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

James W Denham, David Joseph, David S Lamb, Nigel A Spry, Gillian Duchesne, John Matthews, Chris Atkinson, Keen-Hun Tai, David Christie, Lizbeth Kenny, Sandra Turner, Nirdosh Kumar Gogna, Terry Diamond, Brett Delahunt, Chris Oldmeadow, John Attia, Allison Steigler

Summary

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

Methods For this randomised, phase 3, 2×2 factorial trial, eligible men were 18 years or older with locally advanced prostate cancer (either T2b-4, N0 M0 tumours or T2a, N0 M0 tumours provided Gleason score was ≥7 and baseline prostate-specific antigen [PSA] concentration was ≥10 μg/L). We randomly allocated participants in a 2×2 factorial design by computer-generated randomisation (using the minimisation technique, and stratified by centre, baseline PSA concentration, clinical tumour stage, Gleason score, and use of a brachytherapy boost) in a 1:1:1:1 ratio to four treatment groups. Patients in the control group received 6 months of neoadjuvant androgen suppression with leuprorelin (22·5 mg every 3 months, intramuscularly) and radiotherapy alone (short-term androgen suppression [STAS]); this treatment was either followed by another 12 months of adjuvant androgen suppression with leuprorelin (22·5 mg every 3 months, intramuscularly; intermediate-term androgen suppression [ITAS]), or accompanied by 18 months of zoledronic acid (4 mg every 3 months, intravenously) starting at randomisation (STAS plus zoledronic acid), or both (ITAS plus zoledronic acid). All patients received radiotherapy to the prostate and seminal vesicles, starting from the end of the fifth month of androgen suppression; dosing options were 66, 70, and 74 Gy in 2-Gy fractions per day, or 46 Gy in 2-Gy fractions followed by a high-dose-rate brachytherapy boost dose of 19·5 Gy in 6·5-Gy fractions. Treatment allocation was open label. The primary endpoint was prostate cancer-specific mortality and was analysed according to intention-to-treat using competing-risks methods. The trial is closed to follow-up and this is the final report of the main endpoints. This trial is registered with ClinicalTrials.gov, number NCT00193856.

Findings Between Oct 20, 2003, and Aug 15, 2007, 1071 men were enrolled and randomly assigned to STAS (n=268), ITAS (n=268), STAS plus zoledronic acid (n=268), and ITAS plus zoledronic acid (n=267). Median follow-up was 10·4 years (IQR 7·9–11·7). At this 10-year follow-up, no interactions were observed between androgen suppression and zoledronic acid so the treatment groups were collapsed to compare treatments according to duration of androgen suppression: 6 months of androgen suppression plus radiotherapy (6AS+RT) versus 18 months of androgen suppression plus radiotherapy (18AS+RT) and to compare treatments according to whether or not patients received zoledronic acid. The total number of deaths was 375 (200 men receiving 6AS+RT and 175 men receiving 18AS+RT), of which 143 (38%) were attributable to prostate cancer (81 men receiving 6AS+RT and 62 men receiving 18AS+RT). When analysed by duration of androgen suppression, the adjusted cumulative incidence of prostate cancer-specific mortality was 13·3% (95% CI 10·3–16·0) for 6AS+RT versus 9·7% (7·3–12·0) for 18AS+RT, representing an absolute difference of 3·7% (95% CI 0·3–7·1; sub-hazard ratio [sHR] 0·70 [95% CI 0·50–0·98], adjusted p=0·035). The addition of zoledronic acid did not affect prostate cancer-specific mortality; the adjusted cumulative incidence of prostate cancer-specific mortality was 11·2% (95% CI 8·7–13·7) with zoledronic acid *vs* 11·7% (9·2–14·1) without, representing an absolute difference of –0·5% (95% CI –3·8 to 2·9; sHR 0·95 [95% CI 0·69–1·32], adjusted p=0·78). Although safety analysis was not prespecified for this 10-year analysis, one new serious adverse event (osteonecrosis of the mandible, in a patient who received 18 months of androgen suppression plus zoledronic acid) occurred since our previous report, bringing the total number of cases

Lancet Oncol 2019; 20: 267–81

Published Online December 19, 2018 http://dx.doi.org/10.1016/S1470-2045(18)30757-5

See Comment page 176

School of Medicine and Public Health, University of Newcastle, Newcastle, NSW, Australia (Prof J W Denham FRANZCR, C Oldmeadow PhD, Prof J Attia MD, A Steigler BMath); **Sir Charles Gairdner Hospital, Perth, WA, Australia** (Prof D Joseph FRANZCR, Prof N A Spry FRANZCR); **Department of Medicine and Surgery, University of Western Australia, Perth, WA, Australia** (Prof D Joseph); **Wellington School of Medicine and Health Sciences, University of Otago, Wellington, New Zealand** (D S Lamb FRANZCR, Prof B Delahunt MD); **Peter MacCallum Cancer Centre and University of Melbourne, Melbourne, VIC, Australia** (Prof G Duchesne FRANZCR, K-H Tai FRANZCR); **Auckland City Hospital, Auckland, New Zealand** (J Matthews FRANZCR); **St Georges Cancer Care Centre, Christchurch, New Zealand** (C Atkinson FRANZCR); **Genesiscare, Tugun, QLD, Australia** (Prof D Christie FRANZCR); **Royal Brisbane and Women's Hospital, Brisbane, QLD, Australia** (L Kenny FRANZCR); **School of Medicine, University of Queensland, QLD, Australia** (L Kenny); **Crown Princess Mary Cancer Centre, Westmead Hospital, Sydney, NSW, Australia** (S Turner FRANZCR); **Mater Radiation Oncology Centre, Princess Alexandra**

Hospital, Brisbane, QLD, Australia (N K Gogna FRANZCR); St George Hospital, Department of Endocrinology, Kogarah, NSW, Australia (T Diamond MD); and Hunter Medical Research Institute, Newcastle, NSW, Australia (C Oldmeadow, Prof J Attia)

Correspondence to: Prof James W Denham, School of Medicine and Public Health, University of Newcastle, Newcastle, NSW 2310, Australia jim.denham@newcastle.edu.au

of this serious adverse event to three (<1% out of 530 patients who received zoledronic acid evaluated for safety) and the total number of drug-related serious adverse events to 12 (1% out of all 1065 patients evaluable for safety). No treatment-related deaths occurred during the study.

Interpretation **18 months of androgen suppression plus radiotherapy is a more effective treatment option for locally advanced prostate cancer than 6 months of androgen suppression plus radiotherapy, but the addition of zoledronic acid to this treatment regimen is not beneficial. Evidence from the RADAR and French Canadian Prostate Cancer Study IV trials suggests that 18 months of androgen suppression with moderate radiation dose escalation is an effective but more tolerable option than longer durations of androgen suppression for men with locally advanced prostate cancer including intermediate and high risk elements.**

Funding **National Health and Medical Research Council of Australia, Novartis Pharmaceuticals Australia, AbbVie Pharmaceuticals Australia, New Zealand Health Research Council, New Zealand Cancer Society, Cancer Standards Institute New Zealand, University of Newcastle (Australia), Hunter Medical Research Institute, Calvary Mater Newcastle Radiation Oncology Fund, and Maitland Cancer Appeal.**

Introduction

The optimal duration of androgen suppression therapy to use alongside radiotherapy in the curative management of locally advanced prostate cancer remains unclear[1–3] after three decades of trials. However, radiotherapy up to a dose of 66 Gy to the prostate by itself is clearly ineffective in 87% of patients 10 years after treatment who experience recurrence in the prostate and often develop metastases and die.[4] Since 2000, radiotherapy equipment has undergone remarkable improvements, enabling, for example, higher doses of radiation to be given to the prostate alongside lower doses to surrounding healthy tissue. Unfortunately, similar progress has not been achieved in the use of androgen suppression. Neoadjuvant androgen suppression regimens have ranged in duration between 3 and 8 months, whereas for men with very high-risk cancers, post-radiotherapy adjuvant regimens that range between 6 and 36 months are often prescribed.[5,6] Until 2009, 36 months of adjuvant androgen suppression after prostatic and pelvic nodal radiotherapy was regarded to be the most effective treatment for locally advanced and high-risk prostate cancer and continues to be widely used globally, despite

Research in context

Evidence before this study

Before we started this study on Oct 1, 2003, we searched PubMed, MEDLINE, and existing international clinical trials registries between Jan 1, 1990, and Sept 30, 2003, for all studies of men with locally advanced and high-risk prostate cancer using search terms including “androgen suppression therapy”, “zoledronic acid”, “Gleason grading”, and “bone metastases”. This search was done to identify oncological outcomes and treatment-related morbidity. Up until 2003, 28–36 months of androgen suppression together with prostatic and pelvic nodal radiotherapy were generally regarded as the most oncologically effective treatments. These durations of androgen suppression continue to be used widely around the world, despite their multiple toxicities and adverse effects 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 been greatly improved, enabling higher doses to be given to the prostate alongside lower doses to surrounding healthy regions. In clinical studies, zoledronic acid has been shown to reverse loss of bone mineral density caused by androgen suppression and to improve outcomes in men with castration-resistant bone metastases. In-vitro studies also suggested that zoledronic acid might have activity against castration-sensitive prostate cancer cells, but clinical studies have yet to confirm this.

