PACE-B results: Stereotactic Body Radiotherapy in localised prostate cancer

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Abstract (250 word maximum)
Word count: 250

Background:

Localised prostate cancer is commonly treated with external beam radiotherapy; stereotactic body radiotherapy (SBRT) may be preferable to standard duration radiotherapy as the treatment course is shorter. PACE-B aims to demonstrate non-inferiority of SBRT compared to conventionally or moderately hypo-fractionated regimens for biochemical and/or clinical failure.

Methods:

PACE-B is an international phase III open-label randomised controlled trial. Men with stage T1-T2 prostate cancer, Gleason ≤3+4, PSA ≤20 ng/mL were randomised (1:1) to SBRT (36.25 gray (Gy) in 5 fractions (f) over 1-2 weeks) or control radiotherapy (CRT) (78Gy/39f over 7.5 weeks, or 62Gy/20f over 4 weeks) to the planning target volume. Androgen deprivation therapy was not permitted. The primary endpoint was freedom from biochemical/clinical failure with a critical hazard ratio for non-inferiority of 1.45. Analysis was by intention to treat.

Results:

874 patients were randomised from 38 centres (CRT=441, SBRT=433) between August 2012 and January 2018. Median age was 69.8 years, median PSA 8.0 ng/mL, NCCN risk group was 9.3% low, 90.7% intermediate. After 74.0 months median follow-up, 5-year biochemical/clinical failure free-rate (95% CI) was CRT: 94.6% (91.9%, 96.4%) vs SBRT: 95.8% (93.3%, 97.4%). SBRT was non-inferior to CRT with unadjusted hazard ratio 0.73 (90% CI: 0.48, 1.12; p-value for non-inferiority 0.004). Estimated absolute difference in 5-year event-free proportion was: 1.43% (90% CI: -0.60, 2.78) in favour of SBRT.

Conclusion:

Five-fraction SBRT is non-inferior to CRT for biochemical/clinical failure and should be a new standard of care for patients with low/favourable intermediate risk localised prostate cancer.

ClinicalTrials.gov registration: NCT01584258.

Key words: Prostate Cancer, Stereotactic body radiotherapy, Hypofractionation, Randomised controlled trial.

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Introduction

Prostate cancer is a significant global healthcare challenge with nearly 1.5 million men diagnosed annually(1). In England in 2021, 12% of newly diagnosed prostate cancers were low risk and 29% intermediate risk(2). These men have a number of treatment options including radiotherapy which is considered curative in the majority.

Innovations in image guidance and radiotherapy treatment delivery have enabled delivery of higher biologic doses of radiation, significantly improving oncologic outcomes and side effects associated with treatment(3-5). Hypofractionation, involving higher doses per treatment, is appealing due to its potential to maintain the efficacy of the treatment but reduce the total number of treatment sessions, which could make the treatment more attractive to patients and healthcare systems. Previous studies have confirmed non-inferiority for moderately hypofractionated radiotherapy compared with conventionally fractionated radiotherapy, and moderate hypofractionation has been established as a standard-of-care option (6-8). Stereotactic body radiotherapy (SBRT) builds on these developments to allow ultra-hypofractionated radiotherapy to be delivered with precision.

PACE is a multiple cohort platform trial assessing whether five-fraction SBRT is non-inferior to surgery (PACE-A), and conventionally or moderately hypofractionated radiotherapy (PACE-B and PACE-C) in the treatment of localised prostate cancer. PACE-B included men with low and intermediate risk disease and has already demonstrated the safety of 5 fraction SBRT(9, 10). Here we report the primary outcome assessing non-inferiority for biochemical or clinical failure.

Methods

Eligible patients were ≥18 years, had histologically confirmed prostate adenocarcinoma, WHO performance status 0-2 and life expectancy >5 years. All participants had T1 or T2 disease (defined on MRI) categorised as NCCN low (Gleason 3+3 and PSA≤10ng/ml) or favourable intermediate (at least one of the following factors: Gleason 3+4, PSA 10.1-20.0ng/ml) risk. Exclusion criteria included, previous pelvic radiotherapy, previous treatment for prostate cancer or bilateral hip prostheses.

