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Title

Intensity Modulated Fractionated Radiotherapy Versus Stereotactic Body Radiotherapy for Prostate Cancer (PACE-B): Acute Toxicity Results From a Randomised Open-label Phase III Non-inferiority Trial

Authorship

Douglas H Brand*
Alison C Tree*
Peter Ostler
Hans van der Voet
Andrew Loblaw
William Chu
Daniel Ford
Shaun Tolan
Suneil Jain
Alexander Martin
John Staffurth
Philip Camilleri
Kiran Kancherla
John Frew
Andrew Chan
Ian S Dayes
Daniel Henderson
Stephanie Brown
Clare Cruickshank
Stephanie Burnett
Aileen Duffton
Clare Griffin
Victoria Hinder
Kirsty Morrison
Olivia Naismith
Emma Hall
Nicholas van As
On behalf of the PACE Trial Investigators

*Contributed equally to this article

The Royal Marsden Hospital, London, UK (D H Brand MRes, A C Tree MD(Res), K Morrison FRCR, O Naismith MSc, N van As MD(Res));
Mount Vernon Cancer Centre, Northwood, UK (P Ostler FRCR);
The James Cook University Hospital, Middlesbrough, UK (H van der Voet MD);
Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, ON, Canada (A Loblaw MD, W Chu MD);
University Hospitals Birmingham, Birmingham, UK (D Ford FRCR, D Henderson MD(Res));
The Clatterbridge Cancer Centre, Birkenhead, UK (S Tolan MB BCh);
Queen's University Belfast, Belfast, UK (S Jain MB PhD);

Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK (A Martin MD(Res));
Cardiff University, Cardiff, UK (Prof. J Staffurth MD);
Churchill Hospital, Oxford, UK (P Camilleri FRCR);
University Hospitals of Leicester, Leicester, UK (K Kancherla FRCR);
Freeman Hospital, Newcastle, UK (J Frew FRCR);
University Hospitals Coventry & Warwickshire, Coventry, UK (A Chan FRCR);
Department of Oncology, McMaster University, Hamilton, ON, Canada (I S Dayes MD)
Beatson West of Scotland Cancer Centre, Glasgow, UK (A Duffton MSc)
The Institute of Cancer Research, London, UK (D H Brand MRes, A C Tree MD(Res), S Brown PhD, C Cruickshank BSc(Hons), S Burnett BSc, C Griffin MSc, V Hinder BSc, K Morrison FRCR, Prof E Hall PhD, N van As MD(Res));

Correspondence to:
Dr Nicholas van As
Department of Uro-oncology
The Royal Marsden NHS Foundation Trust
Fulham Rd
UK
SW3 6JJ
nicholas.vanas@rmh.nhs.uk

Research in context Panel

Evidence before this study

At the time of initiation of this study, 2011, there were no published randomised controlled trials of ultra-hypofractionated stereotactic body radiotherapy compared to conventional fractionated or moderately hypofractionated radiotherapy for localised prostate cancer. Standard treatment was radiotherapy in 2 Gy per fraction, to a dose of 74 or 78 Gy. A subsequent change of standard-of-care practice to moderate hypofractionation in 2016 was reflected in the control arm of this study. Subsequent data were found by searching PubMed using the terms ["SBRT" OR "Stereotactic Body Radiotherapy"] AND "Prostate", covering up to 31st March 2019. References of papers found were searched, with the search also supplemented by the authors' knowledge of the field. 16 studies reporting acute toxicity outcomes from SBRT to the prostate were identified. This included a full article for a single randomised phase III study (HYPO-RT-PC). Grade 2+ acute toxicity estimates for ultra-hypofractionation were similar to standard fractionation, ranging from 4 – 24% for gastrointestinal and 4 – 40% for genitourinary toxicity.

Added value of this study

To our knowledge, this is the first published phase III randomised evidence of acute toxicity after ultra-hypofractionated stereotactic body radiotherapy, delivered over five fractions, compared with standard fractionation schedules. Overall, this study shows similar acute toxicity with ultra-hypofractionation, with only CTCAE Grade 2+ gastrointestinal toxicity being significantly worse. Proportions of patients experiencing acute grade 3 toxicity appear low. This adds to the evidence of low acute toxicity, as was also seen for seven fraction hypofractionated radiotherapy in the recently reported HYPO-RT-PC trial.

Implications of all the available evidence

Ultrahypofractionated radiotherapy over five fractions appears tolerable in the short term. The HYPO-RT-PC trial demonstrated that a schedule 42·7 Gy delivered every other day in 2·5 weeks (6·1Gy/fraction) was non-inferior in terms of failure-free survival compared with conventional fractionation of 78Gy over 8 weeks (2Gy/f) with similar proportions of late toxicity in each group. Late toxicity and efficacy data for PACE-B are awaited and are required before a new standard of care for localised prostate cancer can be recommended.

Summary

Background

Localised prostate cancer is commonly treated with external beam radiotherapy. Moderate hypofractionation has been shown non-inferior to conventional fractionation. Ultra-hypofractionated stereotactic body radiotherapy (SBRT), would allow shorter treatment courses, but may increase acute toxicity compared to conventionally fractionated or moderately hypofractionated radiotherapy (CFMHRT). We report acute toxicity findings from a randomised trial of CFMHRT versus SBRT.

Methods

PACE is a multi-cohort international phase III randomised controlled trial. In PACE-B, eligible men, aged ≥18 years, performance status 0-2, had low or intermediate risk prostate adenocarcinoma (Gleason 4+3 excluded) and were scheduled to receive radiotherapy. Computerised central 1:1 randomisation (stratifications: centre, risk group), was between CFMHRT (78 Gy / 39 fractions / 7·8 weeks OR 62 Gy / 20 fractions / 4 weeks) or SBRT (36·25 Gy / 5 fractions / 1-2 weeks). Neither participants nor investigators were blinded to allocation. Androgen deprivation was not permitted. The joint main outcomes for this acute toxicity substudy were worst Radiation Therapy Oncology Group (RTOG) grade 2+ (G2+) gastrointestinal or genitourinary toxicity, up to 12 weeks after radiotherapy. Analysis was per protocol. PACE-B recruitment is complete and follow-up continues (NCT01584258).

Findings

Between 07/12/2012 and 04/01/2018, 37 centres randomised 874 men. 432/441 patients allocated CFMHRT and 415/433 allocated SBRT received at least 1 fraction of allocated treatment. Worst acute RTOG gastrointestinal toxicity proportions were: G2+ 12·3% (53/432) CFMHRT, versus 10·4% (43/415) SBRT (difference −1.9%, 95% CI −6.2% to 2.4%, p=0·38); G3+ 0.9% (4/432) CFMHRT, versus 0.2% (1/415) SBRT (difference −0.7%, 95% CI −1.7 to 0.3%, p=0·37). Worst acute RTOG genitourinary toxicity proportions were: G2+ 27·3% (118/432) CFMHRT versus 23·1% (96/415) SBRT (difference −4.2%, 95% CI −10 to 1.7%, p=0·16); G3+ 1.6% (7/432) CFMHRT versus 2.4% (10/415) SBRT (difference 0.8%, 95% CI −1.1 to 2.7%, p=0·47). No treatment related deaths occurred.

Interpretation

Our results show that significantly shortening treatment courses, using SBRT, does not increase either gastrointestinal or genitourinary toxicity.

Funding

Accuray Incorporated.

Main Body

Background

Prostate cancer is the most common non-cutaneous malignancy amongst men living in developed countries[1–3]. For patients with National Comprehensive Cancer Network (NCCN) low or intermediate risk disease[4], it is reasonable to consider several management approaches, including external beam radiotherapy (EBRT), brachytherapy, surgery, and, for some, active surveillance. Data from the randomised ProtecT trial (comparing surgery, EBRT and active monitoring) has given reassurance that cancer outcomes are similar, for low and intermediate risk disease, regardless of management option utilised[5]. Side effects may therefore exert influence over decision making, with gastrointestinal (GI), genitourinary (GU), and sexual side effects being of common concern[6]. Additionally, the tolerability of treatment for a given patient is crucial, with the anaesthetic and intra-operative risks balanced against the inconvenience of multi-week courses of EBRT.

Hypofractionation, defined as increasing dose per fraction above the conventional 2 Gy, thus reducing total fractions required, is appealing. The key advantages are twofold: firstly, prostate cancer's greater fraction size sensitivity (indicated by a lower α/β ratio[7–10]), relative to the relevant late GI and GU side effects, means that the therapeutic ratio may be improved by hypofractionation[11]. Secondly, fewer fractions are needed, allowing for quicker and more cost-effective EBRT treatment courses[12].