Added value of this study

The 10-year results of the TROG 03.04 RADAR trial have shown that 18 months of androgen suppression produced better oncological outcomes than 6 months of neoadjuvant androgen suppression with only small increases in adverse patient-reported outcomes lasting 2–3 years after randomisation. Although zoledronic acid 4 mg given intravenously every 3 months reversed the loss of bone mineral density caused by 6-month and 18-month durations of androgen suppression, it did not prevent bone metastases or other oncological endpoints.

Implications of all the available evidence

Less morbid treatments using intermediate durations of androgen suppression such as 18 months, alongside better targeted, increased doses of prostatic radiotherapy, will result in better outcomes and will provide an effective and tolerable treatment option for men with locally advanced prostate cancer including high and intermediate risk elements.

many associated toxicities and adverse effects on patient-reported outcomes. However, in 2018, the French Canadian Prostate Cancer Study (PCS) IV trial[7] reported that 18 months of androgen suppression and radiotherapy produced much reduced adverse patient-reported outcomes than 36 months of androgen suppression. The identification of an optimal duration of androgen suppression for locally advanced prostate cancer and high-risk diagnostic presentations, which causes only modest toxicities and small impairments in patient-reported quality-of-life outcomes, is therefore a research priority.

In 2003, the Trans-Tasman Radiation Oncology Group (TROG) took the most effective treatment group of its 96.01 trial,[4] 6 months of neoadjuvant androgen suppression before and during radiotherapy (known as short-term androgen suppression [STAS]), as the control group for 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 (ITAS) would be superior to STAS in terms of prostate cancer-specific mortality but without compromising quality-of-life outcomes. A secondary objective was to test whether bisphosphonate therapy would help to reduce some of the adverse effects of androgen suppression and prevent bone progression. Using a 2×2 factorial design, the RADAR trial therefore sought to determine whether 12 months of adjuvant androgen suppression, or 18 months of zoledronic acid, or both, improved the outcomes of men receiving STAS.

In our preliminary trial report in *The Lancet Oncology* in 2014,[8] we identified an unexpected interaction between the use of zoledronic acid and an important baseline prognostic factor, Gleason score of the primary tumour at the cutpoint of a score up to 7 versus a score higher than 7. This finding obliged us to compare our four treatment groups in a pairwise manner, with consequent loss of power to discern differences in treatment outcomes. Unfortunately, there are still no data in the published literature to explain this 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 p 10). Because no further interactions have since been identified, we can now reasonably combine the treatment groups to compare 6 months of androgen suppression versus 18 months of androgen suppression, as well as no zoledronic acid versus 18 months of zoledronic acid.

Taken together, the results of the RADAR trial and the PCS IV trial might therefore be able to help us determine which of the 6-month, 18-month, and 36-month durations of neoadjuvant and adjuvant androgen suppression, when added to radiotherapy, can provide the optimal balance between efficacy and adverse patient-reported outcome profiles. We aimed to investigate this question in this 10-year follow-up of the RADAR trial.

Methods

Study design and participants

The TROG 03.04 RADAR trial is a randomised, open-label, first-line, phase 3 trial with a 2×2 factorial design done at 23 treatment centres in Australia and New Zealand. Eligible men were aged 18 years or older with an estimated life expectancy of longer than 5 years; with histologically confirmed adenocarcinoma of the prostate without lymph node or systemic metastases, either cT2b–4 stage primary tumours regardless of Gleason score or baseline prostate-specific antigen (PSA) concentration, or cT2a stage primary tumours with Gleason score of 7 or more and baseline PSA of at least 10 μg/L; and an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1. Tumour assessment before randomisation included digital rectal examination and either transrectal ultrasound biopsy or transurethral resection of the prostate. Presence of metastases was investigated by chest x-ray, CT scan of the 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, and calcium, phosphate, and vitamin D measurements. Exclusion criteria included previous androgen suppression, prostatectomy, pelvic radiotherapy, bisphosphonate therapy, or prolonged glucocorticoid therapy (>10 mg prednisone for >6 months); other malignancy within the previous 5 years (except for non-melanomatous skin cancer); osteoporosis resulting in spinal fracture; liver disease (alanine aminotransferase or aspartate aminotransferase more than three times the upper limit of normal); serum creatinine more than two 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 all participants provided written informed consent. An Independent Data Monitoring Committee comprising Peter Hoskin (London, UK), 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 plus zoledronic acid treatment group in 2014.[8]

See **Online** for appendix

The RADAR trial protocol is available online.

For the **trial protocol** see http://hdl.handle.net/1959.13/1391555

Randomisation and masking

Computer-based randomisation was done at the Central Trials Office (Newcastle, NSW, Australia), using minimisation with a random element and stratified by baseline PSA concentration (<10 μg/L *vs* 10–20 μg/L *vs* >20 μg/L), Gleason score (≤6 *vs* ≥7), T stage (T2 *vs* T3–4), and treatment centre. Centres opting to use both high-dose rate brachytherapy boost techniques and three-dimensional conformal external beam techniques in different patient subgroups were classed as two different centres for the purposes of stratification. Patients were assigned equally (1:1:1:1) in a 2×2 factorial design to one of four treatment groups: short-term androgen suppression before radiotherapy (STAS; control group); an additional intermediate term (12 months) of androgen suppression (ITAS); STAS with 18 months of zoledronic acid; or ITAS with 18 months of zoledronic acid. In this open-label study, treatment allocation was not masked to investigators, patients, or the study statistician.

Procedures

After randomisation, all patients received 6 months of neoadjuvant androgen suppression with leuprorelin (22·5 mg intramuscularly every 3 months). 5 months after randomisation, all patients received radiotherapy to the prostate and seminal vesicles. After this, they then received either no further treatment (STAS) or an additional 12 months of leuprorelin (22·5 mg intramuscularly every 3 months; ITAS). In addition to androgen suppression treatment, patients allocated to the two bisphosphonate treatment groups received 4 mg zoledronic acid intravenously every 3 months for 18 months starting at randomisation (STAS plus zoledronic acid and ITAS plus zoledronic acid). The trial schema is in appendix p 2.

We did a regulated radiation dose-escalation programme substudy by asking participating centres to select their preferred dosing options from a predetermined range of doses and techniques. The dosing options were 66 Gy, 70 Gy, and 74 Gy using 2-Gy fractional increments per day to the International Commission on Radiation Units and Measurements (ICRU) point using external beams alone, or 46 Gy in 2 Gy fractions to the ICRU point using external beams followed by a high-dose-rate brachytherapy (HDRB) boost dose of 19·5 Gy in three fractions of 6·5 Gy. Brachytherapy dose was prescribed to the isodose encompassing the prostate gland and any identified extracapsular extensions. Full details of the methods used 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 used ensured that radiation dose and technique were balanced across all four trial groups (since centres opting to use both techniques in different patient subgroups were classed as two different centres in stratification).

Patients were monitored for adverse events every 3 months during androgen suppression and zoledronic acid treatments, and weekly during radiotherapy. For androgen suppression, this monitoring included clinical examinations, full blood counts, and PSA and testosterone readings. For participants receiving zoledronic acid, additional tests were done to monitor urea and electrolytes, creatinine clearance, and serum calcium and phosphate concentrations, and if participants experienced jaw pain 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, zoledronic acid treatment was recommended to be postponed for 3 months in participants who required an urgent invasive dental procedure, with the possibility of dose reduction or discontinuation in the event of ongoing dental issues or poor oral health. Additionally, elevated creatinine concentrations 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 were to be reported within 24 h of their initial occurrencs, 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 the clinic every 3 months until 30 months, then every 6 months for up to 5 years after randomisation, then every year for a further 5 years. At each visit, we recorded PSA concentrations and clinician-assessed outcomes, and did a digital rectal examination. Serial rising PSA concentrations every 2 months were used to ascertain the possibility of prostatic recurrence or metastatic progression. The first indication was a rise of 2 μg/L above the post-treatment nadir value (known as Phoenix failure). Local prostatic progression was diagnosed using serial digital rectal examinations including fine-needle biopsy according to Response Evaluation Criteria In Solid Tumors (RECIST) version 1.0 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 that these assessments were necessary or if the PSA concentration reached 20 μg/L. Although the protocol did not mandate the type of secondary therapeutic intervention, it recommended that any secondary therapeutic intervention should be delayed until clinical progression was diagnosed or PSA concentration had reached 20 μg/L.