Trial design and randomisation

PACE-B was an international, phase III, open-label, non-inferiority randomised controlled trial. Participants were randomly assigned (1:1) to SBRT or control radiotherapy (CRT; conventionally or moderately hyopfractionated radiotherapy). Randomisation was performed centrally by the Institute of Cancer Research Clinical Trials and Statistics Unit (ICR-CTSU) using computer generated random permuted blocks (size 4 and 6), stratified by NCCN risk group (low vs intermediate) and randomising centre. Treatment was not masked.

Treatment and assessments

For SBRT, insertion of three or more prostatic fiducial markers was recommended. Moderate bladder filling and bowel preparation (enemas) was advised for treatment planning. CT scan was completed with radiotherapy planning MRI recommended. CT and MRI scans were fused by fiducial matching. Clinical target volume (CTV) was defined as prostate only for low-risk participants or prostate plus proximal 1cm of seminal vesicles for intermediate-risk participants. CTV to planning target volume (PTV) margin was 4-5mm isotropic, except 3-5mm posteriorly. 36.25Gy in five fractions over 1-2 weeks (daily or alternate days) was delivered to 95% of the PTV and a secondary target dose of 40Gy to 95% of the CTV only was delivered. SBRT was permitted on non-coplanar robotic linear accelerators and (since protocol v5.0, August 2014) conventional linear accelerator platforms. For CRT, initially the protocol mandated 78 gray (Gy) in 39 fractions (f) but following a protocol amendment (version 7.1

24/03/2016), 62Gy/20f was also permitted. Centres were required to choose a schedule to be used for all their participants. Androgen deprivation therapy (ADT) was not permitted.

PSA was recorded at 12 weeks, 6, 9, 12 months following treatment and annually thereafter. Participants were assessed using the Common Terminology Criteria for Adverse Events (CTCAE version 4.03.(5) and the Radiation Therapy Oncology Group (RTOG) assessment tool prior to treatment, every three months to 24 months, every 6 months years 2-5 and then annually to year 10.

Patient-reported outcomes (PRO) were assessed at baseline, months 6, 9, 12 and then annually to year 5 using the Expanded Prostate Cancer Index Composite short form (EPIC-26)(11), the International Prostate Symptom Score (IPSS), the Vaizey faecal incontinence score and the International Index of Erectile Function 5-Questionaire (IIEF-5; omitted at month 9). PROs were collected via paper questionnaires distributed in clinic or posted by centres. The protocol is available online(9).

Trial oversight

PACE is an investigator-initiated trial approved by the London Chelsea Research Ethics Committee (11/LO/1915) in the UK and the relevant institutional review boards in Ireland and Canada. From protocol v5.0, August 2014, the trial was sponsored by the Royal Marsden NHS Foundation Trust and co-ordinated by the ICR-CTSU. Prior to this the trial was sponsored by Accuray. Accuray had no role in data collection (managed by a third party before February 2014) or statistical analysis (ICR-CTSU). The trial was conducted in accordance with the principles of Good Clinical Practice. Participants were recruited by their clinical teams and provided written, informed consent before enrolment. The Trial Management Group (TMG) was overseen by an Independent Data Monitoring Committee (IDMC) and an independent Trial Steering Committee (TSC).

Outcome measures

The primary outcome was biochemical or clinical failure (BCF). Biochemical failure was based on PSA rises, commencement of ADT or date of orchidectomy and clinical failure was based on local recurrence, nodal recurrence, distant metastases and/or death from prostate cancer. The time point of primary interest was 5 years. Participants without an event were censored on date of last PSA assessment. Secondary outcome measures included commencement of ADT, diagnosis of metastatic disease, disease free survival, overall survival, clinician and patient assessed side effects.

