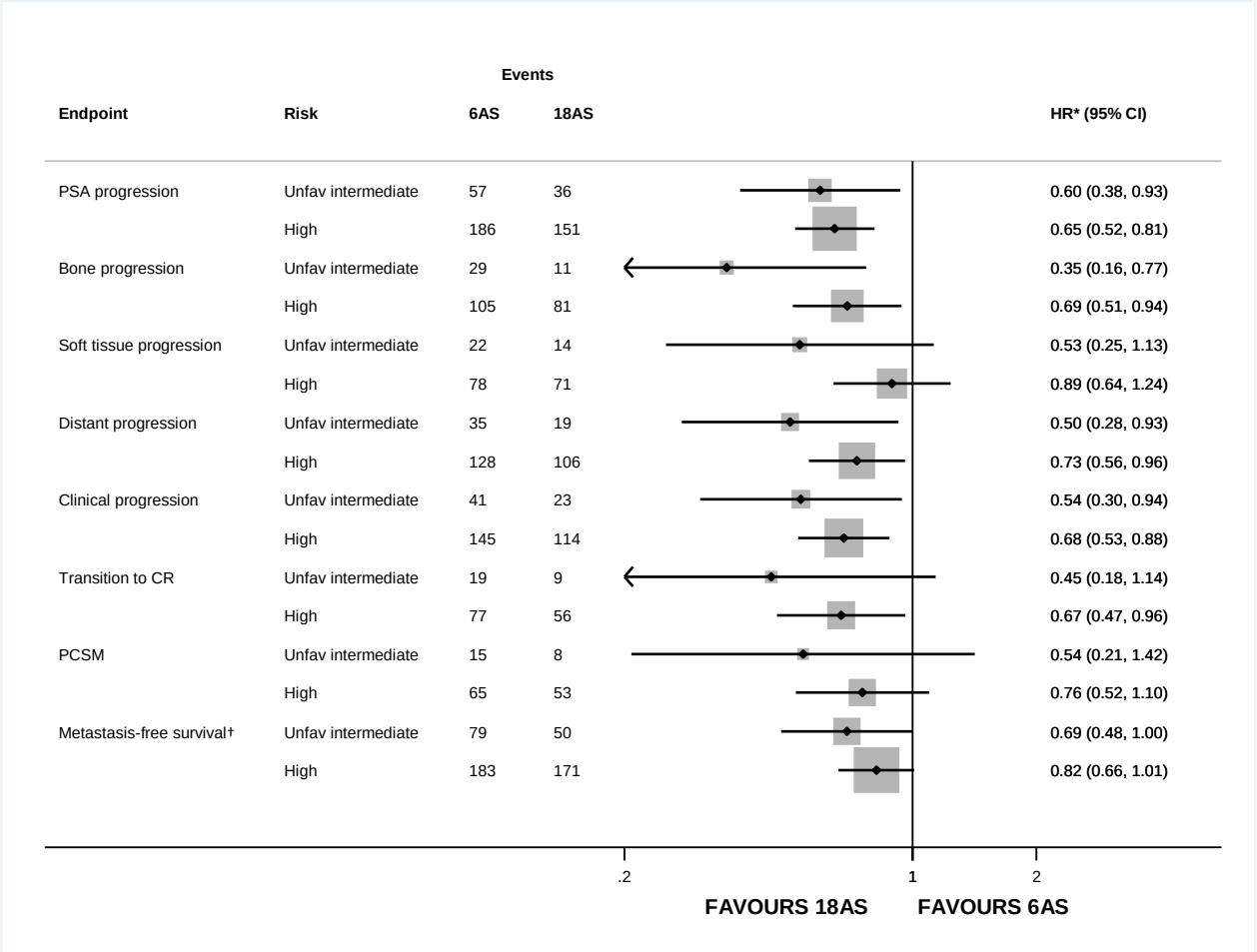


The RADAR trial showed that 18AS+RT is more effective than 6AS+RT in men with locally advanced prostate cancers. We also performed a post-hoc, hypothesis-generating analysis to explore the effect of AS duration according to NCCN risk classification. The forest plot (Figure S3) provides evidence that 18AS+RT may be more effective than 6AS+RT in both unfavourable intermediate and high risk cancers.