Participants completed questionnaires for patient-reported outcomes at baseline, 3 months, 7 months (at the end of radiotherapy), 12 months, 18 months, 24 months, 36 months, 60 months, and then yearly. These questionnaires included the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 (version 3) and prostate cancer module PR25. Results for the secondary endpoint of patient-reported outcomes presented in this updated analysis are the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 global health status and quality of life, and EORTC PR25 domain scores for sexual activity and hormone treatment-related, urinary, and bowel symptoms.[11] All domain scores were derived as per the EORTC QLQ C-30 scoring manual.[12] If a participant no longer wished or was unable to complete scheduled treatments or clinic follow-ups (eg, due to transport problems or intercurrent medical conditions such as dementia), the participant (or their guardian) was offered the option of remote follow-up, whereby consent was given to continue to collect study-related data from the patient's family doctor 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 their guardian.

Quality control measures included radiotherapy treatment review processes[13–15] and site monitoring visits. The primary and secondary oncological endpoints were reviewed annually by a group of senior clinicians in the Trial Endpoints Committee, who were masked to patient identity and treatment allocation, and reviewed copies of all de-identified imaging, pathology, and endpoint correspondence. Re-reviews of endpoints were done by the Endpoints Committee to ensure consistency in the adjudication process.

Outcomes

The primary endpoint was prostate cancer-specific mortality. Death was attributed to prostate cancer 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.

Secondary oncological endpoints were PSA progression, local progression, distant progression, bone progression, soft tissue progression, time to secondary therapeutic intervention, and all-cause mortality. 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 μg/L above the post-treatment nadir). Local progression was defined as a recurrent prostatic mass diagnosed by digital rectal examination, imaging techniques, or both. 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. Bone progression was defined as the development of bony metastases, most commonly in the axial skeleton but sometimes also outside this region. Soft tissue progression was defined as non-bony metastases, most commonly in lymph nodes but also in the lungs, pleura, liver, and brain. Secondary therapeutic intervention was defined as treatment (usually androgen suppression) following evidence of cancerous recurrence after primary protocol treatment. Transition to castration resistance was a post-hoc exploratory endpoint (see appendix pp 5, 11 for definition). Patient-reported outcomes was a secondary endpoint.

Statistical analysis

The previously observed interaction between the use of zoledronic acid and the Gleason score of the primary tumour reported in 2014[8] has dissipated with additional participant follow-up (appendix p 10). After data cutoff on Aug 31, 2017, omnibus testing (the likelihood ratio test) for interactions showed no significant differences between the four treatment groups; therefore, we were able to collapse the treatment groups to compare the trial factors separately. First, we compared the combined 6-month neoadjuvant androgen suppression (with or without the addition of zoledronic acid) group, hereafter abbreviated as 6AS+RT, with the combined 18-month androgen suppression (with or without zoledronic acid) group, hereafter abbreviated as 18AS+RT, to determine whether or not 12 months of adjuvant androgen suppression commencing after radiotherapy was beneficial. Second, we compared the combined zoledronic acid groups with the two groups who received no zoledronic acid to determine whether or not the addition of 18 months of zoledronic acid commencing at randomisation was beneficial.

Based on the primary endpoint data from our 2014 report, the power to detect reductions in the primary endpoint, prostate cancer-specific mortality, from the use of an additional 12 months of androgen suppression was low. With the assumption that there would be 148 deaths from prostate cancer at data cutoff in 2017 and assuming a two-sided type 1 (α) error of less than 0·05, a hazard ratio (HR) of 0·55 would be needed to provide 80% power for the analysis of prostate cancer-specific mortality. This requirement was because the frequency of prostate cancer deaths was lower than anticipated, probably because of the use of newly available tertiary drugs, such as docetaxel, enzalutamide, and abiraterone, to treat men whose cancers had recurred but were no longer responding to conventional androgen suppression treatment approaches. Under these circumstances, it was decided by the trial statistician in August, 2017, 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 the primary and secondary endpoints. The trial stratification scheme used the traditional Gleason scoring system at the cutpoint of a score less than 7 versus a score of 7 or higher. When the trial was designed, we assumed that this cutpoint would divide the trial population into roughly equal groups. However, the distribution of Gleason scores changed rapidly during the recruitment phase. This occurred because of 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 p 4). This change in policy led to a large reduction in the proportion of men assigned a Gleason score of less than 7, from the anticipated 50% down to 9%, and a large increase in the proportion of men assigned Gleason score of 7 or higher to 91%. The large subgroup of men with Gleason score of 7 or

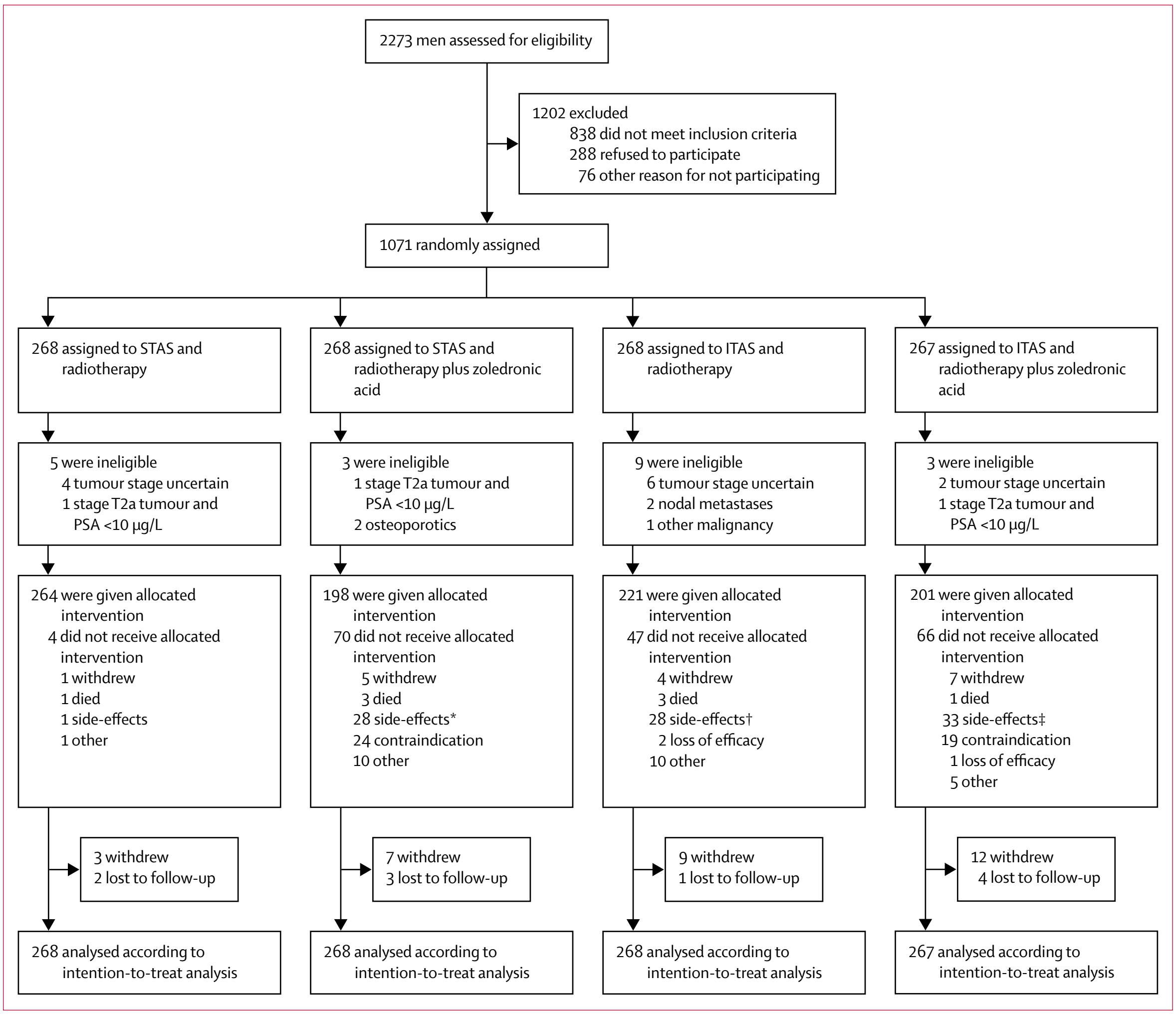

Figure 1: **Trial profile**
STAS=short-term (6 months) androgen suppression therapy. ITAS=intermediate-term (18 months) androgen suppression. *All 28 side-effects in this group were attributable to zoledronic acid (none were due to STAS). †Patients in the ITAS and radiotherapy group had many more side-effects than those in the STAS and radiotherapy group because they received an additional 12 months of androgen suppression. ‡Patients in this group had the highest number of side effects because they received both experimental treatments (ie, an extra 12 months of androgen suppression plus 18 months of zoledronic acid).

higher would therefore have effectively been distributed at random to all four treatment groups without stratification. In particular, more than half 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 subgroup of men with a Gleason score of 7 or higher, we therefore reassigned these men post hoc to the modified Gleason (ISUP) grade groups 2–5 after randomisation (appendix pp 4–5). For these reasons, the five-level grade group was used in place of the stratified Gleason score (<7 *vs* ≥7).