Statistical analysis

PACE-B was designed to assess non-inferiority of SBRT compared to CRT for BCF. The sample size assumed 85% BCF-free at 5 years with CRT. A non-inferiority margin of 6% at 5 years (critical hazard ratio (HR) 1.45), 80% power, 5% one-sided significance and a 10% loss to follow-up allowance gave a sample size of 858 patients. Following recommendation by the IDMC, the TMG and TSC independently agreed (prior to any data release) to fix the critical HR at 1.45, if the observed control group BCF-free estimate differed from that assumed. The protocol specified the principal analysis would take place once the required number of events had been observed (194) or a minimum of five years follow-up on all participants, whichever occurred first.

Efficacy analyses were on the intention to treat population with a primary endpoint sensitivity analysis conducted in the per protocol population. Kaplan Meier methods were used to estimate event rates. Estimates of treatment effect were made using unadjusted and adjusted (NCCN risk group) Cox regression models. For the primary outcome the HR is reported with the 90% confidence interval. An HR< 1 favours SBRT. The absolute treatment difference in BCF-free rates at 5 years are presented by applying the HR to the control group BCF-free estimate and 90% confidence interval(12). HR with 95% confidence intervals is presented for all other efficacy outcomes. The log-rank test was used to compare groups. The proportional hazards assumption was assessed using Schoenfeld residuals and held for all time to event endpoints. A competing risks analysis was done for the primary outcome with

non-prostate cancer deaths the competing event and differences between SBRT and CRT assessed using the Gray's test. Pre-planned subgroup analyses of the primary outcome by NCCN risk group, age and Gleason score were conducted.

For clinician assessed toxicity (genitourinary (GU), gastrointestinal (GI) and erectile dysfunction), the proportion of grade≥2 toxicity at 5 years is reported with Chi-squared or Fisher's Exact tests used to compare treatment groups. Time to first late adverse event was compared using Kaplan Meier methods. For PRO, EPIC-26 was analysed as composite scores (bowel, urinary, sexual and hormonal) and single item EPIC questions for overall bowel, urinary and sexual bother were presented at each time point assessed. Side effects data were analysed by treatment received.

A 5% significance level was used for the efficacy outcomes (one-sided for the primary endpoint) and 1% for all side effect outcomes to account for multiple testing. Analyses are based on a data snapshot taken on 11th September 2023 and were conducted using Stata version 17.0. The study is registered: ClinicalTrials.gov NCT01584258.

Results

Between August 2012 and January 2018, 874 men (441 CRT, 433 SBRT) were randomised from 38 centres across the UK, Ireland and Canada (Supplementary Appendix S1). 424/441 randomised to CRT and 414/433 randomised to SBRT received their allocated treatment; 25 received neither study treatment (Figure 1). Eleven (8 CRT, 3 SBRT) participants were deemed ineligible but included in analyses. Reasons for ineligibility were: less than ten core biopsies being taken (n=5); prostate volume not measured within 6 months of randomisation (n=3); significant urinary symptoms not identified until planning scan (n=1); no MRI done (n=1), biopsy not performed within 18 months of consent (n=1).

Baseline characteristics were well balanced across randomised groups (Table 1). Median age was 69.8 years (IQR 65.4, 74.0), median PSA ng/mL was 8.0 (IQR 5.9, 11.0) and 81/874 (9.3%) and 793/874 (90.7%) were low and intermediate NCCN risk groups respectively.

With a median follow-up of 74.0 months (IQR 64.8, 86.3), 36 and 26 BCF events had occurred in the CRT and SBRT groups respectively. Five-year BCF event free-rates (95% CI) were 94.6% (91.9, 96.4) for CRT and 95.8% (93.3, 97.4) for SBRT. SBRT was non-inferior to CRT with an unadjusted HR 0.73 (90%CI 0.48, 1.12), p-value for non-inferiority=0.004 (Figure 2A and Supplementary Appendix S2). A test for superiority was not significant (HR 0.73; 95% CI: 0.44 1.21; p=0.22). The estimated absolute difference in the proportion of participants event free in the SBRT group compared with that in the CRT group at 5 years was: 1.43% (90% CI: -0.60, 2.78). An adjusted Cox model (HR 0.72; 90%CI 0.47, 1.10) and analysis in the per-protocol population (HR 0.65; 90%CI 0.42, 1.01) supported non-inferiority. Competing risks analysis indicated no evidence of a difference in BCF rates between treatment groups (p=0.18). Pre-specified sub-group analysis showed no significant interactions with treatment group (Supplementary Appendix S4).