Three major non-inferiority phase III randomised controlled trials (RCTs) have confirmed the safety and efficacy of moderate hypofractionation (2·5-3·0 Gy per fraction) [11,13,14], which has gained acceptance as a standard-of-care option[15,16]. Whilst proportions experiencing late toxicity were low, some inter-trial differences in acute toxicity proportions were seen. The CHHiP trial reported significantly worse peak acute Radiation Therapy Oncology Group (RTOG) grade 2+ (G2+) GI toxicity proportions of 38% in both hypofractionated arms, compared to 25% with conventional fractionation ($p<0{\cdot}0001$ for both comparisons)[11]. Similarly, the PROFIT trial reported significantly ($p=0{\cdot}003$) greater cumulative acute RTOG GI G2+ toxicity in the hypofractionated arm (16·7%) versus conventional fractionation (10·5%) [14]. For both trials, acute G2+ GU toxicity was similar between randomised groups. In contrast, the RTOG-0415 hypofractionation trial did not find a significant difference in acute GI or GU toxicity [13]. Whilst more profound hypofractionation beyond 3·0 Gy per fraction would allow further reductions in the overall treatment time, the accelerated schedule may worsen acute toxicity, as seen in the CHHiP trial[11], potentially leading to consequential late effects[17].

Substantial evidence exists for ultra-hypofractionation, with over 6000 patients treated in prospective studies, and excellent 5-year biochemical progression free survival in recent meta-analysis (95·3%, 95% CI 91·3 - 97·5%)[18]. A single phase III (HYPO-RT-PC) has reported randomised data for seven fraction ultra-hypofractionated radiotherapy, with good biochemical progression free survival and acceptable proportions experiencing toxicity[19]. Phase III randomised toxicity data for five fraction treatment has not previously been reported.

Here we report the acute toxicity findings (both clinician and patient reported) from the PACE-B RCT comparing standard-of-care conventionally fractionated or moderately hypofractionated radiotherapy (CFMHRT) to five fraction stereotactic body radiotherapy (SBRT), for low to intermediate risk localised prostate cancer.

Methods

Study design and Participants

PACE-B is a multicentre, international, phase III, open-label, RCT aiming to demonstrate non-inferiority of SBRT compared with CFMHRT for biochemical/clinical failure; a full list of PACE-B secondary endpoints is available in the protocol (**Appendix pp79-81**). The trial was approved by the London Chelsea Research Ethics Committee (REC) (ref 11/LO/1915) in the UK and the relevant institutional review boards in Ireland and Canada. PACE-B was conducted in accordance with the principles of Good Clinical Practice. The trial is sponsored by The Royal Marsden Hospital NHS Foundation Trust, funded by Accuray Incorporated (Sunnyvale, CA, USA) and endorsed by Cancer Research UK. The Clinical Trials and Statistics Unit at the Institute of Cancer Research (ICR-CTSU) coordinated the trial. The study was overseen by a trial steering committee and an independent data monitoring committee (IDMC) (**Appendix p3**).

The PACE study comprises multiple cohorts (PACE-A, PACE-B, and PACE-C) with independent randomisations. This study, PACE-B, recruited only patients suitable for radical radiotherapy, but not willing and/or not suitable for radical prostatectomy. Eligible patients were men aged ≥18 years, with World Health Organisation (WHO) performance status 0-2[20], life expectancy of ≥5 years and histologically confirmed prostate adenocarcinoma. All patients had NCCN low or intermediate risk disease [4]. Low risk patients were: cT1c-T2a (TNM 6th edition [21]), N0/X, M0/X; Gleason score ≤ 6 ; PSA < 10ng/mL. Intermediate risk patients had ≥1 of: T2c; Gleason score 3+4 (Gleason 4+3 was excluded); PSA 10-20 ng/mL. Distant staging wasn't mandated. A minimum 10 biopsy cores, ≤18 months pre-randomisation, were required, except for those progressing on active surveillance, whose last biopsy was suitable for PACE-B, and required treatment (e.g. PSA/MRI progression). These patients were stratified as intermediate risk. No PSA adjustment was made for 5-alpha reductase inhibitor (5-ARI) use at randomisation. Treating physicians had discretion to exclude patients for comordid conditions making radiotherapy inadvisable (e.g. inflammatory bowel disease, significant urinary tract symptoms). Detailed criteria are in the protocol (**Appendix p82-83**). All participants provided voluntary, written, informed consent.

Randomisation and masking

Patients were randomised 1:1 to either CFMHRT or SBRT. Randomisation was undertaken centrally by the ICR-CTSU, by telephone (UK and Ireland) or fax (Canada), with allocation by computer generated random permuted blocks (size 4 and 6) and stratified by centre and risk group (low or intermediate). Treatment assignment was open-label to participants and researchers.

Procedures

Before radiotherapy, three or more prostatic fiducial markers were strongly recommended for all participants, to permit more accurate image guided radiotherapy (IGRT) and CT/MRI fusion. Bowel preparation (enemas) was suggested, along with moderate bladder filling. The radiotherapy planning CT scan, took place at least 7 days after fiducial placement. A radiotherapy planning MRI scan was strongly recommended, to be fused to the CT scan (preferably by fiducial match) for improved prostate anatomical definition. The clinical target volume (CTV) was the prostate only (low risk patients) or prostate and proximal 1cm of seminal vesicles (intermediate risk patients).

Recommended CFMHRT CTV to planning target volume (PTV) expansion was 5-9mm isometric, except posteriorly 3-7mm. Recommended SBRT CTV to PTV expansion was 4-5mm isometric, except posteriorly 3-5mm. Dose constraints were applied to organs at risk (OARs) and were amended during the trial. A history of the constraints used with numbers of patients randomised to each iteration, is in the **Appendix (pp4-5)**. Additional detail on radiotherapy preparation and final dose constraints used from 24th March 2016 are in the protocol (**Appendix pp93-100**). Androgen deprivation therapy (ADT) was not permitted.

CFMHRT PTV dose was 78 Gy in 39 daily fractions or, following approved protocol amendment (24th March 2016), 62 Gy in 20 daily fractions. This change followed the CHHiP trial data supporting moderate hypofractionation [11], but with a higher dose (62 Gy versus 60 Gy) because PACE-B prohibits ADT. Data from PROFIT for 60 Gy in 20 fractions, without ADT, were not available at that time[14]. After the amendment, centres were required to choose either 78 Gy in 39 fractions or 62 Gy in 20 fractions as their control treatment for all subsequent patients. The SBRT PTV dose was 36·25 Gy in 5 fractions over 1-2 weeks (i.e. daily or alternate days, at centre discretion), with an additional secondary CTV dose target of 40 Gy. The CyberKnife (CK) treatment platform (Accuray Incorporated, Sunnyvale, CA, USA) was initially mandatory for all SBRT, however challenging accrual prompted an approved protocol amendment (24th October 2014) permitting SBRT delivery on conventional linear accelerators (LINACs). Detailed prescription objectives, along with minor variations permitted, are in the protocol (**Appendix pp93-100**).

Treatment was mandated to commence within 12 weeks of randomisation, with ≤8 weeks strongly recommended. IGRT (preferably fiducial based) was mandated. For SBRT, intra-fractional motion monitoring was permitted; otherwise a repeat static image was required for SBRT fraction delivery extending beyond 3 minutes. A radiotherapy quality assurance programme was undertaken for each centre to ensure consistency with trial protocol and quality of RT treatments: details in protocol (**Appendix p113**).

Participants were assessed alternate weeks during CFMHRT and on the final fraction for SBRT and weeks 2, 4, 8 and 12 after the end of treatment. Two clinician reported outcomes (CROs) were collected: RTOG (GI and GU domains) at baseline and every visit; Common Terminology Criteria for Adverse Events (CTCAE) at baseline and follow-up weeks 2, 4, 8 and 12, with additional end-of-treatment assessment for SBRT patients. Paper questionnaires collected four patient-reported outcome (PRO) measures: Expanded Prostate Cancer Index Composite Short Form (EPIC-26) and the Vaizey Faecal Incontinence Score, at baseline, weeks 4 and 12; International Prostate Symptom Score (IPSS), at baseline, weeks 2, 4, 8 and 12; the International Index of Erectile Function 5-question (IIEF-5) score, at baseline and week 12. Subsequent follow-up is ongoing, with the full schedule, along with criteria for removal of patients from the study, available in the protocol (**Appendix pp84-92**).