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

For each endpoint, we calculated the 10-year adjusted cumulative incidence rates and 95% CIs in multivariable competing risks models using the Fine and Gray method[18] and direct adjustment method to derive adjusted sub-HRs (sHRs) and 95% CIs for treatment factor effects. We derived all-cause mortality HRs and 95% CIs from a Cox regression model. All models were adjusted for the stratification factors: baseline PSA concentration (<10 μg/L *vs* 10–20 μg/L *vs* >20 μg/L), T stage (T2 *vs* T3–T4), and grade group (1 [Gleason score ≤6] *vs* 2 [Gleason score 3+4] *vs* 3 [Gleason score 4+3] *vs* 4 [Gleason score 8] *vs* 5 [Gleason score 9–10]).

Competing risks for prostate cancer-specific mortality were defined as deaths from other or unknown causes. Competing risks for local progression were defined as distant progression diagnosed more than 2 months before local progression and death from any cause. For all other oncological endpoints, the competing risk was death from any cause. We tested the proportional hazards assumption 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, we tested the proportional hazards assumption 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[19] for avoiding false-positive results with many comparisons.

We did a post-hoc, hypothesis-generating exploratory analysis to explore the treatment effect of androgen suppression on oncological endpoints according to National Comprehensive Cancer Network risk classification (unfavourable intermediate-risk and high-risk subgroups). Unfavourable intermediate risk was defined as Gleason 4+3 (grade group 3), at least 50% positive biopsy cores, or several intermediate risk factors (clinical stage T2b–c, Gleason score 7, or PSA concentration 10–20 µg/L). High risk was defined as clinical stage T3 or T4, Gleason score 8–10 (grade group 4 or 5), or PSA concentration higher than 20 µg/L. We adjusted these models for age at randomisation and use of high-dose brachytherapy (no *vs* yes) in addition to prostate-specific antigen concentration, T stage, and grade group.

We calculated compliance with completion of patient-reported outcome questionnaires for each scheduled data collection timepoint as the proportion of participants on study at that timepoint. We compared longitudinal changes in mean scores from baseline for each patient-reported outcome[20] between treatment groups at each timepoint using independent t-tests. We assessed significant findings for clinical relevance by ascertaining the proportions of men in each treatment group who had increases or decreases of 10 points or more, or intermediate changes of less than 10 points, on the patient-reported outcome scales from baseline to each follow-up time.[21] These univariable proportions were compared by χ^2 testing. Because we were doing multiple tests, we judged a two-sided p value of less than 0·01 as significant in patient-reported outcome analyses.

We did all analyses on an intention-to-treat basis. We considered an adjusted two-sided p-value less than 0·05 as statistically significant for all endpoints except for patient-reported outcomes. We used Stata/IC version 14.2 and SAS version 9.4 for all analyses.

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. JWD, JA, CO, and AS had access to the raw data. The corresponding author had full access to all data in the study, and had final responsibility for the decision to submit the paper for publication.

Results

Between Oct 20, 2003, and Aug 15, 2007, 2273 men at 23 treatment centres across Australia and New Zealand were screened for the study, of whom 1071 eligible patients were enrolled and randomly allocated to the four treatment groups (figure 1). Baseline characteristics

	STAS group (n=268)	STAS + zoledronic acid group (n=268)	ITAS group (n=268)	ITAS + zoledronic acid group (n=267)
Age, years				
Median (IQR)	69 (64–73)	69 (64–73)	68 (63–73)	68 (63–72)
T stage				
T2*	170 (63%)	171 (64%)	170 (63%)	169 (63%)
T3 or T4	98 (37%)	97 (36%)	98 (37%)	98 (37%)
Gleason score				
≤6	26 (10%)	25 (9%)	25 (9%)	25 (9%)
7	155 (58%)	155 (58%)	138 (52%)	151 (57%)
8	48 (18%)	44 (16%)	40 (15%)	51 (19%)
9	36 (13%)	41 (15%)	61 (23%)	38 (14%)
10	3 (1%)	3 (1%)	4 (1%)	2 (1%)
ISUP grade group				
1 (Gleason score ≤6)	26 (10%)	25 (9%)	25 (9%)	25 (9%)
2 (Gleason score 7 [3+4])	88 (33%)	86 (32%)	85 (32%)	88 (33%)
3 (Gleason score 7 [4+3])	67 (25%)	69 (26%)	53 (20%)	63 (24%)
4 (Gleason score 8)	48 (18%)	44 (16%)	40 (15%)	51 (19%)
5 (Gleason score 9–10)	39 (14%)	44 (16%)	65 (24%)	40 (15%)
PSA concentration (µg/L)				
<10	74 (28%)	74 (28%)	72 (27%)	73 (27%)
10–20	110 (41%)	109 (40%)	110 (41%)	110 (41%)
>20	84 (31%)	87 (32%)	86 (32%)	84 (32%)
NCCN risk group				
Intermediate	92 (34%)	98 (37%)	81 (30%)	89 (33%)
High	176 (66%)	170 (63%)	187 (70%)	178 (67%)
Radiation dose				
66 Gy	30 (11%)	30 (11%)	32 (12%)	33 (12%)
70 Gy	111 (41%)	108 (40%)	106 (40%)	102 (38%)
74 Gy	68 (25%)	65 (24%)	64 (24%)	65 (24%)
High-dose-rate brachytherapy	57 (21%)	57 (21%)	61 (23%)	62 (23%)
Not given	2 (1%)	8 (3%)	5 (2%)	5 (2%)

Data are median (IQR) or n (%). STAS=short-term (6 months) androgen suppression. ITAS=intermediate-term (18 months) androgen suppression ISUP=International Society of Urological Pathologists. PSA=prostate-specific antigen. NCCN= National Comprehensive Cancer Network. Gy=Gray. *T2a tumours were eligible provided that the patient had Gleason score ≥7 and baseline PSA concentration ≥10 µg/L.

Table 1: **Baseline characteristics**

	6AS+RT (n=536)	18AS+RT (n=535)	Total
Prostate cancer	81	62	143
New primary cancer	43	47	90
Abdominal	16	16	32
Lung	8	12	20
Other	19	19	38
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 n. 6AS+RT=6 months of androgen suppression plus radiotherapy. 18AS+RT=18 months of androgen suppression plus radiotherapy.

Table 2: **Causes of death by duration of androgen suppression**

were similar across the groups (table 1). These data are also presented according to duration of androgen suppression group and zoledronic acid group (appendix pp 12–13). The proportion of patients with protocol treatment compliance, defined as those who received 100% of their scheduled dose, were 99% (532 out of 536) for men allocated to 6 months of androgen suppression, 85% (456 out of 535) for 18 months of androgen suppression, and 77% (409 out of 535) for zoledronic acid.

At data cutoff on Aug 31, 2017, 10 years after the final participant was randomly assigned to treatment, median follow-up was 10·4 years (IQR 7·9–11·7). The total number of deaths was 375 (200 men receiving 6AS+RT and 175 men receiving 18AS+RT), of which 143 (38%) were attributable to prostate cancer (81 men receiving 6AS+RT and 62 men receiving 18AS+RT). A breakdown of cause of death by duration of androgen suppression is shown in table 2. At 10 years, the cumulative incidence of prostate cancer-specific mortality was 13·3% (95% CI 10·3–16·0) for 6 months of androgen suppression and radiotherapy (6AS+RT), and 9·7% (7·3–12·0) for 18 months of androgen suppression and radiotherapy (18AS+RT), representing an absolute difference of 3·7% (95% CI 0·3–7·1; sHR 0·70 [95% CI 0·50–0·98], adjusted p=0·035; figure 2A). The 10-year cumulative incidence of all-cause mortality was 32·3% (95% CI 28·4–36·0) for 6AS+RT and 28·0% (24·2–31·5%) for 18AS+RT (HR 0·83 [95% CI 0·68–1·02], adjusted p=0·081; figure 2B). The number needed to treat is 27 men to prevent one death from prostate cancer over 10 years.