Twenty-nine participants commenced hormone therapy (19 CRT, 10 SBRT), with no evidence of a difference between groups HR 0.55 (95%CI 0.26, 1.20), p=0.13 (Figure 2C and Supplementary Appendix S2). Seventy-nine participants had died (33 CRT and 46 SBRT) with four deaths due to prostate cancer and 28 to other primary cancers (Supplementary appendix S5). There was no evidence of a difference in overall survival between treatment groups HR 1.41 (95%CI 0.90, 2.20), p=0.13 (Figure 2D and Supplementary Appendix S2).

At 5 years, RTOG grade≥2 GU toxicity was seen in 16/355(4.5%) participants who received CRT and 26/355 (7.3%) who received SBRT (p=0.11). CTCAE grade≥2 GU toxicity was reported in 24/357 (6.7%) and 31/355 (8.7%) in the CRT and SBRT groups respectively at 5 years (p=0.32) (Figure 3,

Supplementary Appendix S6 & S8). There was evidence of a difference in cumulative incidence rates for both RTOG and CTCAE grade≥2 GU toxicity (Supplementary Appendix S7). For RTOG GU, incidence of grade≥2 at any time to 5 years was 18.3% (95%CI 14.8, 22.5%) and 26.9% (95%CI 22.8, 31.5%) for CRT and SBRT respectively (HR 1.59 (95%CI 1.18, 2.12), p<0.001).

At 5 years, RTOG grade≥2 GI toxicity was seen in 1/355(0.3%) receiving CRT and 3/354(0.8%) receiving SBRT (p=0.37) (Figure 3, Supplementary Appendix S6 & S8). There was also no evidence of a difference in CTCAE GI grade≥2 events reported at 5 years: 6/357 (1.7%) CRT vs 9/355 (2.5%) SBRT (p=0.43). There was no evidence of a difference in cumulative incidence rates for RTOG or CTCAE grade≥2 GI toxicity (Supplementary Appendix S7). For RTOG GI, incidence rates of grade≥2 by 5 years were 10.2% (95%CI 7.7, 13.5%) and 10.7% (95%CI 8.1, 14.2%) for CRT and SBRT respectively (HR 1.03 (95%CI 0.68, 1.56), p=0.94.

At 5 years, 86/296 (29.1%) CRT and 78/296 (26.4%) SBRT participants reported grade≥2 CTCAE erectile dysfunction (p=0.46). Clinician reported grade≥2 erectile symptoms were similar between treatment groups at baseline and were stable from 2 to 5 years after treatment (Figure 3, Supplementary Appendix S6).

Participants reported stable urinary and bowel symptoms from 2 to 5 years, with little difference between treatment groups (Figure 4 and Supplementary Appendix 9). At 5 years, median EPIC urinary incontinence scores of 100 (IQR 79.3, 100) and 96.9 (IQR 73.0, 100) were reported for CRT and SBRT respectively (p=0.45) (Supplementary Appendix 9). There was no evidence of a difference in EPIC urinary obstruction scores at 5 years with median 93.8 (IQR 81.3, 100) for CRT and 93.8 (IQR 81.3, 100) for SBRT. Similar EPIC bowel subdomain scores were reported at 5 years with a median of 95.8 (IQR 87.5, 100) for CRT and 100 (IQR 87.5, 100) for SBRT (p=0.10). EPIC sexual subdomain scores declined from 2 to 5 years with no evidence of a difference between treatments at 5 years (p=0.87).