Outcomes

The PACE-B trial's primary endpoint is freedom from biochemical or clinical failure, the data for which is not yet mature. This acute toxicity report is a pre-specified sub-analysis of the PACE-B trial. A statistical analysis plan (SAP) for this sub-study (**Appendix p129 onwards**) was prospectively written, with G2+ worst RTOG toxicity score, up to week 12 follow-up post-radiotherapy, for both GI and GU systems, as co-primary sub-study endpoints. Separately for GI and GU, the numerator was patients with recorded RTOG G2+ toxicity at any point after baseline, up to week-12 post

radiotherapy. The denominator was all patients with at least one RTOG score completed after baseline, up to week-12 post radiotherapy. Patients were missing if no such score was returned. This endpoint was pragmatically chosen, as only RTOG assessments were conducted for CFMHRT patients during radiotherapy. Secondary endpoints focussed on clinician (Common Terminology Criteria for Adverse Events) and patient (Expanded Prostate Cancer Index Composite 26 Question; International Prostate Symptom Score; International Index of Erectile Function 5 Question; Vaizey Incontinence Score) reported scales. For each scale, the baseline, worst, worst above baseline and week-12 (i.e. residual) toxicity were of interest; with exact definitions detailed in the SAP **(Appendix p145-147).**

Statistical analysis

For this acute toxicity analysis, the patients were analysed per protocol, with those receiving one or more fractions of CFMHRT or SBRT radiotherapy included. Patients not receiving radiotherapy were excluded from this analysis. Those patients receiving both CFMHRT and SBRT fractions were excluded unless the reason was toxicity related, where analysis was on first treatment fraction received. The PACE-B trial as a whole targeted recruitment of 858 patients to exclude a hazard ratio of 1.45 in biochemical/clinical failure at 5 years, with consideration given to also excluding a 6% increase in grade 2 GI or GU late toxicity at 2 years (**Appendix p107-108**). For this acute toxicity substudy, we assumed CFMHRT arm acute RTOG G2+ toxicity proportions of 25% (GI) and 40% (GU) respectively, per CHHiP and PROFIT[11,14]. With two-sided α=0·025 for each endpoint, we estimated that ongoing PACE-B recruitment would provide 83% power to exclude a 10% increase in acute GI toxicity and 84·5% power to exclude an 11% increase in acute GU toxicity, for the SBRT arm (**Appendix pp139-140**).

The chi-square test was used to compare treatment groups for the co-primary endpoints. Secondary endpoints were compared with appropriate statistical tests (**Appendix pp145-147**). To reduce the impact of multiple comparisons, a p-value of 0·001 was considered significant for secondary comparisons. The different durations of radiotherapy (CFMHRT 4 or 7.8 weeks; SBRT 1 or 2 weeks) led to differing time points of toxicity assessment. RTOG (assessed during radiotherapy) and CTCAE (assessed at end of radiotherapy for SBRT) graphical presentation is therefore both as four groups and just CFMHRT and SBRT (interpolation detailed in **Appendix p6**). Confidence intervals for the difference in proportions were calculated using normal approximation.

EPIC-26 scores were rescaled to a 0-100 point scale, with higher scores representing better quality of life (QoL) [22]. Subdomains were scored if sufficient questions were completed: urinary incontinence (4/4 questions), urinary obstructive (4/4), bowel (5/6), sexual (5/6), hormonal (4/5)[22]. A clinically important point reduction in EPIC-26 subdomain score was: urinary incontinence (8 points) urinary obstructive (6 points), bowel (5 points), sexual (11 points), hormonal (5 points)[23]. IPSS severity categories were assessed as none (0 points), mild (1-7 points), moderate (8-19 points), severe (20-35 points)[24].

Exploratory examination of CyberKnife versus standard LINAC for SBRT patients was prospectively included in the protocol, when amendment permitted standard LINACs (5th August 2014). The prespecified SAP called for a multivariate analysis, which will be published subsequently, but a post-hoc decision was made (in discussion with reviewers) to analyse the worst RTOG G2+ GI and GU toxicity for SBRT patients, split by CyberKnife and non-CyberKnife usage, interpreted at a significant p-value of 0·001. Since centre-level effects my influence this non-randomised analysis (e.g. variation

in toxicity reporting), we present similar analysis for CFMHRT patients; separated by whether their centre used CyberKnife or non-CyberKnife for SBRT treatments.

Analyses are based on a snapshot of data taken on 28/05/2019 and were conducted using STATA version 15.1 (StataCorp LLC, Texas, USA). The IDMC gave approval for release of acute toxicity results prior to release of primary endpoint (efficacy) results. The PACE study was prospectively registered at clinicaltrials.gov (NCT01584258).

Role of the funding source
The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between 07/08/2012 and 04/01/2018, 874 men were randomised (441 CFMHRT; 433 SBRT) from 37 centres (**Appendix p7**) across three countries (UK, Ireland & Canada). Median follow-up completed was 12 weeks (IQR 12 – 12 weeks), matching the time period authorised for data release. The CONSORT diagram details per-protocol assignment (**Figure 1**), including ineligibility reasons and exact radiotherapy regimens delivered. Eleven patients received non-protocol regimens, which are detailed with reasons in the **Appendix (p8)**; one was toxicity related (an SBRT patient with G3 urinary toxicity). Baseline characteristics for each per protocol treatment group appeared balanced (**Table 1**). Four of the 19 patients on 5-ARI at baseline had a PSA value of 10-20 ng/mL. Radiotherapy delivery techniques (planning, IGRT, margins) expectedly differed between arms, although recorded supportive prescribing appears similar (**Appendix pp9-11**). Despite fiducial recommendation for both arms, more SBRT patients received fiducial markers (303/415, 73·0%) than CFMHRT (245/427, 56·7%). RTOG and CTCAE form completion was excellent at all timepoints (**Appendix p12**)**.** Patient illness caused non-completion of 3 RTOG forms (2 CFMHRT, 1 SBRT) and 1 SBRT CTCAE form. The PRO assessment completion varied by scale (**Appendix pp13-14**). A single patient randomised to SBRT died due to myocardial infarction prior to receiving trial treatment and is excluded from this per-protocol analysis; no other deaths were reported up to 12 weeks post radiotherapy.

Worst RTOG acute toxicity adverse events, by GI and GU organ systems, are shown in **Table 2**. Regarding the co-primary endpoints of interest for this sub-study**:** worst acute RTOG G2+ GI toxicity, compared between CFMHRT (53/432, 12·3%) and SBRT (43/415, 10·4%) did not differ significantly (difference −1.9%, 95% CI −6.2% to 2.4%, p=0·38). Worst acute RTOG G2+ GU toxicity, compared between CFMHRT (118/432, 27·3%) and SBRT (96/415, 23·1%) also did not differ significantly (difference −4.2%, 95% CI −10 to 1.7%, p=0·16). For RTOG secondary endpoints, no significant differences were seen comparing CFMHRT and SBRT by any comparison for GI (**Appendix p15**), including worst RTOG GI G3+ toxicity (4/432, 0·9% vs 1/415, 0·2%, difference −0.7%, 95% CI −1.7 to 0.3%, p=0·37); nor GU (**Appendix p16**), including worst RTOG GU G3+ toxicity (7/432, 1·6% vs 10/415, 2·4%, difference 0.8%, 95% CI −1.1 to 2.7%, p=0·47). RTOG acute toxicity is shown over time for GI (**Figure 2, Panel A**) and GU toxicity (**Figure 2, Panel B**). Graphical representation of the four different durations of treatment separately (SBRT 1 week, SBRT 2 weeks, CFMHRT 4 weeks and CFMHRT 7·8 weeks) is shown in **Appendix (p17)**. The RTOG baseline, worst, worst (exceeding baseline) and week-12 post-RT toxicities are summarised in tabular form for GI and GU (**Appendix p15-16**).

A summary table of all common and serious CTCAE adverse events is in the **Appendix (pp18-19)**. A total of 17 SAEs were reported (5 CFMHRT; 12 SBRT) up to 12 weeks post-radiotherapy, of which 15 (5 CFMHRT, 10 SBRT) were related to treatment (**Appendix p20**). CTCAE acute toxicity over time is demonstrated for composite GI (**Figure 3, Panel A**) and GU (**Figure 3, Panel B**) toxicity. Graphical representation of the four different durations of treatment separately (SBRT 1 week, SBRT 2 weeks, CFMHRT 4 weeks and CFMHRT 7·8 weeks) is shown in the **Appendix (p21)**. Data for composite GI and GU, at baseline, worst, worst (exceeding baseline), and week 12 post RT are summarised in **Appendix (pp22-23)**, along with results of hypothesis testing performed. SBRT was statistically significantly worse for two of the CTCAE secondary endpoints analysed: CTCAE worst G2+ GI toxicity (36/430, 8·4% vs 65/415, 15·7%; difference 7.3%, 95% CI 2.9 to 11.7%, **p=0·0011**), corroborated by CTCAE worst G2+ GI toxicity exceeding baseline (34/427, 8·0% vs 63/413, 15·3%; difference 7.3%, 95% CI 3.0 to 11.6%, **p=0·00095**) (**Appendix p22**). Regarding most contributory individual endpoints, diarrhoea G2 and worst proctitis G2 occurred more frequently in the SBRT arm. There was no significant difference in worst CTCAE G2+ GI toxicity by week-12. No other significant differences in CTCAE GI secondary endpoints were seen comparing CFMHRT and SBRT (**Appendix p22**), including worst CTCAE GI G3+ toxicity (3/430, 0·7% vs 3/415, 0·7%). No significant differences in CTCAE GU secondary endpoints were seen comparing CFMHRT and SBRT (**Appendix p23**), including worst CTCAE GU G3+ toxicity (3/430, 0·7% vs 7/415, 1·7%). Further tables broken down into individual CTCAE toxicity items, separately for GI and GU, show: baseline CTCAE toxicity, worst acute CTCAE toxicity, worst (exceeding baseline) acute CTCAE toxicity, and week 12 CTCAE (**Appendix pp24-39**).