Distant progressions were reported in 293 men (164 in the 6AS+RT group *vs* 129 in the 18AS+RT group) and cumulative incidences were 27·5% (95% CI 23·9–31·0%) for 6AS+RT and 20·7% (17·6–23·9%) for 18AS+RT (sHR 0·71 [95% CI 0·56–0·90], adjusted p=0·0044; figure 2C). Bone progressions were diagnosed in 229 men (135 in the 6AS+RT group *vs* 94 in the 18AS+RT group), with cumulative incidences of 23·3% (95% CI 20·0–26·7) for 6AS+RT and 15·8% (12·9–18·7) for 18AS+RT (sHR 0·63 [95% CI 0·48–0·82], adjusted p=0·00071; figure 2D). Soft tissue progressions were not reduced by the longer duration of androgen suppression. There were a total of 189 soft tissue progressions (101 in the 6AS+RT group *vs* 88 in the 18AS+RT group), with cumulative incidences of 16·5% (95% CI 13·5–19·5) for 6AS+RT and 14·1% (11·3–16·9) for 18AS+RT (sHR 0·84 [95% CI 0·63–1·12], adjusted p=0·21). Local progression was recorded in 93 patients (57 in the 6AS+RT group *vs* 36 in the 18AS+RT group) and cumulative incidences were 7·9% (95% CI 5·7–10·1) for 6AS+RT and 4·9% (3·0–6·8) for 18AS+RT (sHR 0·61 [95% CI 0·40–0·93], adjusted p=0·022; figure 2E). At 10 years, PSA progression had occurred in 436 men (246 in the 6AS+RT group *vs* 190 in the 18AS+RT group) and cumulative incidences were 45·9% (95% CI 41·9–49·9%) for 6AS+RT and 34·0% (30·2–37·7) for 18AS+RT (sHR 0·65 [95% CI 0·54–0·79], adjusted p<0·0001). A total of 366 participants required secondary therapeutic intervention (209 in the 6AS+RT group *vs* 157 in the 18AS+RT group), with cumulative incidences of 36·8% (32·9–40·6%) in men who received 6AS+RT and 26·6% (23·1–30·1%) for 18AS+RT (sHR 0·66 [95% CI 0·53–0·81], adjusted p=0·00010).

In our exploratory post-hoc analysis of time to transition to castration resistance, castration resistance was identified in 163 (45%) of 364 men who underwent androgen suppression as a secondary treatment following failure of the primary treatment (97 in the 6AS+RT group *vs* 66 in the 18AS+RT group). Of these 364 men, 201 (55%) were diagnosed with distant progression prior to the start of secondary treatment (111 in the 6AS+RT group *vs* 90 in the 18AS+RT group). The cumulative incidence of transition to castration resistance was significantly lower in men receiving 18AS+RT (11·3% [95% CI 8·7–13·9%]) than in those receiving 6AS+RT (17·1% [14·1–20·1]; sHR 0·63 [95% CI 0·46–0·86], adjusted p=0·004). In a further post-hoc exploratory analysis, time to transition to castration resistance showed a strong correlation with time to prostate cancer-specific mortality (appendix p 6). Median time between transition to castration resistance and prostate cancer-specific mortality was 22 months (95% CI 17–25; appendix p 6).

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

To determine whether or not an overall survival benefit could be achieved with the intermediate (18-month)

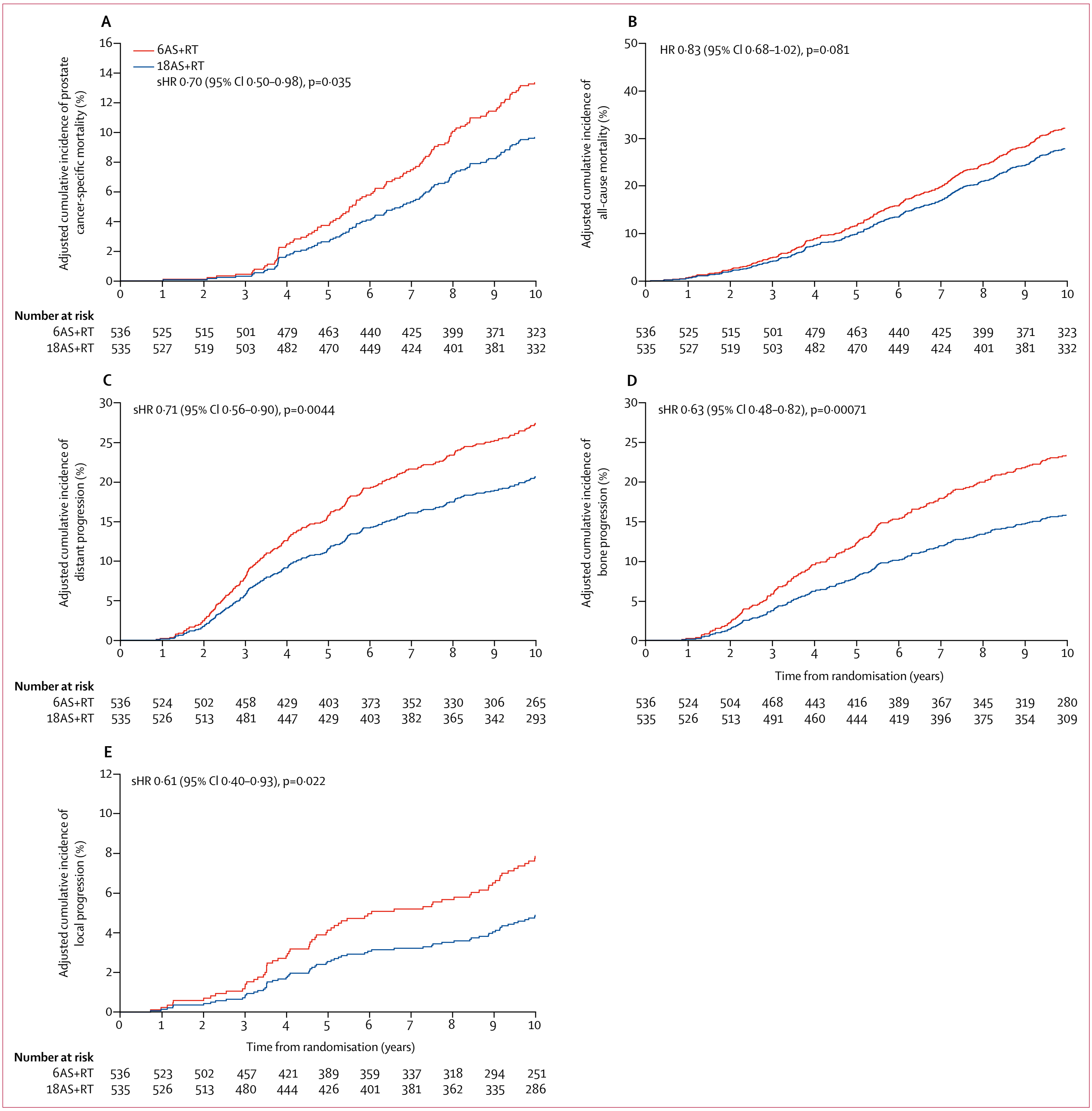

Figure 2: **Adjusted cumulative incidence of mortality and progression outcomes by duration of androgen suppression group**
(A) Prostate cancer-specific mortality. (B) All-cause mortality. (C) Distant progression. (D) Bone progression. (E) Local progression. 6AS+RT=6 months of androgen suppression plus radiotherapy. 18AS+RT=18 months of androgen suppression plus radiotherapy. sHR=sub-hazard ratio. HR=hazard ratio. Crude numbers at risk are shown. Models were adjusted for the stratification factors and use of zoledronic acid (yes *vs* no).

duration of androgen suppression if follow-up was extended beyond 10 years, we did an exploratory post-hoc analysis using the endpoint metastasis-free survival, which has been shown in meta-analyses conducted by the Intermediate Clinical Endpoints in Cancer of the Prostate (ICECaP) Working Group to be a strong surrogate