Discussion

PACE-B has demonstrated non-inferiority of 5 fraction SBRT compared to moderately fractionated image-guided radiotherapy with excellent 5-year BCF rates in both arms of the trial. The previous UK fractionation trial, CHHiP, included a slightly higher risk group and reported 5-year BCF-rate of 90.6% with moderately fractionated 60Gy/20f(6). The PACE-B BCF-free rates of 95% and 96% for CRT and SBRT respectively were achieved without ADT and exceeded the expectations of the trial design. The authors believe these excellent oncological outcomes reflect improvements in radiotherapy delivery since the trial began.

PACE-B is the first randomised controlled trial to demonstrate non-inferiority of SBRT in this setting. The results support and complement the findings of the HYPO-RT-PC phase 3 non-inferiority trial in which 1200 men were randomised between 78Gy/39f and 42.7Gy/7f delivered over 2.5weeks. HYPO-RT-PC demonstrated a failure-free survival at 5 years of 84% in both arms of the trial (95% CI 80–87) in both treatment groups, with an adjusted HR of 1·00 (95% CI 0·76, 1·33; log-rank p=0·99)(13). The difference in outcomes between the two trials is likely due to the inclusion of non-prostate cancer death as an event in the HYPO-PC-RT study.

The strengths of the PACE-B trial include the size of the study and the multi centre recruitment across three countries. The trial was delivered with quality assured radiotherapy in both the control and experimental arms, in a well-defined and homogenous trial population. There was no hormonal therapy in either arm of the study ensuring that the trial outcomes were not confounded by variable use of hormone therapy. The main limitation is that recommendations for 5f SBRT are necessarily limited to those who were eligible for the trial i.e., men with low and favourable intermediate risk prostate cancer. The efficacy results of the PACE-C trial testing non-inferiority of 5f SBRT to 60Gy/20f in men with higher risk disease requiring ADT are awaited.

We have previously shown a significant increase in grade 2 or higher genitourinary toxicity measured at 2 years after treatment, 12% compared to 7% after treatment(10). This updated toxicity analysis at 5 years showed that these symptoms improve and that there was no difference between the two arms at 5 years, with low levels of side effects overall. Nevertheless, patients need to be aware of the higher risk of GU toxicity in the medium term and some patients, especially those with significant lower urinary tract symptoms (LUTS) at baseline, may have better symptomatic outcome with 20 fraction IMRT. We have shown that those with baseline LUTS and/or significant acute toxicity are more like to experience toxicity at 2 years, offering the chance to better select patients for SBRT and to more carefully counsel and monitor those with acute toxicity symptoms(14).

Prostate cancer radiotherapy accounts for a significant proportion of workload in radiotherapy departments across the world. In England in 2022, over 16,000 patients were treated with prostate radiotherapy(2). We estimate that approximately 4,800 would have met the eligibility criteria for PACE-B. Switching these patients to a 5 fraction regime would result in an approximately 72,000 fraction reduction across the UK. Five fraction SBRT also minimises the socioeconomic and psychological burden of treatment for patients.

The PACE-B trial confirms that 5 fractions of SBRT can be considered a standard of care for this population of patients and that patients can safely avoid the potential side effects of hormonal therapy. When the results are combined with the PACE-A trial which compares 5 fraction SBRT to robotic prostatectomy in exactly the same eligibility cohort, we show that SBRT is likely to offer the best chance of avoiding the need for second treatment for prostate cancer. Patients considering surgery should be given this data prior to making a treatment decision.

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Competing interests / Declarations:

N. van As and A. Tree declare research funding from Accuray.

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A. Tree declares honoraria from Elekta, Accuray, Bayer and Janssen and research grants for radiotherapy research from Elekta.

A. Tree declares travel support from Elekta.

A. Tree declares her role of lead GU editor for the International Journal of Radiation Oncology, Biology and Physics (paid personally) and chair of the MRlinac consortium steering committee (institutional financial support).

A. Tree declares her participation on the Data Safety and Monitoring Board for the KORTUC and NEPTUNES academic trials (no compensation).

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J. Frew declares his participation on the Bayer Advisory Board, October 2023.