EPIC-26 average changes in subdomain scores over time appear similar, both for change from baseline (**Figure 4**) and absolute scores. (**Appendix p40**)**.** Comparison, over each of the 5 EPIC-26 subdomains and overall urinary bother, for scores at baseline, worst, worst minus baseline and week 12 post RT showed no statistically significant differences between arms (**Appendix p41**). No statistically significant difference, between arms, in the proportion of patients experiencing a clinically significant reduction from baseline occurred for any EPIC-26 subdomain score area: neither assessed at any time (**Appendix p42**), nor at week-12 only (**Appendix p43**).

IPSS sub-scores, total score and QoL over time appear similar between arms, both for change from baseline (**Appendix p44**) and absolute scores (**Appendix p45**). No statistically significant differences, between treatment arms, were seen for median scores of: worst IPSS total, week-12 IPSS total, worst IPSS QoL, or week-12 IPSS QoL (**Appendix p46**). IPSS severity categories (none, mild, moderate, severe) over time appear similar between treatment arms (**Appendix p47**), with no statistically significant differences in IPSS total score categories at baseline, worst and week-12 post RT (**Appendix p48)**.

For IIEF-5, no statistically significant differences were seen between CFMHRT and SBRT at baseline, nor week-12 post-radiotherapy (**Appendix p49**). Vaizey score changes appear similar between treatment arms for both change from baseline and absolute scores (**Appendix pp50-51**)**.** No statistically significant differences between treatment arms were seen for Vaizey scores at baseline, worst, worst change from baseline, and week-12 post-RT (**Appendix p52**).

For SBRT patients, RTOG GI G2+ worst (without reference to baseline) toxicity for non-CK (27/245, 11·0%) vs CK (16/170, 9·4%) delivery was not statistically different (difference −1.6%, 95% CI −7.5 to 4.3%, p=0.597); consistent with appearances over time in **Appendix (p53)**. For SBRT patients, RTOG G2+ worst GU (without reference to baseline) for non-CK (75/245, 30·6%) vs CK (21/170, 12·4%) delivery was significantly less (difference −18.3%, 95% CI −10.7 to −25.9%, p<0·001); consistent with

appearances over time in **Appendix (p54)**. Given the non-randomised nature of comparing non-CK vs CK, the CFMHRT toxicity in non-CK-centres vs CK-centres was examined. For CFMHRT patients, RTOG G2+ worst GI (without reference to baseline) in non-CK-using-centres (25/252, 9·9%) vs CK-centres (28/180, 15·6%) was not statistically different (difference 5.6%, 95% CI −0.8 to 12.1%, p=0·078); consistent with G2/3 appearances over time in **Appendix (p55)**. For CFMHRT patients, RTOG G2+ worst GU (without reference to baseline) in non-CK-using-centres (73/252, 29·0%) vs CK-using-centres (45/180, 25·0%) was not statistically different (difference −4.0%, 95% CI −12.4 to 4.5%, p=0·361), contrary to possible graphical interpretation over time (**Appendix p56**).

Discussion

This pre-planned analysis of the PACE-B trial acute toxicity, occurring up to 12 weeks from radiotherapy delivery, does not suggest that patients suffer greater acute RTOG toxicity with SBRT than CFMHRT. Of all secondary endpoints examined, only CTCAE worst G2+ GI composite toxicity (both with and without reference to baseline) showed significantly higher proportions experiencing toxicity with SBRT. Differences in CTCAE toxicity were resolved by week 12. Patient reported outcomes were similar. Overall, we do not think these results suggest consistent evidence of higher acute toxicity with SBRT relative to CFMHRT.

It is notable that the control arm (CFMHRT) has apparently lower acute toxicity than the preceding CHHiP trial[11], with control toxicity more comparable to the PROFIT trial[14] (**Appendix p57**). Regarding possible causes of this difference, whereas IGRT was mandatory in both PACE and PROFIT, it was only used in 30% of CHHiP participants. PACE also utilised smaller margins, plus has benefitted from use of highly conformal techniques such as VMAT, compared to CHHiP or PROFIT. CHHiP used ADT for most patients, which was not permitted in PACE or PROFIT, however ADT is not known to alter acute toxicity. We note both PROFIT and CHHiP assessed acute RTOG weekly during radiotherapy, versus effectively two-weekly in PACE. Conceivably the higher RTOG G2+ cumulative percentage seen in CHHiP and PROFIT, versus PACE-B, may result from more frequent sampling due to recall selection bias.

The most comparable phase III RCT is the Scandinavian HYPO-RT-PC trial, which randomised intermediate-high risk prostate cancer patients (1:1) between 78 Gy in 39 fractions over 7·8 weeks and 42·7 Gy in 7 fractions over 2·5 weeks, without ADT[19]. Important differences were HYPO-RT-PC recruited 11% high risk patients 89% intermediate (versus 8% low, 92% intermediate in PACE-B), treated a CTV of prostate only, and mostly (80%) utilised 3-dimensional conformal radiotherapy (3DCRT). IGRT (fiducial markers or guidance catheter) plus planning MRI were used for all patients. The control arms differ between HYPO-RT-PC (all 78 Gy in 39 fractions) and PACE-B (70% receiving 62 Gy in 20 fractions). This difference is important, given the higher acute GI toxicity seen for moderate hypofractionation in the CHHiP trial[11]. HYPO-RT-PC made only a single end-of-treatment toxicity assessment during the acute toxicity window. Their study suggested statistically significantly higher RTOG GU and PRO acute toxicity with ultra-hypofractionation. Comparing RTOG toxicity for PACE against HYPO-RT-PC (estimates approximated from graphs in paper[19]), we see comparable figures, although reported G3-4 toxicity for HYPO-RT-PC is higher than most reports of ultra-hypofractionation (**Appendix p58**): GI grade 2 (10·4% vs 7·5%), GI grade 3-4 (0·2% vs 1%), GU grade 2 (20·7% vs 22%), and GU grade 3-4 (2·4% vs 6%). Although measured on different PRO scales to HYPO-RT-PC, our results do not suggest a difference in PRO acute side effects.

No up to date systematic literature review of acute toxicity in this setting was found. Therefore, prospectively collected acute toxicity data from smaller studies of SBRT in low-intermediate risk prostate cancer was collated (**Appendix p58**). The PACE-B outcomes appear broadly in line with results anticipated from earlier phase work. For example, a multicentre phase II study of 309 men[25] recorded cumulative acute toxicity of CTCAE GI G2+ 12% and CTCAE GU G2+ 26%, similar to 15·7% and 30·8% respectively for SBRT patients in PACE-B.

Strengths of this data relate predominantly to trial design. This is a large phase III RCT, and represents, to our knowledge, the first published phase III acute toxicity data on 5 fraction SBRT compared to standard fractionation. PACE-B reflects real world prostate radiotherapy practice, with multiple centres recruiting in the UK, Canada and Ireland. It incorporates modern planning practice, with no patients receiving 3DCRT. The control arm protocol amendment strengthened the trial by allowing most CFMHRT patients to receive moderate hypofractionation at 62 Gy in 20 fractions – close to the 60 Gy in 20 fractions regimen shown effective in CHHiP[11] and PROFIT[14]. The PACE-B acute toxicity sampling frequency exceeded HYPO-RT-PC (assessed only at end of RT and then 6 months). In combination with high proportions of assessment form returned, this is a major strength given the dynamic nature of acute toxicity.

Limitations arise from the external applicability of the patients recruited into PACE-B. These results cannot necessarily be extrapolated to higher risk patients, nor alternative treatment techniques. Randomised data regarding toxicity after SBRT, with concurrent ADT, and a larger target volume will be acquired by the PACE-C trial. This trial cohort will randomise unfavourable-intermediate and lower high-risk patients to either SBRT or moderately hypofractionated radiotherapy. The lack of treatment blinding is always a limitation for subjective endpoints, such as toxicity. Whilst blinding has been achieved in radiotherapy trials in the past[26,27], this is not feasible for most studies. We also note the greater fiducial usage for IGRT in SBRT patients compared to CFMHRT. Mandatory fiducials would have prevented some centres participating, slowing trial recruitment. Furthermore, the multiple radiotherapy schedule durations meant that some undesirable interpolation was needed to present two arm graphs (RTOG & CTCAE). It also means that the concept of 12 weeks post-radiotherapy refers to a quite different period of time for someone receiving 1 week SBRT (i.e. 13 weeks), versus 7.8 week conventional fractionation (i.e. 19.8 weeks). Future trials should consider a follow-up schedule fixed by radiotherapy start date rather than end date.