"Locally advanced" prostate cancers were originally designated as being T2b and above and are therefore included in the unfavourable intermediate and high risk categories. Most are seen to benefit more from 18AS+RT than 6AS+RT.

The current NCCN guidelines (Version 3.2018) recommend the use of dose-escalated radiotherapy (DERT) +/- 4-6 months of AS for men with unfavourable intermediate risk prostate cancers. In view of the RADAR findings, this raises the question whether these men would benefit from a trial comparing 6 months of AS plus dose-escalated radiotherapy (DERT) with 18 months of AS plus DERT.

Figure S3. Duration of androgen suppression effects by NCCN risk classification



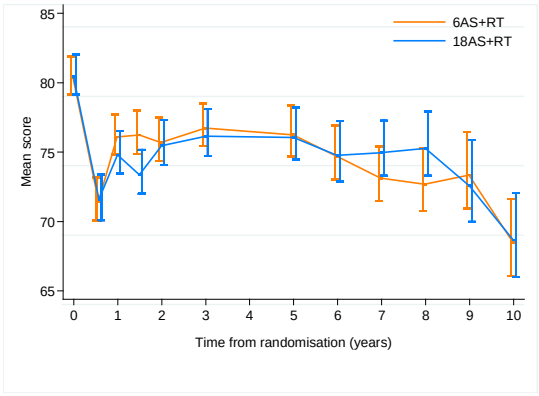
* Adjusted hazard ratio is presented for metastasis-free survival and adjusted sub hazard ratios for all other outcomes. Models are adjusted for baseline age, PSA (continuous), T stage (2a, 2b, 2c, 3/4), Grade group (1 = Gleason score (GS) ≤6; 2=3+4; 3=4+3, 4= GS8, 5=GS9/10), use of zoledronic acid (no, yes), use of high dose rate brachytherapy (no, yes)

† Time to distant progression or death from any cause (identified as a surrogate for PCSM and overall survival)[4]

Favourable intermediate subgroup not presented due to very small number of cases (24/1071 men)

Figure S4. Patient-reported outcomes by duration of androgen suppression group (intention to treat analysis)

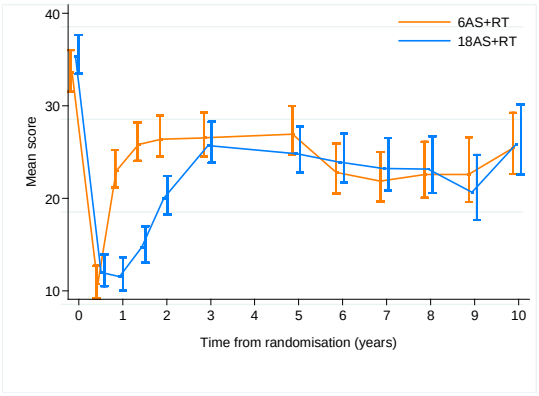
A. Global health status and quality of life†