D. Ford declares funding from Janssen to attend GUASCO 2024.

D. Ford declares he is employed by Genesiscare as advisor/clinician on an MRLinac facility.

A. Martin declares is he is a paid employee of GenesisCare UK on the MR Linac rota and SABR advisory team.

P. Camilleri declares support for attending meetings and/or travel from GenesisCare UK and a leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid

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A. Loblaw declares his role as a member of the ASCO Prostate Cancer Guideline Committee, chair/founder of the Prostate Cure Foundation, co-chair of Program in Evidence Based Care Genitourinary Site CancerCare Ontario, co-chair Genitourinary Site Sunnybrook Health Sciences Centre, chair of the Genitourinary Radiation Oncology Clinical Study Group Sunnybrook Health Sciences Centre.

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Table 1 – Baseline demographics by randomised treatment

Baseline Characteristics	CRT (N=441)		SBRT (N=433)		Total (N=874)	
	n	%	n	%	n	%
Ethnic origin						
Black	26	(5.9)	35	(8.1)	61	(7.0)
East Asian	3	(0.7)	4	(0.9)	7	(0.8)
Mixed heritage	2	(0.5)	2	(0.5)	4	(0.5)
Southern Asian	10	(2.3)	20	(4.6)	30	(3.4)
White	393	(89.1)	367	(84.8)	760	(87.0)
Other*	7	(1.6)	5	(1.2)	12	(1.4)
Family history of prostate cancer						
No	326	(73.9)	312	(72.1)	638	(73.0)
Yes	88	(20.0)	89	(20.6)	177	(20.3)
Unknown	27	(6.1)	32	(7.4)	59	(6.8)
WHO status						
WHO status 0	391	(88.7)	389	(89.9)	780	(89.2)
WHO status 1	48	(10.9)	44	(10.2)	92	(10.5)
WHO status 2	2	(0.5)	0	(0.0)	2	(0.2)
T-Stage						
T1c	81	(18.4)	82	(18.9)	163	(18.6)
T2a	133	(30.2)	105	(24.2)	238	(27.2)
T2b	59	(13.4)	81	(18.7)	140	(16.0)
T2c	168	(38.1)	162	(36.4)	330	(37.8)
Unknown	0		3	(0.8)	3	(0.4)
NCCN risk score						
Low	43	(9.8)	38	(8.8)	81	(9.3)
Intermediate	398	(90.2)	395	(91.2)	793	(90.7)
Gleason score						
3+3	90	(20.4)	63	(14.5)	153	(17.5)
3+4	351	(79.6)	370	(85.3)	721	(82.5)
Prostate volume						

<40 mL	163	(37.0)	192	(44.3)	355	(40.6)
40 - <80 mL	223	(50.6)	198	(45.7)	421	(48.2)
80+ mL	28	(6.3)	22	(5.3)	51	(5.8)
Unknown	27	(6.1)	20	(4.6)	47	(5.4)
Alpha blockers at randomisation						
Yes	68	(15.4)	72	(16.6)	140	(16.0)
No	368	(83.4)	356	(82.2)	724	(82.8)
Unknown	5	(1.1)	5	(1.2)	10	(1.1)
Aspirin at randomisation						
Yes	80	(18.1)	73	(16.9)	153	(17.5)
No	356	(80.7)	354	(81.8)	710	(81.2)
Unknown	5	(1.1)	6	(1.4)	11	(1.3)
Statin at randomisation						
Yes	159	(36.1)	137	(31.6)	296	(33.9)
No	277	(62.8)	289	(66.7)	566	(64.8)
Unknown	4	(0.9)	7	(1.6)	12	(1.4)
Anticholinergic for bladder symptoms at randomisation						
Yes	14	(3.2)	12	(2.8)	26	(3.0)
No	423	(95.9)	415	(95.8)	838	(95.9)
Unknown	4	(0.9)	6	(1.4)	10	(1.1)
5-alpha reductase inhibitors at randomisation						
Yes	9	(2.0)	11	(2.5)	20	(2.3)
No	422	(95.7)	402	(92.8)	824	(94.3)
Unknown	10	(2.3)	20	(4.6)	30	(3.4)
Phosphodiesterase-5 inhibitors for erectile dysfunction at randomisation						
Yes	13	(3.0)	6	(1.4)	19	(2.3)
No	408	(94.9)	393	(94.9)	801	(94.9)
Unknown	9	(2.1)	15	(3.6)	24	(2.8)
Age at randomisation (years)						
Median (IQR)	69.7	(65.5, 73.9)	69.8	(65.4, 74.1)	69.8	(65.4, 74.0)
N (Range)	441	(48.1, 86.7)	433	(45.8, 84.5)	874	(45.8, 86.7)