SBRT is already standard of care in some global centres, and is an option for men with low and favourable intermediate risk prostate cancer in the NCCN guidelines[28]. HYPO-RT-PC has suggested similar oncological outcomes with ultra-hypofractionation[19]. This was attenuated by increased acute toxicity in the study, notably higher grade 3-4 toxicity than other reports of SBRT. This may potentially be driven by the 3DCRT technique predominantly utilised in the HYPO-RT-PC study. Other earlier phase studies, most of which used the same 36·25 Gy dose as PACE (see **Appendix p58**), suggest good oncological outcomes and low late toxicity with SBRT, but the mature results of PACE-B are required before definite oncological outcome statements may be made.

The method of SBRT delivery, e.g. CyberKnife versus non-CyberKnife, may influence acute toxicity; a prespecified area of interest after the introduction of conventional LINAC SBRT. There are many reasons why there may be a systematic difference between Cyberknife and non-Cyberknife SBRT outcomes, including variations in dosimetry, image-guidance and treatment times (typically 45 minutes for Cyberknife and <5 minutes for conventional LINAC). Our post-hoc analysis of same primary endpoint RTOG metrics show similar G2+ GI toxicity, but less G2+ GU toxicity with

Cyberknife. We have compared CFMHRT toxicity between those centres using CK versus non-CK, finding no statistically significant difference for either RTOG G2+ GI or GU. We caution that this is hypothesis generating and we intend to explore this further in multivariate analysis once DICOM data has been centralised for all patients.

Conclusion

We present, to our knowledge, the first published prospective phase III acute toxicity results randomising patients between five fraction SBRT and either conventional or moderately hypofractionated radiotherapy. The lack of increased toxicity in the SBRT arm is reassuring given the higher acute toxicity suggested in the only previously published phase III ultra-hypofractionation trial (HYPO-RT-PC). This is particularly relevant, given the more abbreviated (5 fraction) investigational radiotherapy protocol utilised in PACE-B. Results on late toxicity and biochemical control from PACE-B will be reported in the next 3-4 years.

Contributions

NvA is the Chief Investigator.
DH, CG, EH, NvA undertook trial design.
DH, CC, S Burnett, CG, EH, NvA developed the protocol.
AT, PO, HvdV, AL, WC, DF, ST, SJ, AM, JS, PC, KK, JF, AC, ID, DH, AD, NvA recruited participants.
AT, PO, HvdV, AL, WC, DF, ST, SJ, AM, JS, PC, KK, JF, AC, ID, DH, S Brown, CC, S Burnett, AD, CG, KM, NvA undertook data collection.
DB, AT, PO, AL, WC, DF, ST, SJ, AM, JS, S Brown, CC, S Burnett, AD, CG, VH, KM, ON, EH, NvA are members of the PACE Trial Management Group.
DB, CG, VH and EH undertook statistical analyses.
DB, CG, VH, EH, NvA provided data interpretation.
ON leads the Physics Quality Assurance Group.
S Brown, CC, S Burnett undertook trial management.
DB, AT, CG, VH, EH, NvA carried out writing.
All authors provided critical academic review of content for the manuscript.
All authors agreed final approval on the submission of the work to the journal.

Declaration of interests

All authors report funding for the PACE trial from Accuray Incorporated, during the conduct of the trial. Further to this:
DB reports other from Cancer Research UK, during the conduct of the study; .
AT reports grants from Accuray, during the conduct of the study; grants and personal fees from Elekta, grants from MSD, personal fees from Janssen, personal fees from Astellas, personal fees from Ferring, outside the submitted work; .personal fees from Astellas, personal fees from Ferring, outside the submitted work; .
PO has nothing to disclose.
HvdV has nothing to disclose.
AL reports grants from Prostate Cure Foundation to his institution during the conduct of the study; In addition, AL has a patent Prostate immobilization device issued; .
WC has nothing to disclose.
DF reports personal fees from Janssen, personal fees from Sanofi, personal fees from Novartis, personal fees from Ipsen, other from Bayer, outside the submitted work; .

ST has nothing to disclose.
SJ reports grants and personal fees from Augmenix, personal fees from Astellas, personal fees from Bayer, personal fees from Janssen , personal fees from Movember, outside the submitted work; .
AM reports other from Bayer, outside the submitted work; .
JS reports non-financial support from Bayer, personal fees from Janssen, personal fees from Astellas, outside the submitted work; .
PC has nothing to disclose.
KK has nothing to disclose.
JF has nothing to disclose.
AC has nothing to disclose.
ID has nothing to disclose.
DH reports grants from Accuray Inc., during the conduct of the study; personal fees from Accuray Inc., outside the submitted work; .
S Brown reports grants from Accuray Incorporated, during the conduct of the study; .
CC has nothing to disclose.
S Burnett has nothing to disclose.
AD has nothing to disclose.
CG reports grants from Accuray Incorporated, from null, during the conduct of the study; .
VH reports grants from Accuray Incorporated, during the conduct of the study; .
KM reports grants from Accuray International, from null, from null, during the conduct of the study; .
ON has nothing to disclose.
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NvA reports grants and personal fees from Accuray, during the conduct of the study; .

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The trial funder, Accuray Incorporated, was also the Sponsor of the trial until February 2014 when sponsorship was transferred to The Royal Marsden NHS Foundation Trust. Accuray had no role in data collection which was managed by a third party prior to February 2014. All data analysis was performed by ICR- CTSU, the funders of the study had no role in data collection, data analysis, data interpretation, or writing of the report.

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Data sharing

The ICR-CTSU supports the wider dissemination of information from the research it conducts, and increased cooperation between investigators. Trial data is collected, managed, stored, shared and archived according to ICR-CTSU Standard Operating Procedures in order to ensure the enduring quality, integrity and utility of the data. Formal requests for data sharing are considered in line with ICR-CTSU procedures with due regard given to funder and sponsor guidelines. Requests are via a standard proforma describing the nature of the proposed research and extent of data requirements. Data recipients are required to enter a formal data sharing agreement which describes the conditions for release and requirements for data transfer, storage, archiving, publication and Intellectual Property. Requests are reviewed by the Trial Management Group (TMG) in terms of scientific merit and ethical considerations including patient consent. Data sharing is undertaken if proposed projects have a sound scientific or patient benefit rationale as agreed by the TMG and approved by the Independent Data Monitoring and Steering Committee as required.

Restrictions relating to patient confidentiality and consent will be limited by aggregating and anonymising identifiable patient data. Additionally, all indirect identifiers that may lead to deductive disclosures will be removed in line with Cancer Research UK Data Sharing Guidelines.

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Figure 1. Per Protocol CONSORT Diagram for Acute Toxicity Sub-study

Diagrammatic representation of patient flow through the trial, with reasons stated where possible for any deviation from expected treatments. Crossovers between treatment arms analysed per-protocol for this acute toxicity substudy. A single death occurred in a patient randomised to receive SBRT, but died of myocardial infarction (unrelated to prostate cancer) before receiving study treatment and is excluded from this per-protocol analysis. Dose-fractionation regimens administered within each arm are shown. Two men received both SBRT and CFMHRT treatments: included is one patient who received two fractions of SBRT (14·5 Gy) then developed grade 3 toxicity (urosepsis) and switched to CFMHRT (further 46 Gy in 23 fractions). Excluded is one patient who received a single incomplete fraction of SBRT (<7·25 Gy, set-up issues) and switched to CFMHRT (further 55 Gy in 20 fractions). Reasons for other non-protocol regimens are in the **Appendix (p8).**

Abbreviations: CFMHRT = Conventionally or Moderately Hypofractionated Radiotherapy; SBRT = Stereotactic Body Radiotherapy; RT = Radiotherapy; ADT = Androgen Deprivation Therapy; n = number of patients.