Number at risk

6AS+RT	534	507	482	461	388	357	334	277	182	217
18AS+RT	528	514	481	462	404	371	328	289	187	211

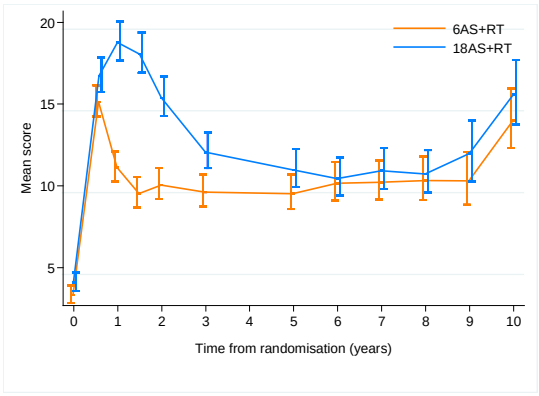
B. Sexual activity†



Number at risk

6AS+RT	530	511	489	463	390	361	338	279	178	214
18AS+RT	521	515	481	464	403	374	336	285	186	209

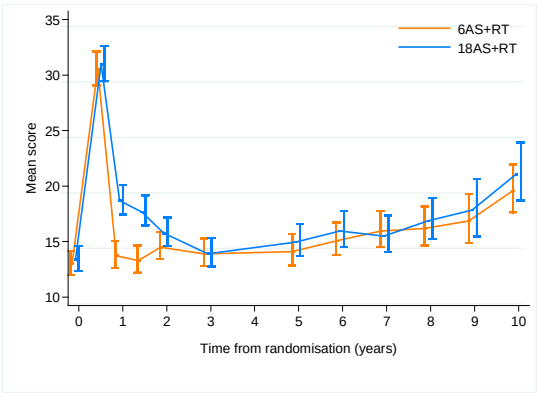
C. Hormone treatment-related symptoms‡



Number at risk

6AS+RT	533	514	492	467	395	364	341	282	184	218
18AS+RT	533	518	486	468	410	382	341	296	192	212

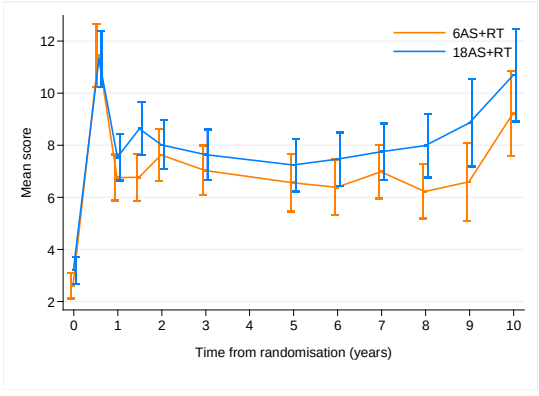
D. Urinary symptoms‡



Number at risk

6AS+RT	533	509	491	465	391	362	338	281	182	218
18AS+RT	532	517	484	463	410	377	338	293	188	211

E. Bowel symptoms‡



Number at risk

6AS+RT	534	507	482	461	388	357	334	277	182	217
18AS+RT	528	514	481	462	404	371	328	289	187	211

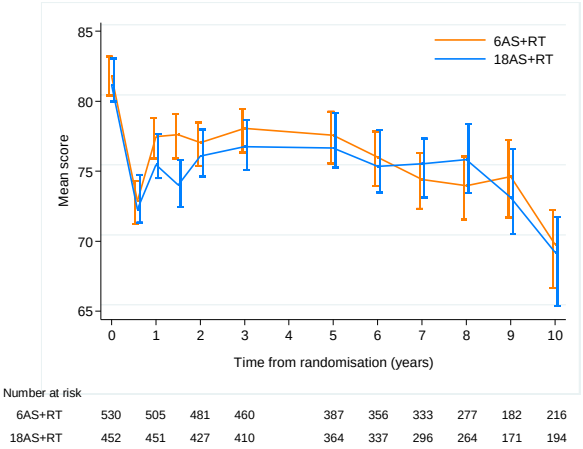
Data are mean scores and 95% confidence intervals. Scores are normalised to a 0-100 scale.

† Higher score means better level of functioning.
‡ Higher score means worse level of symptoms.

Abbreviations: 6AS+RT, 6 months of androgen suppression plus radiotherapy; 18AS+RT, 18 months of androgen suppression plus radiotherapy

Figure S5. Patient-reported outcomes by duration of androgen suppression group (per-protocol, post-hoc exploratory analysis)

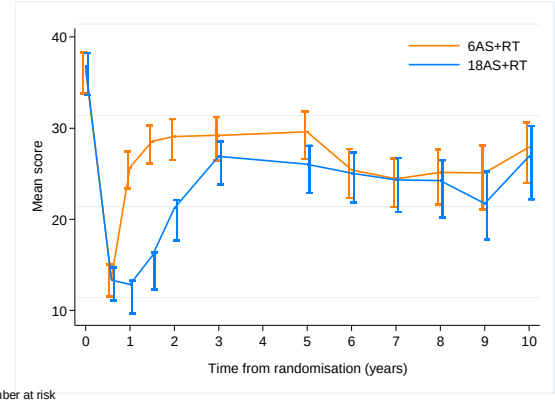
A. Global health status and quality of life†