	Events: No zoledronic acid (n=536)	Events: Zoledronic acid (n=535)	HR* (95% CI)
Prostate cancer-specific mortality	74	69	0·95 (0·69–1·32)
PSA progression	215	221	1·07 (0·88–1·30)
Local progression	39	54	1·45 (0·96–2·18)
Bone progression	115	114	1·04 (0·80–1·35)
Soft tissue progression	104	85	0·80 (0·60–1·07)
Distant progression	151	142	0·95 (0·76–1·20)
Second therapeutic intervention	183	183	1·01 (0·82–1·25)
Transition to castration resistance	82	82	1·03 (0·76–1·41)
All-cause mortality	197	178	0·90 (0·73–1·10)

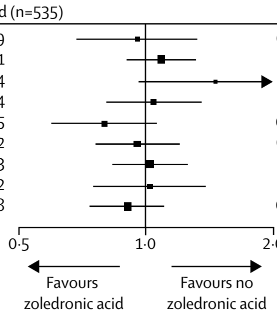

Figure 3: **Summary of treatment effects by zoledronic acid group for oncological endpoints**
PSA=prostate-specific antigen. HR=hazard ratio. *Adjusted HR is presented for all-cause mortality, whereas adjusted sub-HRs are presented for all other endpoints. Models were adjusted for the stratification factors and duration of androgen suppression therapy (6 months *vs* 18 months).

endpoint for disease-specific and overall survival.[22] This exploratory post-hoc analysis showed a significant improvement in metastasis-free survival for 18AS+RT (10-year metastasis-free survival 63·5% [95% CI 59·8–67·4] with 18AS+RT *vs* 55·9% [52·1–60·8] with 6AS+RT (sHR 0·77 [95% CI 0·65–0·92], adjusted p value=0·0044).

Our post-hoc, hypothesis-generating exploratory analysis of oncological outcomes by 18AS+RT versus 6AS+RT in unfavourable intermediate-risk and high-risk cancers according to the NCCN risk group classification is in appendix p 7. Notably, distant progression, bone progression, clinical progression, and PSA progression were significantly reduced in both risk groups by the longer duration of androgen suppression (appendix p 7). However, subsequent reductions in prostate cancer-specific mortality did not reach statistical significance in either risk group (appendix p 7).

In an earlier report[23] we showed that zoledronic acid prevented loss of bone mineral density due to androgen suppression but did not reduce fractures. In this 10-year update, none of the comparisons between the no zoledronic acid group and the zoledronic acid group showed any significant differences between groups for the oncological endpoints described above (figure 3).

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, urinary, and bowel symptom domains. Compliance with completion of patient-reported outcome questionnaires was similar between the two treatment groups (appendix p 14). Longitudinal mean change from baseline scores and longitudinal mean raw scores of each patient-reported outcome according to duration of androgen suppression are shown in figure 4 and appendix p 8, respectively. These plots show that separations between the two groups, favouring 6AS+RT, begin after radiotherapy (7 months) for most outcomes. However, these separations reach statistical and clinical significance for relatively short periods of time; by 2 years the separations between the two groups diminish considerably, and after 3 years virtually disappear out to 10 years' follow-up. These findings were replicated in a post-hoc exploratory, per-protocol analysis (appendix p 9). Statistically significant differences in mean changes from baseline scores favouring 6AS+RT were observed in sexual activity (at 1, 1·5, and 2 years), hormone treatment-related symptoms (at 1, 1·5, and 2 years) and urinary symptoms (at 1 and 1·5 years appendix pp 15–16). The clinical relevance of these differences was confirmed in the χ^2 analyses, which showed that a greater proportion of men in the 18AS+RT group had adverse changes of 10 points or more compared with the 6AS+RT group (appendix p 17). Differences between the two groups in global health status and bowel symptoms did not reach statistical significance at any timepoint (appendix pp 15–16).

In a post-hoc exploratory analysis, recovery to normal testosterone concentrations (8 nmol/L) was significantly slower in the men receiving the longer duration of androgen suppression (median time 29·9 months [95% CI 29·7–30·0] for 18AS+RT *vs* 12·0 months [11·9–12·1] for 6AS+RT, p<0·0001; figure 4F). This prolonged suppression of testosterone in the 18AS+RT group could explain the increase in adverse patient-reported outcomes in this group in the first 3 years. However, men in the 6AS+RT group were more likely to experience disease progression and receive further androgen suppression as a secondary treatment (209 [39%] of 536 compared with 155 [29%] of 535 in the 18AS+RT group; p=0·0005). A more detailed analysis of longitudinal changes in patient-reported outcomes will be reported separately.

Serious adverse events have been summarised previously.[8] 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 of androgen suppression, and the third case, reported in March, 2016, occurred in a man who received 18 months of androgen suppression.

This third case of osteonecrosis brings the total number of drug-related serious adverse events to 12 (1% of 1065 patients in the safety population), six of which resulted in dose discontinuations. No treatment-related deaths occurred in the study; however, 90 participants had dose reductions or discontinuations because of drug-related toxicity. A total of 12 men (six in each of the ITAS and ITAS plus zoledronic acid groups) required dose reductions of leuprorelin, and 16 men (7 in the STAS plus zoledronic acid group and 9 in the ITAS plus zoledronic acid group) required reductions of zoledronic acid. The total number of discontinuations was 40 for leuprorelin and 40 for zoledronic acid. In the control STAS group, one patient stopped treatment after the first

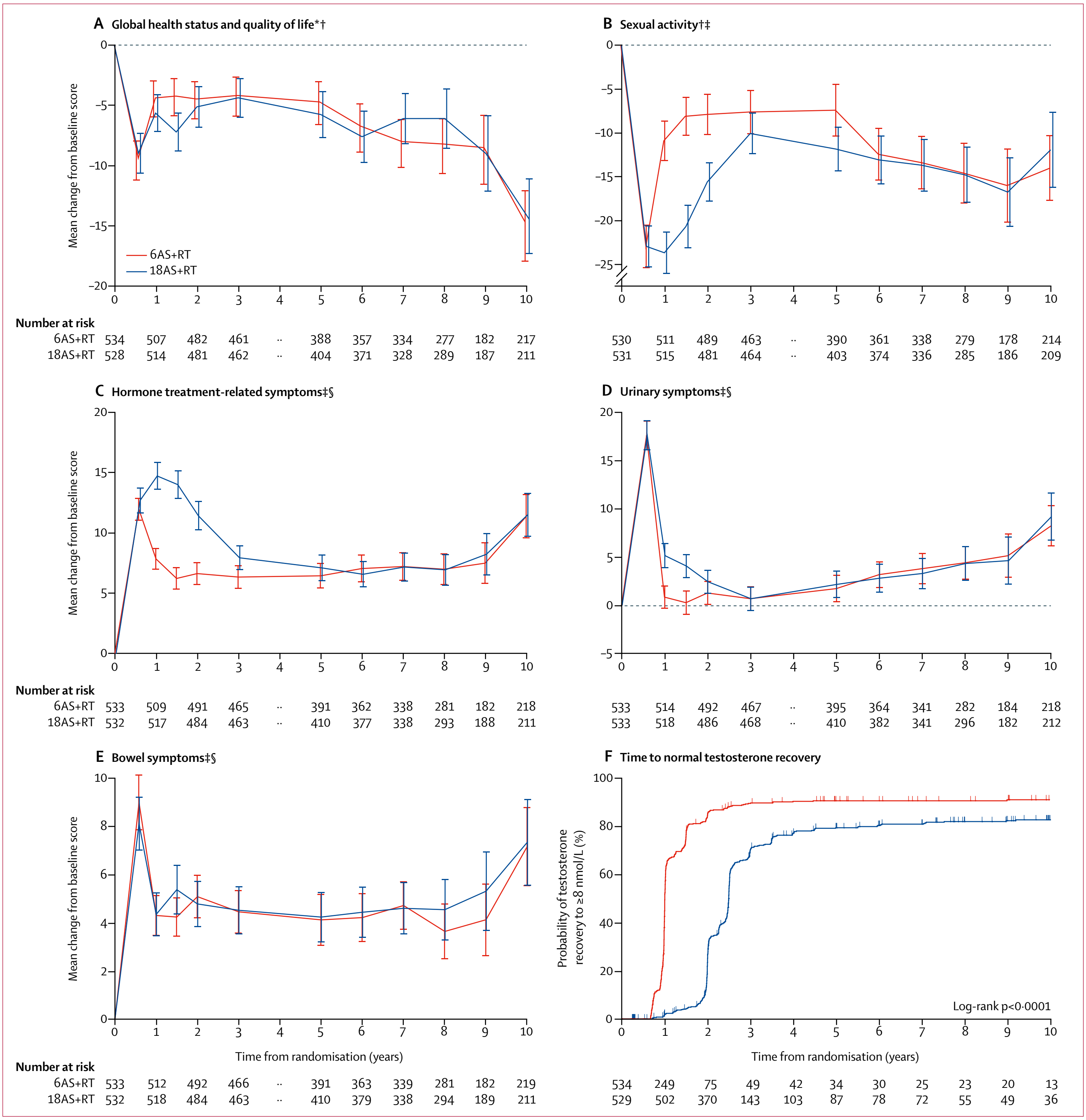

Figure 4: **Mean change from baseline score in patient-reported outcomes and time to normal testosterone recovery by duration of androgen suppression therapy**
(A) Global health status and quality of life. (B) Sexual activity. (C) Hormone treatment-related symptoms. (D) Urinary symptoms. (E) Bowel symptoms. (F) Time to testosterone recovery. 6AS+RT=6 months of androgen suppression plus radiotherapy. 18AS+RT=18 months of androgen suppression plus radiotherapy. Data on graphs A–E are mean change scores from baseline (error bars are 95% CIs). *Assessed using European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire. †Negative score means worse level of functioning. ‡Assessed using EORTC prostate cancer module PR25. §Higher score means worse degree of symptoms.