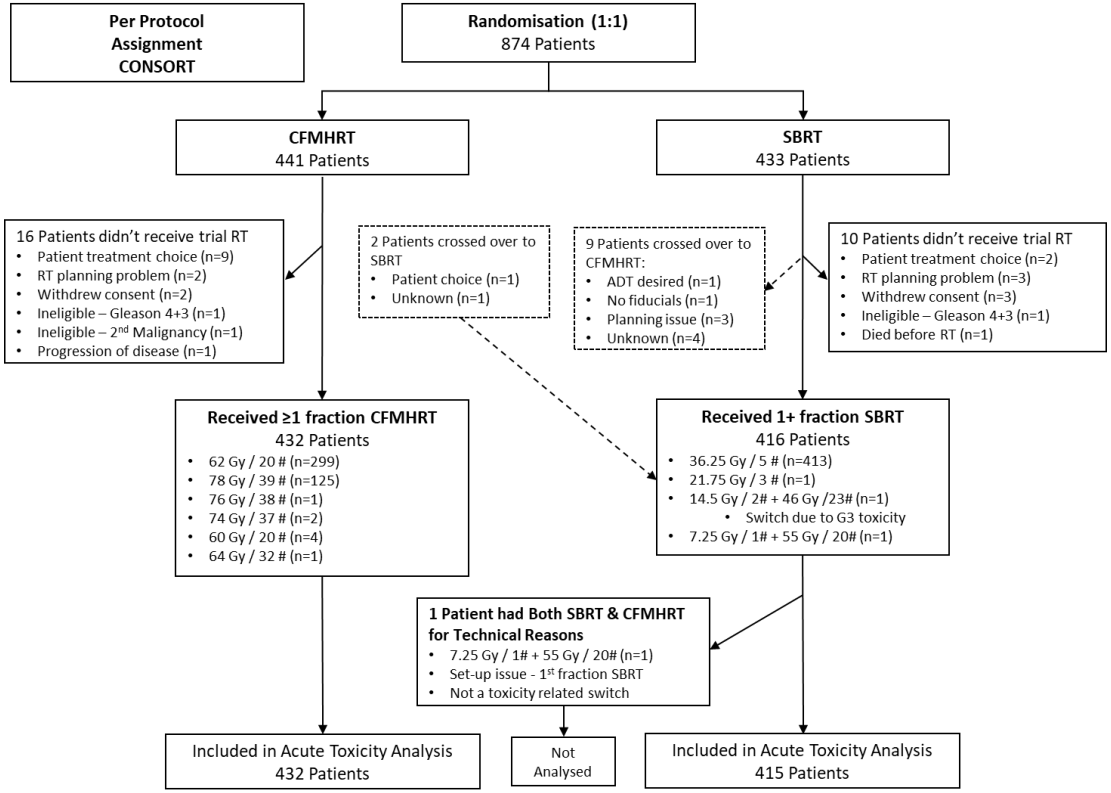


Table 1. Baseline Characteristics by Arm

Baseline Characteristic	Per Protocol Treatment				Total	
	CFMHRT		SBRT			
	No.	%	No.	%	No.	%
Age (Years)						
Mean	69.5	N/A	69.3	N/A	69.4	N/A
Min	48	N/A	45	N/A	45	N/A
Max	86	N/A	84	N/A	86	N/A
Ethnic Origin						
Black	25	5.8%	35	8.4%	60	7.1%
East Asian	3	0.7%	4	1.0%	7	0.8%
Mixed Heritage	2	0.5%	2	0.5%	4	0.5%
Southern Asian	9	2.1%	19	4.6%	28	3.3%
White	386	89.4%	352	84.8%	738	87.1%
Other	7	1.6%	3	0.7%	10	1.2%
Family History of Prostate Cancer						
No	321	74.3%	300	72.3%	621	73.3%
Yes	85	19.7%	85	20.5%	170	20.1%
Unknown	26	6.0%	30	7.2%	56	6.6%
WHO Performance Status						
PS 0	382	88.4%	372	89.6%	754	89.0%
PS 1	48	11.1%	43	10.4%	91	10.7%
PS 2	2	0.5%	0	0.0%	2	0.2%
NCCN Risk Score						
Low	38	8.8%	30	7.2%	68	8.0%
Intermediate	394	91.2%	385	92.8%	779	92.0%
T-Stage						
T1c	78	18.1%	76	18.3%	154	18.2%
T2a	130	30.1%	105	25.3%	235	27.7%
T2b	57	13.2%	81	19.5%	138	16.3%
T2c	167	38.7%	153	36.9%	320	37.8%
Gleason Grade						
3+3	84	19.4%	61	14.7%	145	17.1%
3+4	348	80.6%	354	85.3%	702	82.9%
Pre-treatment PSA						
Mean	8.7	N/A	8.6	N/A	8.7	N/A
Median	8.0	N/A	8.0	N/A	8.0	N/A
Range	0.8 - 20	N/A	0.5 - 20	N/A	0.5 - 20	N/A
PSA Categories						
<10 ng/mL	299	69.2%	283	68.2%	582	68.7%
10 - 20 ng/mL	133	30.8%	132	31.8%	265	31.3%
Pre-treatment Testosterone						
<1.7 nmol/L	0	0.0%	2	0.5%	2	0.2%

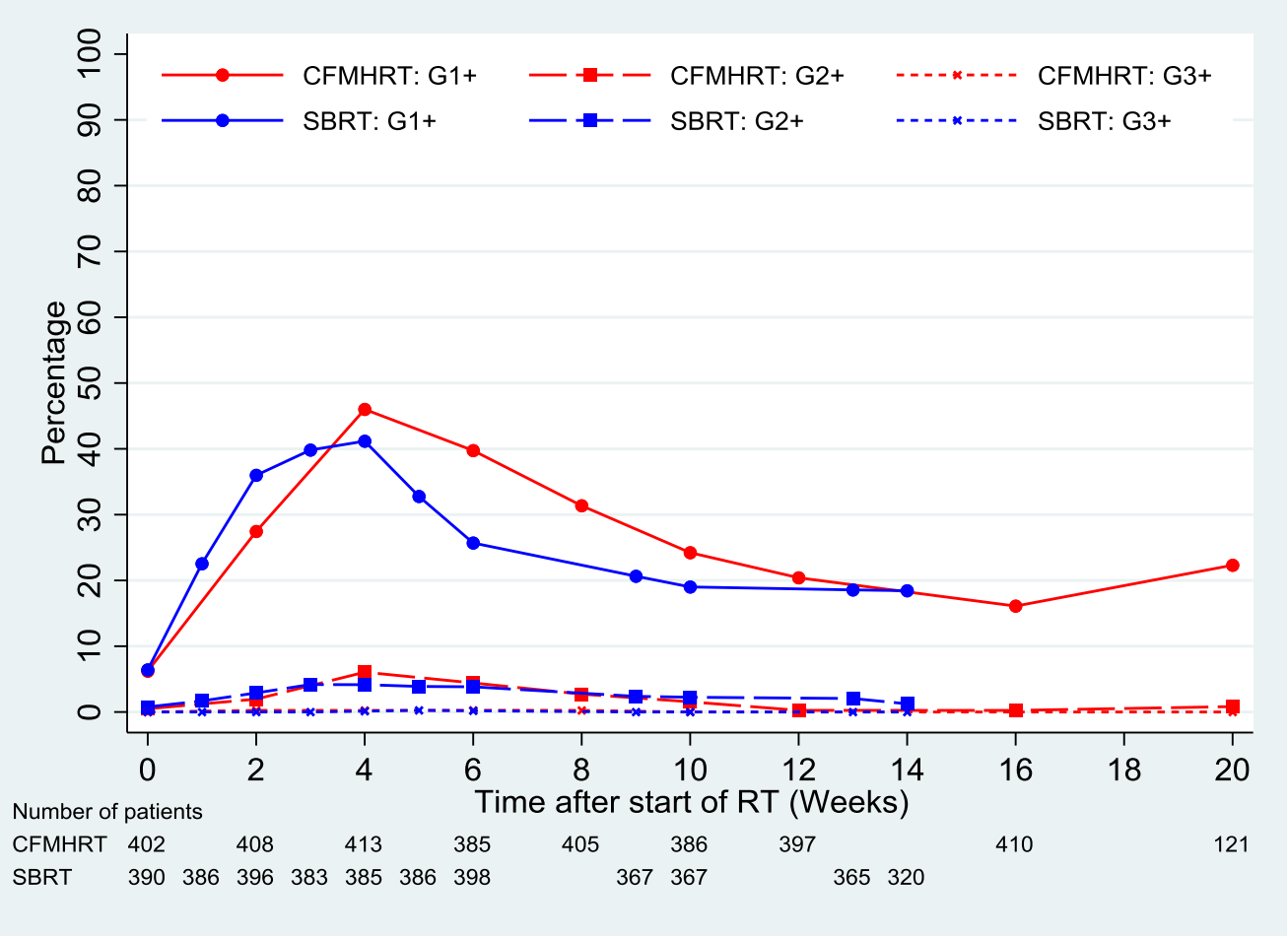
1.7+ nmol/L	391	90.5%	376	90.6%	767	90.6%
Unknown	41	9.5%	37	8.9%	78	9.2%
Active Surveillance Before Trial Enrolment						
Yes	160	37.0%	146	35.2%	306	36.1%
No	258	59.7%	256	61.7%	514	60.7%
Unknown	14	3.2%	13	3.1%	27	3.2%
Prostate Volume						
<40 mL	153	35.4%	160	38.6%	313	37.0%
40 - <80 mL	200	46.3%	170	41.0%	370	43.7%
80+ mL	16	3.7%	21	5.1%	37	4.4%
Unknown	63	14.6%	64	15.4%	127	15.0%
Alpha Blockers at Randomisation						
Yes	68	15.7%	67	16.1%	135	15.9%
No	361	83.6%	344	82.9%	705	83.2%
Unknown	3	0.7%	4	1.0%	7	0.8%
Aspirin at Randomisation						
Yes	74	17.1%	63	15.2%	137	16.2%
No	355	82.2%	347	83.6%	702	82.9%
Unknown	3	0.7%	5	1.2%	8	0.9%
Statin at Randomisation						
Yes	153	35.4%	126	30.4%	279	32.9%
No	275	63.7%	283	68.2%	558	65.9%
Unknown	4	0.9%	6	1.4%	10	1.2%
Anticholinergic for Bladder Symptoms at Randomisation						
Yes	16	3.7%	10	2.4%	26	3.1%
No	414	95.8%	400	96.4%	814	96.1%
Unknown	2	0.5%	5	1.2%	7	0.8%
5-Alpha Reductase Inhibitor at Randomisation						
Yes	9	2.1%	10	2.4%	19	2.2%
No	416	96.3%	387	93.3%	803	94.8%
Unknown	7	1.6%	18	4.3%	25	3.0%
Phosphodiesterase-5 Inhibitor at Randomisation						
Yes	12	2.8%	6	1.4%	18	2.1%
No	412	95.4%	392	94.5%	804	94.9%
Unknown	8	1.9%	17	4.1%	25	3.0%
Total	**432**	**100.0%**	**415**	**100.0%**	**847**	**100.0%**