Number at risk

6AS+RT	530	505	481	460	387	356	333	277	182	216
18AS+RT	452	451	427	410	364	337	296	264	171	194

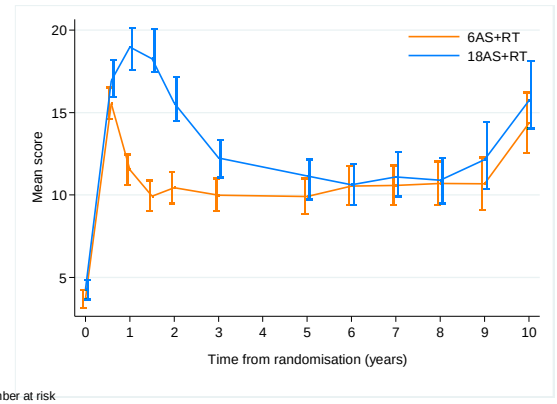
B. Sexual activity†



Number at risk

6AS+RT	526	509	488	462	389	360	337	279	178	213
18AS+RT	453	451	426	411	363	341	307	260	170	192

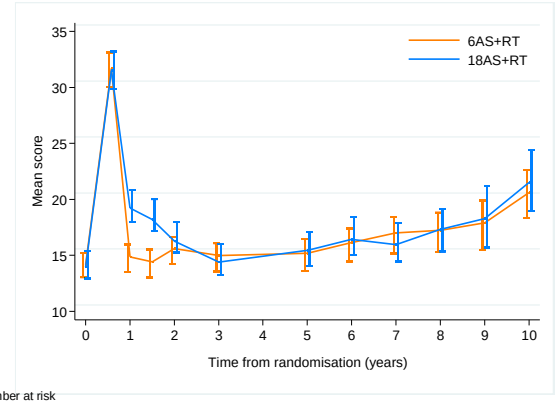
C. Hormone treatment-related symptoms‡



Number at risk

6AS+RT	529	512	491	466	394	363	340	282	184	217
18AS+RT	455	454	431	415	369	347	310	271	176	196

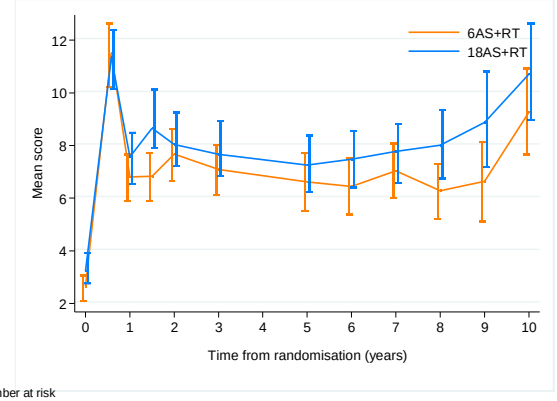
D. Urinary symptoms‡



Number at risk

6AS+RT	529	507	490	464	390	361	337	281	182	217
18AS+RT	454	453	429	410	369	344	307	269	173	195

E. Bowel symptoms‡



Number at risk

6AS+RT	529	510	491	465	390	362	338	281	182	218
18AS+RT	454	454	429	411	369	345	307	269	173	195

Data are mean scores and 95% confidence intervals. Scores are normalised to a 0-100 scale.

† Higher score means better level of functioning.
‡ Higher score means worse level of symptoms.

Abbreviations: 6AS+RT, 6 months of androgen suppression plus radiotherapy; 18AS+RT, 18 months of androgen suppression plus radiotherapy

Table S1. Multiplicative interaction estimates between Gleason score (≤7/>7) and zoledronic acid

Endpoint	Year	No. events	Sub hazard ratio	p-value
Bone progression	2014	176	0.51	0.031
	2017	229	0.71	0.20
Distant progression	2014	218	0.50	0.012
	2017	293	0.73	0.18

Table S2. TROG 03.04 RADAR Trial Guidelines for the timing of transition to castration resistance

RADAR GUIDELINES FOR THE TIMING OF CRPC TRANSITION (10-4-17)

Clinical scenarios

1. **Serial testosterone and PSA concentrations available:**

   (a) A new diagnosis, or a diagnosis of worsening metastatic progression while testosterone levels remain in the castrate range (i.e. ≤0.7nmol/L). Evidence of on-going LHRH desirable. Timing of CRPC transition is the date of diagnosis of metastatic progression as defined above has occurred.