leuprorelin injection because of depression. In the STAS plus zoledronic acid group, all patients received their full dose of leuprorelin as prescribed, but 21 men discontinued zoledronic acid. Reasons for discontinuation included two serious adverse events of osteonecrosis, multiple side-effects (n=7), bone pain (n=2), elevated creatinine levels (n=3), injection reaction (n=2), flu symptoms (n=1), skin rash (n=1), muscle cramps (n=1), painful teeth (n=1), and gout (n=1). In the ITAS group, 22 patients discontinued leuprorelin, of whom 14 chose to stop because of multiple hormone treatment-related side-effects. Additional reasons included two serious adverse events involving a cerebrovascular accident and peripheral neuropathy, fractures (n=2), mood disorders (n=2), abnormal liver function (n=1), and exacerbation of pre-existing diabetes (n=1). 17 men in the ITAS plus zoledronic acid group discontinued leuprorelin, the majority (n=10) because of multiple hormone treatment-related side-effects. Other reasons for stopping included mood disorders (n=3), fatigue (n=1), hot flushes (n=1), muscle weakness (n=1), and sexual dysfunction (n=1). Additionally, 19 men in this group discontinued zoledronic acid, including two because of serious adverse events involving syncope during drug infusion and an ischaemic toe. Other reasons were patient decision due to side-effects (n=8), injection reactions (n=5), bone pain (n=1), fatigue (n=1), flu symptoms (n=1), and iritis (n=1).

Discussion

The RADAR trial has shown that when compared to 6 months of androgen suppression and radiotherapy, the use of an additional 12 months of adjuvant androgen suppression in men with locally advanced prostate cancer resulted in a significant improvement in prostate cancer-specific mortality. The number needed to treat is 27 men to prevent one death from prostate cancer over 10 years. Unfortunately, no significant difference in all-cause mortality was observed between the two treatment groups. All other secondary endpoints, with the exception of soft tissue progression, were significantly improved in participants receiving 18AS+RT compared with those receiving 6AS+RT, including bone progression and transition to castration resistance, which might help to explain why the longer duration of androgen suppression was effective in preventing prostate cancer deaths. However, longer durations of androgen suppression might preferentially deplete well-differentiated, slowly evolving tumour clones, which could potentially lead to an overgrowth of highly malignant, rapidly evolving tumour clones. Median time to death from prostate cancer following transition to castration resistance was short, at just under 2 years. In the earlier years of the trial, drugs which are now widely used to treat castrate-resistant disease were not available or in common use, which could explain the poor outcome after transition to castration resistance.

Although a difference in all-cause mortality was not observed between the two androgen suppression groups, our exploratory post-hoc analysis confirmed a significant increase in the surrogate endpoint metastasis-free survival for the men receiving 18 months of androgen suppression, suggesting that an overall survival advantage might 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 plan to model our final dataset to estimate when an overall survival advantage for 18 months of androgen suppression might be observed.

Notably, the cost of the benefits offered by 18 months of androgen suppression was restricted to a limited increase in adverse patient-reported outcomes lasting only 2–3 years after randomisation. In our earlier report[24] we showed that these adverse patient-reported outcome effects, in particular increased hormone treatment-related symptoms and decreased sexual activity, were largely driven by prolonged testosterone suppression. Moreover, in the present report, our data show that men receiving 6AS+RT were more likely to experience disease progression and receive further androgen suppression as a secondary treatment; therefore, long-term patient-reported outcomes could be impacted by testosterone levels affected by secondary treatment, as well as by ageing. In the patients who received 18 months of androgen suppression, protocol compliance was good at 85% and, although lower than in the 6 months androgen suppression group, this difference did not affect patient-reported outcomes, as evidenced by the similar results produced by intention-to-treat and per-protocol analyses. Two studies that evaluated quality-of-life outcomes for 36 months of androgen suppression 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 of androgen suppression and radiotherapy to the prostate with its modest side-effect profile therefore seems appropriate.

Unfortunately, we are unable to draw any positive conclusions regarding the role of 18 months of zoledronic acid, which did not produce significant improvements 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 androgen suppression diminished with 3·5 years of additional follow-up. Moreover, the RADAR trial confirmed results from the ZEUS randomised trial[25] which reported that a longer duration and more dose-intense regimen of zoledronic acid than that 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 morbidity in men who receive long term androgen suppression.[26] However, three randomised controlled trials in men with high-risk to very-high-risk prostate cancer have evaluated the efficacy of 36 months of adjuvant androgen suppression after radiotherapy with the goal of cure when compared with either no androgen suppression,[27] 6 months of adjuvant androgen suppression,[6] and 18 months androgen suppression in total.[7] The two trials run by the EORTC,[6,27] led by Bolla and colleagues, showed that 36 months of adjuvant androgen suppression was statistically superior in all efficacy outcomes when compared with no adjuvant androgen suppression[27] or 6 months of adjuvant androgen suppression.[6] However, the PCS IV trial led by Nabid and colleagues[7] showed that 36 months of androgen suppression therapy was not superior to 18 months of androgen suppression, with similar overall survival and prostate cancer-specific survival in both treatment groups after 10 years of follow-up,[7] with a hazard ratio for overall survival of 1·02 (95% CI 0·81–1·29) and for prostate cancer-specific survival of 0·95 (0·58–1·55). Since this trial was designed to demonstrate superiority, it cannot be claimed that 36 months of androgen suppression plus radiotherapy is not more efficacious than 18 months of androgen suppression plus the same radiotherapy. Notably, these trials also measured quality-of-life indices using the EORTC QLQ-C30 and PR25 instruments and found that 36 months of adjuvant androgen suppression was statistically inferior in terms of patient-reported quality-of-life outcomes in the two trials that compared 36 months against 6 months[6] and 18 months[7] of androgen suppression. A fourth trial run by the Radiation Therapy Oncology Group (RTOG) in the USA that compared 4 months of neoadjuvant androgen suppression before and during radiotherapy, either alone or followed by 24 months of adjuvant androgen suppression, also reported significant improvements in all outcomes except overall survival.[28,29] Statistically increased morbidity was not observed in the men receiving 24 months of adjuvant androgen suppression, but quality-of-life outcomes were not addressed.

In regard to the serious adverse effects of radiotherapy, 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, it is unlikely that radiation-induced cancers in the rectum and bladder would have occurred 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. First, 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 substantial reduction in the number of primary endpoint events. Another factor potentially reducing power might have been the success of new tertiary treatments for men who became castration resistant during the trial, which prolonged time to prostate cancer death. A second important limitation was that randomisation was done 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 led many institutional pathologists to use the modified Gleason grades defined by ISUP in 2005. Although a central pathology review was done, this review was undertaken after randomisation because of workload constraints and logistical difficulties in getting the institutional biopsy slides transported to New Zealand and reviewed by the trial pathologist before men were randomly assigned to treatment. The revised main objective of this review, which was undertaken during 2010–14 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 1071 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 radiation dose-escalation substudy. Despite this problem, men in the four dosing subgroups were distributed evenly across the trial's four treatment groups using stratification by minimisation, which reduces the possibility that radiation dose escalation would bias any of the treatment groups. 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 our post-hoc exploratory analyses showed 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 detect a reduction in prostate cancer-specific mortality in either risk group (appendix p 7). We have agreed with the ICECaP working party to release our metastasis-free survival data to their team to ascertain whether 18AS+RT will provide a prostate cancer-specific mortality and overall survival benefit in these risk groups.