PSA (ng/mL)						
Median (IQR)	8.1	(6.3, 11.0)	7.9	(5.5, 10.9)	8.0	(5.9, 11.0)
N (Range)	441	(0.8, 20.0)	433	(0.5, 20.0)	874	(0.5, 20.0)
PSA<10	303	(68.7)	297	(68.6)	600	(68.7)
PSA 10<20	138	(31.3)	136	(31.4)	274	(31.6)
Testosterone [µmol/L]						
Median (IQR)	11.3	(8.7, 15.0)	11.5	(9.0, 15.0)	11.3	(8.9, 15.0)
N (Range)	407	(0.4, 30.6)	403	(0.4, 30.5)	810	(0.4, 30.6)
Time from diagnosis to randomisation (weeks)**						
Median (IQR)	11.0	(6.9, 17.0)	9.9	(6.6, 16.1)	10.1	(6.7, 16.6)
N (Range)	441	(0.9, 335.0)	433	(0.1, 225.0)	874	(0.1, 335.0)

Foot note: *6-not disclosed, 1-Spanish, 2-Iranian, 1-Filipino, 1-Middle eastern, 2-Lebanese, 1-Hispanic

**According to protocol, histological confirmation of prostate adenocarcinoma within the last 18 months unless on active surveillance and not clinically indicated

Figure 1. CONSORT flow chart

Figure 2. Efficacy outcomes (A) Kaplan Meier curve for biochemical or clinical failure by randomised treatment group, (B) Nelson Aalen cumulative incidence plot for biochemical or clinical failure by randomised treatment group, (C) Kaplan Meier curve for commencement of hormone therapy by treatment group, (D) Kaplan Meier curve for overall survival by randomised treatment group

Figure 3. Prevalence of clinician reported RTOG and CTCAE assessed genitourinary, gastrointestinal toxicity and erectile dysfunction at each time point assessed by treatment received (A) Prevalence of grade≥1, grade≥2 and grade≥3 RTOG Genitourinary toxicity at each time point assessed by treatment received, (B) Prevalence of grade≥1, grade≥2 and grade≥3 RTOG Gastrointestinal toxicity at each time point assessed by treatment received (C) Prevalence of grade≥1, grade≥2 and grade≥3 CTCAE Genitourinary toxicity at each late time point assessed by treatment received (D) Prevalence of grade≥1, grade≥2 and grade≥3 CTCAE Gastrointestinal toxicity at each time point assessed by

treatment received, (E) Prevalence of grade≥1, grade≥2 and grade≥3 CTCAE Erectile dysfunction at each time point assessed by treatment received

Figure 4. Patient reported mean EPIC subdomain composite scores by treatment received at each time point assessed

NB. EPIC subdomain scores range from 0 to 100 with higher scores indicating better quality of life

(A)Urinary incontinence, (B) Urinary obstruction, (C) Bowel, (D) Sexual, (E) Hormonal

Footnote-Error bars show 95% confidence interval for estimates of mean subdomain scores. Week 0 is the baseline toxicity score taken before start of radiotherapy.

Abbreviations: EPIC-26 = Expanded Prostate Cancer Index Composite (26 question); CRT = Conventional radio therapy; SBRT = Stereotactic Body Radiotherapy