   (b) A PSA rise (*defined below) while testosterone levels remain in the castrate range (i.e. ≤0.7nmol/L). Evidence of on-going LHRH desirable. Timing of CRPC transition is when the required PSA rise has occurred (*defined below).

2. **Serial testosterone concentrations unavailable**:

   (a) A new diagnosis, or a diagnosis of worsening metastatic progression while patient remains on a LHRH agonist commenced at least 2 months prior to diagnosis without evidence of a descent in PSA. Timing of CRPC transition is the date diagnosis of metastatic progression as defined above has occurred.

   (b) A PSA rise (*defined below) while the patient remains on a LHRH agonist or antagonist, alternatively orchidectomy ± anti-androgen (but not anti-androgen alone). Timing of CRPC transition is when the required PSA rise has occurred (*defined below).

***Required rise in PSA for the purpose of determining the timing of CRPC transition**:

While testosterone levels are in castrate range or while patient is on a LHRH preparation or has had an orchidectomy, the following rises in PSA **must** have occurred:

(a) Two or more consecutive PSA rises

and/or (b) A rise amounting to>= 5ng/ml.

Timing is based on the date of the last PSA reading that has triggered the CRPC transition call (not an interpolated time point between PSA's).

The timing of a prescription of a CRPC drug (with the exception of denosumab, bisphosphonates and docetaxel, given alongside ADT for castrate sensitive bone progression) is not essential for the determination of timing of CRPC but provides supporting evidence that the transition to CRPC has occurred.

Table S3. Baseline characteristics by duration of androgen suppression group

	6AS+RT (n=536)		18AS+RT (n=535)	
Age (years)				
Median (IQR)	69 (63-73)		68 (63-72)	
T stage				
T2†	341	(64)	339	(63)
T3,4	195	(36)	196	(37)
Gleason Score (GS)				
≤6	51	(10)	50	(9)
7	310	(58)	289	(54)
8	92	(17)	91	(17)
9	77	(14)	99	(19)
10	6	(1)	6	(1)
ISUP Score				
1 (GS ≤6)	51	(10)	50	(9)
2 (GS 3+4)	174	(32)	173	(32)
3 (GS 4+3)	136	(25)	116	(22)
4 (GS 8)	92	(17)	91	(17)
5 (GS 9,10)	83	(15)	105	(20)
PSA group (ng/ml)				
<10	148	(28)	145	(27)
10-20	219	(41)	220	(41)
>20	169	(32)	170	(32)
NCCN risk group				
Favourable intermediate	9	(2)	15	(3)
Unfavourable intermediate	181	(34)	155	(29)
High	346	(65)	365	(68)
Zoledronic acid (18 months)				
No	268	(50)	268	(50)
Yes	268	(50)	267	(50)
Radiation dose				
66Gy	60	(11)	65	(12)
70Gy	219	(41)	208	(39)
74Gy	133	(25)	129	(24)
High dose rate brachytherapy	114	(21)	123	(23)
Not Given	10	(2)	10	(2)

There were no significant differences between the two groups.
Data are n (%) unless otherwise stated.
Percentages may not add to 100 due to rounding.
Abbreviations: 6AS+RT, 6 months of androgen suppression plus radiotherapy; 18AS+RT, 18 months of androgen suppression plus radiotherapy; IQR, interquartile range; GS, Gleason score; PSA, prostate-specific antigen; NCCN, National Comprehensive Cancer Network; Gy, Gray