Table 2. RTOG Adverse Events Table. **Worst Acute RTOG Toxicity by Organ System, Severity and Per Protocol Treatment Received**				
	Per Protocol Treatment			
	CFMHRT		**SBRT**	
Gastrointestinal	**n**	**Percentage**	**n**	**Percentage**
Grade 0	115	26.6%	153	36.9%
Grade 1	264	61.1%	219	52.8%
Grade 2	49	11.3%	42	10.1%
Grade 3	4	0.9%	1	0.2%
Grade 4	0	0.0%	0	0.0%
Grade 5 (Death)	0	0.0%	0	0.0%
Genitourinary				
Grade 0	60	13.9%	83	20.0%
Grade 1	254	58.8%	236	56.9%
Grade 2	111	25.7%	86	20.7%
Grade 3	6	1.4%	8	1.9%
Grade 4	1	0.2%	2	0.5%
Grade 5 (Death)	0	0.0%	0	0.0%
Total	**432**	**100%**	**415**	**100%**

Figure 2. Acute RTOG Toxicity for GI and GU Systems.

Acute RTOG Toxicity, by radiotherapy received, shown separately for gastrointestinal (**Panel A**) and genitourinary (**Panel B**) toxicities. Because each arm allowed two different treatment durations (CFMHRT: 78 Gy / 39 fractions and 62 Gy / 20 fractions; SBRT: 36.25 Gy / 5 fractions over 1 or 2 weeks) it was necessary to interpolate data where assessments did not overlap, described in **Appendix (p6)**. Raw data is presented in **Appendix (p17)**, with all four schedules presented separately. Numbers at risk for each arm are asynchronous because they are shown only at data collection timepoints (which are non-simultaneous relative to the start of radiotherapy. Week 0 is the baseline toxicity score taken before start of radiotherapy. Abbreviations: RTOG = Radiation Therapy Oncology Group; RT = Radiotherapy; CFMHRT = Conventionally or Moderately Hypofractionated Radiotherapy; SBRT = Stereotactic Body Radiotherapy, GX+ = Grade X or more.

Panel A. RTOG Gastrointestinal Toxicity



Panel B: RTOG Genitourinary Toxicity.

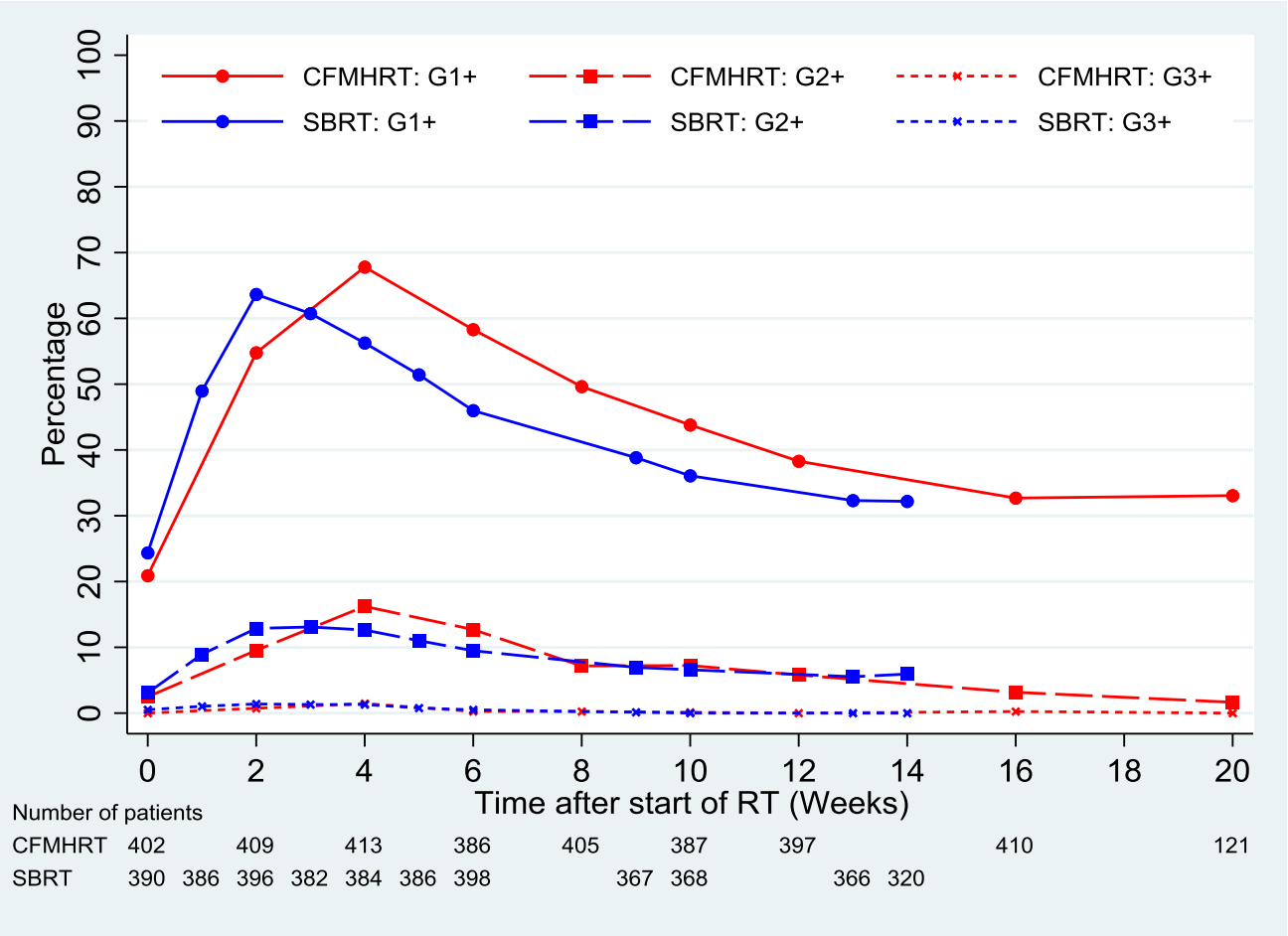
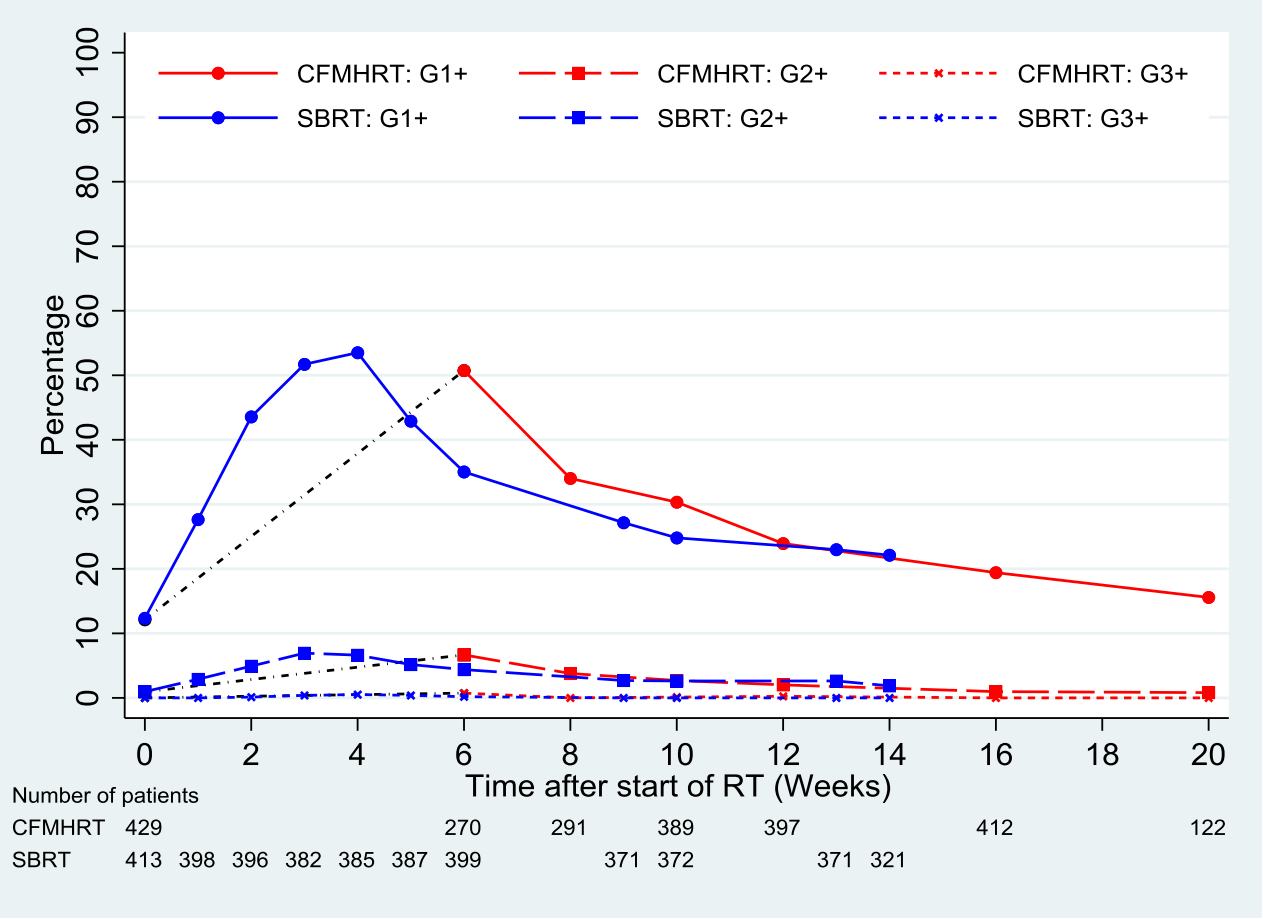