A question that remains unanswered is whether the side-effects of androgen suppression 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, especially in men who have received 18 months of androgen suppression.[31,32] A substudy 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 androgen suppression.[23]

However, when the results of all the trials discussed above are taken together, can it be said that an optimal duration of androgen suppression, which provides a favourable balance between efficacy and adverse patient-reported outcome profiles, has been achieved? To determine the optimal duration of androgen suppression 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 androgen suppression duration and radiation dose escalation in a separate report. Further data are therefore needed to answer these questions with accuracy, but at present, we can conclude that 18 months of androgen suppression plus radiotherapy is an effective and well-tolerated therapeutic option for men with locally advanced prostate cancer including high and intermediate-risk elements.

Contributors

JWD, DJ, DSL, NAS, GD, JM, CA, K-HT, DC, LK, ST, NKG, TD, and BD conceived and designed the study. AS participated in acquisition and quality assurance of data. JWD and AS wrote the manuscript. JWD, AS, CO, and JA designed and interpreted the data analyses. AS, CO, and JA did the statistical analysis. All authors contributed to manuscript revisions. JWD chaired the trial and had full access to the data.

Declaration of interests

JWD received funds for pharmaceutical supplies, and investigations and data management support from AbbVie and Novartis Pharmaceuticals up until August, 2007, in his capacity as Director of the Prostate Cancer Awareness and Treatment Group Inc to assist in the running of the RADAR trial. All other authors declare no competing interests.

References

1 Roach III M. Hormonal therapy and radiotherapy for localized prostate cancer: who, where and how long? *J Urol* 2003; **170:** S35–41.

2 Al-Mamgani A, Lebesque JV, Heemsbergen WD, et al. Controversies in the treatment of high-risk prostate cancer—what is the optimal combination of hormonal therapy and radiotherapy: a review of literature. *Prostate* 2010; **70:** 701–09.

3 Denham JW, Steigler A. Picking the optimal duration of hormonal therapy in men with high-risk and locally advanced prostate cancer treated with radiotherapy. *Semin Radiat Oncol* 2013; **23:** 206–14.

4 Denham JW, Steigler A, Lamb DS, et al. Short-term neoadjuvant androgen deprivation and radiotherapy for locally advanced prostate cancer: 10-year data from the TROG 96.01 randomised trial. *Lancet Oncol* 2011; **12:** 451–59.

5 Bolla M, Gonzalez D, Warde P, et al. Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin. *N Engl J Med* 1997; **337:** 295–300.

6 Bolla M, De Reijke TM, van Tienhoven G, et al. Duration of androgen suppression in the treatment of prostate cancer. *N Engl J Med* 2009; **360:** 2516–27.

7 Nabid A, Carrier N, Martin A-G, et al. Duration of androgen deprivation therapy in high-risk prostate cancer: a randomized phase III trial. *Eur Urol* 2018; **74:** 432–41.

8 Denham JW, Joseph D, Lamb DS, et al. 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): an open-label, randomised, phase 3 factorial trial. *Lancet Oncol* 2014; **15:** 1076–89.

9 Denham JW, Wilcox C, Lamb DS, et al. Rectal and urinary dysfunction in the TROG 03.04 RADAR trial for locally advanced prostate cancer. *Radiother Oncol* 2012; **105:** 184–92.

10 Denham JW, Steigler A, Joseph D, et al. Radiation dose escalation or longer androgen suppression for locally advanced prostate cancer? Data from the TROG 03.04 RADAR trial. *Radiother Oncol* 2015; **115:** 301–07.

11 Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993; **85:** 365–76.

12 Fayers PM, Aaronson NK, Bjordal K, et al. The EORTC QLQ-C30 Scoring Manual, 3rd edn. Brussels: European Organisation for Research and Treatment of Cancer, 2001.

13 Ebert MA, Harrison KM, Howlett SJ, et al. Dosimetric intercomparison for multicentre clinical trials using a patient-based anatomic pelvic phantom. *Med Phys* 2011; **38:** 5167–75.

14 Haworth A, Kearvell R, Greer PB, et al. Assuring high quality treatment delivery in clinical trials—results from the Trans-Tasman Radiation Oncology Group (TROG) study 03.04 "RADAR" set-up accuracy study. *Radiother Oncol* 2009; **90:** 299–306.

15 Ebert MA, Haworth A, Kearvell R, et al. Detailed review and analysis of complex radiotherapy clinical trial planning data: evaluation and initial experience with the SWAN software system. *Radiother Oncol* 2008; **86:** 200–10.

16 Epstein JI, Allsbrook WC, Amin MB, Egevad LL, ISUP Grading Committee. The 2005 International Society of Urological Pathology (ISUP) Consensus Conference On Gleason Grading Of Prostatic Carcinoma. *Am J Surg Pathol* 2005; **29:** 1228–42.

17 Epstein JI, Egevad L, Amin MB, Delahunt B, Srigley JR, Humphrey PA. The 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma: Definition of Grading Patterns and Proposal for a New Grading System. *Am J Surg Pathol* 2016; **40:** 244–52.

18 Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999; **94:** 496–509.

19 Yadav K, Lewis RJ. Gatekeeping strategies for avoiding false-positive results in clinical trials with many comparisons. *JAMA* 2017; **318:** 1385–86.

20 van Andel G, Bottomley A, Fossa SD, et al. An international field study of the EORTC QLQ-PR25: a questionnaire for assessing the health-related quality of life of patients with prostate cancer. *Eur J Cancer* 2008; **44:** 2418–24.

21 Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol* 1998; **16:** 139–44.

22 Xie W, Regan MM, Buyse M, et al. Metastasis-free survival is a strong surrogate of overall survival in localized prostate cancer. *J Clin Oncol* 2017; **35:** 3097–104.

23 Denham JW, Nowitz M, Joseph D, et al. Impact of androgen suppression and zoledronic acid on bone mineral density and fractures in the Trans-Tasman Radiation Oncology Group (TROG) 03.04 Randomised Androgen Deprivation and Radiotherapy (RADAR) randomized controlled trial for locally advanced prostate cancer. *BJU Int* 2014; **114:** 344–53.

24 Denham JW, Wilcox C, Joseph D, et al. Quality of life in men with locally advanced prostate cancer treated with leuprorelin and radiotherapy with or without zoledronic acid (TROG 03.04 RADAR): secondary endpoints from a randomised phase 3 factorial trial. *Lancet Oncol* 2012; **13:** 1260–70.

25 Wirth M, Tammela T, Cicalese V, et al. Prevention of bone metastases in patients with high-risk nonmetastatic prostate cancer treated with zoledronic acid: efficacy and safety results of the Zometa European Study (ZEUS). *Eur Urol* 2015; **67:** 482–91.

26 Freedland SJ, Eastham J, Shore N. Androgen deprivation therapy and estrogen deficiency induced adverse effects in the treatment of prostate cancer. *Prostate Cancer Prostatic Dis* 2009; **12:** 333–38.

27 Bolla M, Van Tienhoven G, Warde P, et al. External irradiation with or without long-term androgen suppression for prostate cancer with high metastatic risk: 10 year results of an EORTC randomised study. *Lancet Oncol* 2010; **11:** 1066–73.

28 Hanks GE, Pajak TF, Porter A, et al. Phase III trial of long-term adjuvant androgen deprivation after neoadjuvant hormonal cytoreduction and radiotherapy in locally advanced carcinoma of the prostate: The Radiation Therapy Oncology Group Protocol 92-02. *J Clin Oncol* 2003; **21:** 3972–78.

29 Horwitz EM, Bae K, Hanks GE, et al. Ten-year follow-up of Radiation Therapy Oncology Group Protocol 92-02: a phase III trial of the duration of elective androgen deprivation in locally advanced prostate cancer. *J Clin Oncol* 2008; **26:** 2497–504.

30 Murray L, Henry A, Hoskin P, Siebert F-A, Venselaar J, PROBATE group of GEC ESTRO. Second primary cancers after radiation for prostate cancer: a systematic review of the clinical data and impact of treatment technique. *Radiother Oncol* 2014; **110:** 213–28.

31 Galvao DA, Spry N, Denham J, et al. A multicentre year-long randomised controlled trial of exercise training targeting physical functioning in men with prostate cancer previously treated with androgen suppression and radiation from TROG 03.04 RADAR. *Eur Urol* 2014; **65:** 856–64.

32 Taaffe DR, Buffart LM, Newton RU, et al. Time on androgen deprivation therapy and adaptations to exercise: secondary analysis from a 12-month randomized controlled trial in men with prostate cancer. *BJU Int* 2018; **121:** 194–202.