Table S4. Baseline characteristics by zoledronic acid group

	No Z (n=536)		Z (n=535)	
Age (years)				
Median (IQR)	69 (63-73)		68 (63-72)	
T stage				
T2	34	(63)	340	(64)
T3,4	196	(37)	195	(36)
Gleason Score (GS)				
≤6	51	(10)	50	(9)
7	293	(55)	306	(57)
8	88	(16)	95	(18)
9	97	(18)	79	(15)
10	7	(1)	5	(1)
ISUP Score				
1 (GS ≤6)	51	(10)	50	(9)
2 (GS 3+4)	173	(32)	174	(33)
3 (GS 4+3)	120	(22)	132	(25)
4 (GS 8)	88	(16)	95	(18)
5 (GS 9,10)	104	(19)	84	(16)
PSA group (ng/ml)				
<10	146	(27)	147	(27)
10-20	220	(41)	219	(41)
>20	170	(32)	169	(32)
NCCN risk group				
Intermediate	173	(32)	187	(35)
High	363	(68)	348	(65)
Radiation dose				
66Gy	62	(12)	63	(12)
70Gy	217	(40)	210	(39)
74Gy	132	(25)	130	(24)
High dose rate brachytherapy	118	(22)	119	(22)
Not Given	7	(1)	13	(2)

There were no significant differences between the two groups.
Data are n (%) unless otherwise stated.
Percentages may not add to 100 due to rounding.
Abbreviations: Z, zoledronic acid; IQR, interquartile range; GS, Gleason score; PSA, prostate-specific antigen; NCCN, National Comprehensive Cancer Network; Gy, Gray

Table S5. Overall compliance with questionnaires for patient-reported outcomes

Time point	Number of participants who completed questionnaires / number of participants on study		
	6AS+RT	18AS+RT	Overall compliance
Baseline	534/536 (99.6%)	533/535 (99.6%)	1067/1071 (99.6%)
7 months*	512/529 (96.8%)	513/529 (97.0%)	1025/1058 (96.9%)
12 months	515/525 (98.1%)	518/527 (98.3%)	1033/1052 (98.2%)
18 months	503/520 (96.7%)	505/523 (96.6%)	1008/1043 (96.6%)
2 years	494/515 (95.9%)	487/519 (93.8%)	981/1034 (94.9%)
3 years	470/501 (93.8%)	470/503 (93.4%)	940/1004 (93.6%)
5 years	398/463 (86.0%)	411/470 (87.4%)	809/933 (86.7%)
6 years	367/440 (83.4%)	382/449 (85.1%)	749/889 (84.4%)
7 years	341/425 (80.2%)	343/424 (80.9%)	684/849 (80.6%)
8 years	284/399 (71.2%)	296/401 (73.8%)	580/800 (72.5%)
9 years	185/371 (49.9%)	192/381 (50.4%)	377/752 (50.1%)
10 years	219/323 (67.8%)	213/332 (64.2%)	432/655 (66.0%)

Data are n/N (%).
* End of radiotherapy
Abbreviations: 6AS+RT, 6 months of androgen suppression and radiotherapy; 18AS+RT, 18 months of androgen suppression and radiotherapy

Table S6. Longitudinal mean changes from baseline scores in patient-reported outcomes according to duration of androgen suppression group (intention-to-treat)