Figure 3. Acute CTCAE Toxicity for GI and GU Systems

Acute CTCAE Toxicity, by treatment arm, shown separately for gastrointestinal (**Panel A**) and genitourinary (**Panel B**) toxicities. CTCAE gastrointestinal toxicity, by radiotherapy received. Specific CTCAE items in the GI composite are: anal pain, colitis, constipation, diarrhoea, diverticulitis, faecal incontinence, fistula, gastrointestinal pain, haemorrhoids, GI haemorrhage, proctitis, rectal pain, GI unspecified, rectal prolapse. Specific CTCAE items in GU composite are: bladder spasm, cystitis, haematuria, prostatic obstruction, urinary frequency, urinary incontinence, urinary retention, urinary urgency, urethral stricture. Because each arm allowed two different treatment durations (CFMHRT: 78 Gy / 39 fractions and 62 Gy / 20 fractions; SBRT: 36.25 Gy / 5 fractions over 1 or 2 weeks) it was necessary to interpolate data, as described in **Appendix (p6)**. Raw data is presented in **Appendix (p21)**, with all four schedules presented separately. Numbers at risk for each arm are asynchronous because they are shown only at data collection timepoints (which are non-simultaneous relative to the start of radiotherapy. The initial points for CFMHRT are connected by grey dash-dot lines to emphasise that there were no CTCAE assessments during radiotherapy delivery. Week 0 is the baseline toxicity score taken before start of radiotherapy.

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; GI = Gastrointestinal; GU = Genitourinary; RT = Radiotherapy; GX+ = Grade X or more; CFMHRT = Conventionally or Moderately Hypofractionated Radiotherapy; SBRT = Stereotactic Body Radiotherapy.

Panel A. CTCAE gastrointestinal toxicity



Panel B. CTCAE genitourinary toxicity

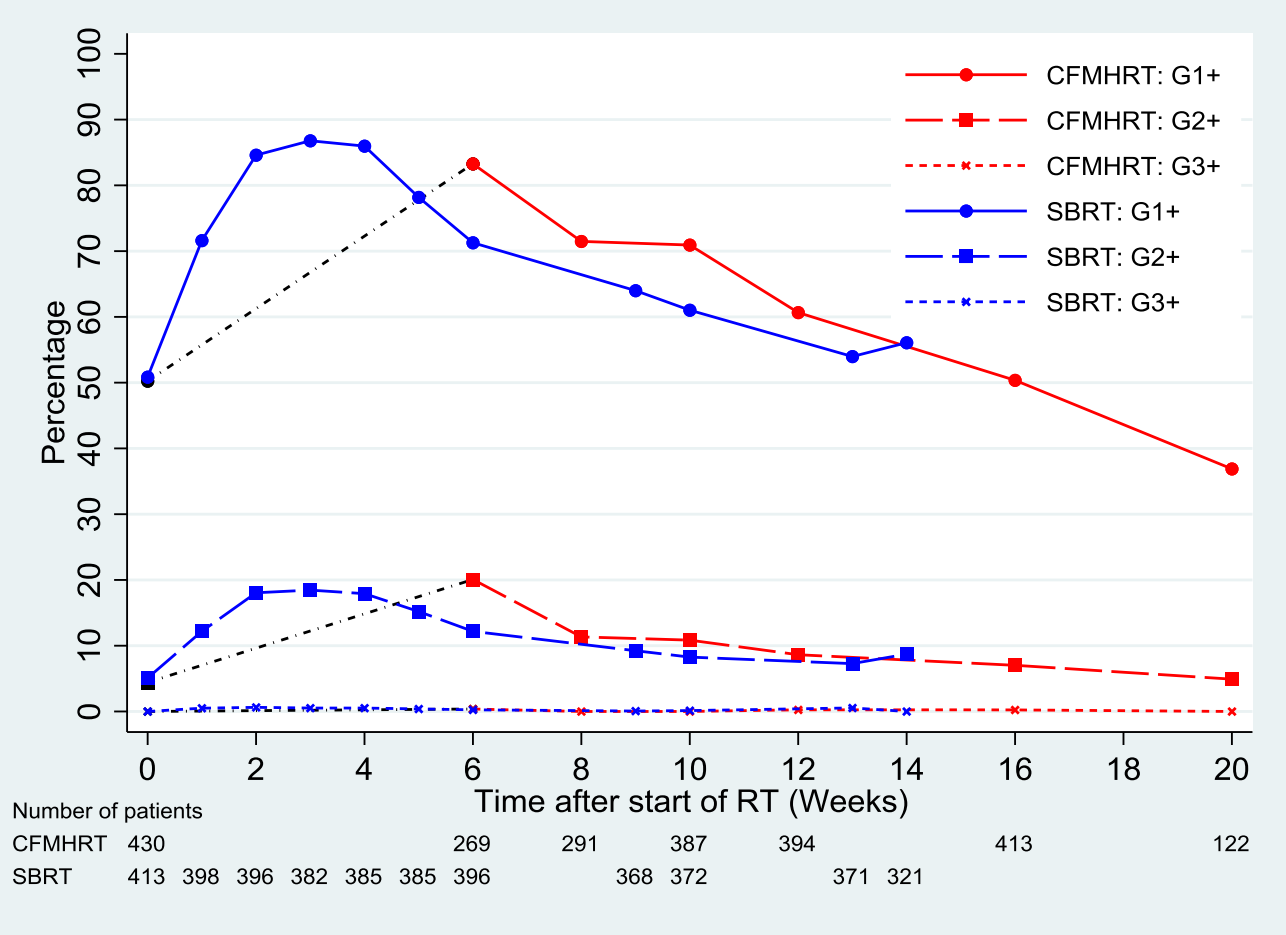


Figure 4. Changes from Baseline in EPIC-26 Subdomains

EPIC-26 subdomain score changes from baseline in the acute toxicity setting, separated by delivered radiotherapy technique. The urinary bother question is graphed separately, as it does not form part of the urinary incontinence or obstructive subdomain scores. Error bars show 95% confidence interval for estimates of mean subdomain scores. Note that the time period between baseline scoring and week 4 post radiotherapy follow-up is variable, since the total time of radiotherapy delivery varied (SBRT in 1 or 2 weeks; CFMHRT in 4 or 7.8 weeks). Week 0 is the baseline toxicity score taken before start of radiotherapy.

Abbreviations: EPIC-26 = Expanded Prostate Cancer Index Composite (26 question); CFMHRT = Conventionally or Moderately Hypofractionated Radiotherapy; SBRT = Stereotactic Body Radiotherapy; BL = Baseline Pre-Radiotherapy; RT = Radiotherapy.