	6AS+RT			18AS+RT			
Patient-reported Outcome	**n**	**Mean***	**95% CI**	**n**	**Mean***	**95% CI**	**p-value**
Global health status and quality of life†							
End of radiotherapy (7 months)	503	-9.6	-11.3 – -7.9	505	-9.0	-10.7 – -7.3	0.61
1 year	506	-4.5	-6.0 – -2.9	509	-5.6	-7.2 – -4.1	0.30
1.5 years	493	-4.3	-5.9 – -2.8	492	-7.2	-8.8 – -5.6	0.012
2 years	481	-4.6	-6.2 – -3.0	476	-5.1	-6.9 – -3.4	0.64
3 years	460	-4.3	-5.9 – -2.6	457	-4.4	-6.0 – -2.7	0.93
5 years	387	-4.8	-6.6 – -3.0	399	-5.8	-7.7 – -3.8	0.49
6 years	356	-6.9	-8.9 – -4.8	368	-7.6	-9.8 – -5.4	0.63
7 years	334	-8.2	-10.2 – -6.2	325	-6.1	-8.2 – -4.0	0.16
8 years	276	-8.4	-10.7 – -6.1	287	-6.1	-8.6 – -3.6	0.19
9 years	182	-8.7	-11.6 – -5.8	186	-9.0	-12.2 – -5.8	0.89
10 years	217	-15.0	-18.0 – -12.0	208	-14.2	-17.4 – -11.1	0.72
Sexual activity‡							
End of radiotherapy (7 months)	501	-23.0	-25.4 – -20.5	510	-23.0	-25.4 – -20.6	0.99
1 year	505	-10.9	-13.2 – -8.6	512	-23.7	-26.1 – -21.3	**<0.0001**
1.5 years	495	-8.1	-10.3 – -5.9	500	-20.7	-23.2 – -18.2	**<0.0001**
2 years	485	-7.9	-10.2 – -5.5	479	-15.6	-17.8 – -13.3	**<0.0001**
3 years	459	-7.6	-10.1 – -5.1	461	-10.1	-12.4 – -7.7	0.16
5 years	386	-7.4	-10.4 – -4.4	400	-11.8	-14.4 – -9.3	0.027
6 years	358	-12.4	-15.5 – -9.4	371	-13.1	-15.9 – -10.3	0.76
7 years	335	-13.4	-16.4 – -10.3	335	-13.7	-16.7 – -10.7	0.89
8 years	275	-14.6	-18.1 – -11.1	283	-14.8	-18.0 – -11.6	0.94
9 years	176	-16.0	-20.3 – -11.8	184	-16.8	-20.7 – -12.8	0.80
10 years	213	-14.0	-17.8 – -10.2	207	-11.9	-16.2 – -7.6	0.47
Hormone treatment-related symptoms‡							
End of radiotherapy (7 months)	507	11.9	11.0 – 12.9	512	12.7	11.6 – 13.7	0.31
1 year	511	7.8	6.9 – 8.7	517	14.7	13.6 – 15.9	**<0.0001**
1.5 years	501	6.2	5.3 – 7.2	503	14.0	12.8 – 15.2	**<0.0001**
2 years	490	6.6	5.7 – 7.6	486	11.4	10.2 – 12.6	**<0.0001**
3 years	465	6.3	5.4 – 7.3	467	7.9	6.9 – 9.0	0.026
5 years	393	6.4	5.4 – 7.5	409	7.1	6.0 – 8.2	0.40
6 years	362	7.0	5.9 – 8.2	381	6.6	5.5 – 7.6	0.55
7 years	340	7.2	6.0 – 8.4	341	7.2	6.0 – 8.4	0.96
8 years	280	7.0	5.7 – 8.3	296	6.9	5.6 – 8.2	0.96
9 years	183	7.5	5.8 – 9.2	192	8.2	6.5 – 10.0	0.55
10 years	217	11.4	9.5 – 13.2	212	11.5	9.7 – 13.3	0.93
Urinary symptoms‡							
End of radiotherapy (7 months)	502	17.6	16.1 – 19.2	509	17.6	16.1 – 19.2	0.98
1 year	506	0.9	-0.4 – 2.1	515	5.2	3.9 – 6.5	**<0.0001**
1.5 years	499	0.3	-1.0 – 1.5	501	4.1	2.8 – 5.3	**<0.0001**
2 years	489	1.3	0.1 – 2.5	483	2.5	1.2 – 3.7	0.20
3 years	463	0.7	-0.6 – 2.0	461	0.7	-0.6 – 2.0	0.997
5 years	389	1.7	0.3 – 3.2	408	2.2	0.8 – 3.6	0.67
6 years	360	3.2	1.8 – 4.6	375	2.8	1.3 – 4.3	0.72
7 years	337	3.8	2.2 – 5.4	338	3.3	1.7 – 4.9	0.67
8 years	279	4.4	2.7 – 6.2	292	4.4	2.6 – 6.1	0.95
9 years	181	5.2	2.9 – 7.4	187	4.6	2.2 – 7.1	0.76
10 years	217	8.2	6.1 – 10.4	211	9.2	6.7 – 11.7	0.56

Table S6. Longitudinal mean changes from baseline scores in patient-reported outcomes according to duration of androgen suppression group (intention-to-treat) (cont.)

	6AS+RT			18AS+RT			
Patient-reported Outcome	**n**	**Mean***	**95% CI**	**n**	**Mean***	**95% CI**	**p-value**
Bowel symptoms‡							
End of radiotherapy (7 months)	506	8.9	7.8 – 10.1	510	8.1	7.8 – 9.2	0.28
1 year	509	4.3	3.4 – 5.1	516	4.3	3.4 – 5.2	0.94
1.5 years	499	4.2	3.4 – 5.0	501	5.3	3.4 – 6.4	0.09
2 years	490	5.1	4.2 – 5.9	483	4.8	4.2 – 5.7	0.65
3 years	464	4.4	3.5 – 5.3	461	4.5	3.5 – 5.5	0.92
5 years	389	4.1	3.0 – 5.2	408	4.2	3.0 – 5.2	0.88
6 years	361	4.2	3.2 – 5.2	377	4.4	3.2 – 5.5	0.77
7 years	338	4.7	3.7 – 5.7	338	4.6	3.7 – 5.6	0.88
8 years	279	3.6	2.5 – 4.8	293	4.5	2.5 – 5.8	0.30
9 years	181	4.1	2.6 – 5.6	188	5.3	2.6 – 6.9	0.30
10 years	218	7.1	5.5 – 8.8	211	7.3	5.5 – 9.1	0.89

p-value < 0.01 indicates statistically significant difference to account for multiple comparisons (in bold)
* Negative mean change score from baseline means worsening in function (global health, sexual activity)
Positive mean change score from baseline means worsening in symptoms (hormone treatment-related, urinary and bowel symptoms)
† EORTC QLQ-C30
‡ EORTC PR25 prostate cancer module
Abbreviations: 6AS+RT, 6 months of androgen suppression and radiotherapy; 18AS+RT, 18 months of androgen suppression and radiotherapy

Table S7. Proportions of men with worsened, improved or stable patient-reported outcome scores from baseline according to duration of androgen suppression group (intention-to-treat)

Patient-reported Outcome*		Worsening (≥10 change from baseline score)		Improvement (≥10 change from baseline score)		Stable (<10 change from baseline score)		
		6AS+RT	18AS+RT	6AS+RT	18AS+RT	6AS+RT	18AS+RT	p-value
Sexual activity†								
	1 year	48.9% (505)	67.2% (512)	16.4% (505)	7.8% (512)	34.7% (505)	25.0% (512)	**<0.0001**
	1.5 years	44.7% (495)	63.8% (500)	20.4% (495)	10.2% (500)	35.0% (495)	26.0% (500)	**<0.0001**
	2 years	45.2% (485)	57.4% (479)	21.0% (485)	11.5% (479)	33.8% (485)	31.1% (479)	**<0.0001**
Hormone treatment-related symptoms†								
	1 year	40.7% (511)	64.8% (517)	2.4% (511)	2.3% (517)	57.0% (511)	32.9% (517)	**<0.0001**
	1.5 years	34.5% (501)	62.0% (503)	3.4% (501)	2.2% (503)	62.1% (501)	35.8% (503)	**<0.0001**
	2 years	35.3% (490)	52.5% (486)	3.5% (490)	3.9% (486)	61.2% (490)	43.6% (486)	**<0.0001**
Urinary symptoms†								
	End of radiotherapy (7 months)							
	1 year	17.4% (506)	31.1% (515)	12.9% (506)	9.7% (515)	69.8% (506)	59.2% (515)	**<0.0001**
	1.5 years	15.6% (499)	26.6% (501)	16.6% (499)	12.2% (501)	67.7% (499)	61.3% (501)	**<0.0001**

Data are percentage (denominator)
p value < 0.01 indicates clinically significant difference (in bold)
* Comparisons presented for timepoints which showed a statistically significant between-group difference in mean change score from baseline (Table S6)
† EORTC PR25 prostate cancer module
Abbreviations: 6AS+RT, 6 months of androgen suppression and radiotherapy; 18AS+RT, 18 months of androgen suppression and radiotherapy

Data Sharing Agreement

Data sharing agreement between the RADAR Trial Executive and TROG:

Secondary analyses of these trial data are encouraged, subject to review by the TROG Scientific Committee. Once all planned analyses have been completed, the data will be made available to the scientific community upon application. The protocol is freely available and can be found on the permanent link http://hdl.handlenet/1959.13/1391555 . Please contact trog@trog.com.au for further details on application procedure.

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