Intensity-modulated radiotherapy versus stereotactic body radiotherapy for prostate cancer (PACE-B): 2-year toxicity results from an open-label, randomised, phase 3, non-inferiority trial

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Summary

Background Localised prostate cancer is commonly treated with external beam radiotherapy and moderate hypofractionation is non-inferior to longer schedules. Stereotactic body radiotherapy (SBRT) allows shorter treatment courses without impacting acute toxicity. We report 2-year toxicity findings from PACE-B, a randomised trial of conventionally fractionated or moderately hypofractionated radiotherapy versus SBRT.

Methods PACE is an open-label, multicohort, randomised, controlled, phase 3 trial conducted at 35 hospitals in the UK, Ireland, and Canada. In PACE-B, men aged 18 years and older with a WHO performance status 0–2 and low-risk or intermediate-risk histologically-confirmed prostate adenocarcinoma (Gleason 4+3 excluded) were randomly allocated (1:1) by computerised central randomisation with permuted blocks (size four and six), stratified by centre and risk group to control radiotherapy (CRT; 78 Gy in 39 fractions over 7·8 weeks or, following protocol amendment on March 24, 2016, 62 Gy in 20 fractions over 4 weeks) or SBRT (36·25 Gy in five fractions over 1–2 weeks). Androgen deprivation was not permitted. Co-primary outcomes for this toxicity analysis were Radiation Therapy Oncology Group (RTOG) grade 2 or worse gastrointestinal and genitourinary toxicity at 24 months after radiotherapy. Analysis was by treatment received and included all patients with at least one fraction of study treatment assessed for late toxicity. Recruitment is complete. Follow-up for oncological outcomes continues. The trial is registered with ClinicalTrials.gov, NCT01584258.

Findings We enrolled and randomly assigned 874 men between Aug 7, 2012, and Jan 4, 2018 (441 to CRT and 433 to SBRT). In this analysis, 430 patients were analysed in the CRT group and 414 in the SBRT group; a total of 844 (97%) of 874 randomly assigned patients. At 24 months, RTOG grade 2 or worse genitourinary toxicity was seen in eight (2%) of 381 participants assigned to CRT and 13 (3%) of 384 participants assigned to SBRT (absolute difference 1·3% [95% CI –1·3 to 4·0]; p=0·39); RTOG grade 2 or worse gastrointestinal toxicity was seen in 11 (3%) of 382 participants in the CRT group versus six (2%) of 384 participants in the SBRT group (absolute difference –1·3% [95% CI –3·9 to 1·1]; p=0·32). No serious adverse events (defined as RTOG grade 4 or worse) or treatment-related deaths were reported within the analysis timeframe.

Interpretation In the PACE-B trial, 2-year RTOG toxicity rates were similar for five fraction SBRT and conventional schedules of radiotherapy. Prostate SBRT was found to be safe and associated with low rates of side-effects. Biochemical outcomes are awaited.

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Introduction

Prostate cancer affects nearly 1·5 million men annually worldwide.[1] The majority of patients with prostate cancer are diagnosed with potentially curable disease and a range of treatments are available (including external beam radiotherapy, surgery, and brachytherapy). Radiotherapy for early disease is associated with high proportions of long-term cancer cure, with a previous study showing that more than 90% of men were relapse-free at 5 years after treatment.[2] Radiotherapy schedules have been shortened over the past decade following the publication of multiple phase 3 trials showing non-inferiority of moderate hypofractionation to longer schedules.[2–4] Although some data suggest worse temporary bowel toxicity with moderate hypofractionation compared with longer radiotherapy schedules, all these trials reported low rates of long-term side-effects, which were similar between groups. Data examining patient-reported quality of life (QOL) suggest no difference in patient-reported outcomes at 5 years between different schedules, and reports of moderate or

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Research in context

Evidence before this study

Before this study, data supporting stereotactic body radiotherapy (SBRT) was only available from small cohort and phase 2 studies, and standard prostate radiotherapy was delivered at 2 Gy per fraction over 7·5–8·0 weeks worldwide. In 2016, due to level one evidence, standard radiotherapy schedule was shortened to 4 weeks worldwide. Subsequent data were found by searching PubMed using the terms ["SBRT" OR "Stereotactic Body Radiotherapy"] AND ["Prostate"[AND ["trial" OR "study"], from inception to Nov 4, 2021, limited to articles published in English. We also searched the references of these papers, with the search also supplemented by the authors' knowledge of the field. Nine studies of more than 90 men, reporting late (>3 months after treatment) toxicity outcomes from SBRT to the prostate in phase 2 or 3 trials of de-novo prostate SBRT, were identified. The search results included a single randomised phase 3 study (HYPO-RT-PC trial) and one meta-analysis of multiple phase 2 studies. The HYPO-RT-PC trial showed that a dose of 42·7 Gy, delivered every other day over 2·5 weeks (6·1 Gy per fraction), was non-inferior in terms of failure-free survival compared with conventional fractionation of 78 Gy over 8 weeks (2 Gy per fraction) with similar proportions of late toxicity in each group. Grade 2 and worse toxicity estimates for ultra-hypofractionation ranged from 1–16% for gastrointestinal toxicity and 3–45% for genitourinary toxicity.

Added value of this study

To our knowledge, this is the first published phase 3 randomised evidence of late toxicity after ultra-hypofractionated SBRT, delivered over five fractions, compared with standard fractionation schedules. Overall, this study shows similar gastrointestinal toxicity with ultra-hypofractionation compared with standard fractionation. Genitourinary toxicity rates were similar between groups using Radiation Therapy Oncology Group scales and patient-reported scales, but we found more grade 2 or worse genitourinary toxicity rates using Common Terminology Criteria for Adverse Events after SBRT than after control radiotherapy (CRT). Proportions of patients experiencing late grade 3 toxicity appear very low, and rates of grade 2 toxicity are similar to, or lower than, previously documented for longer schedules. These findings suggests that, although overall toxicity is low regardless of fractionation, using SBRT techniques could increase the risk of moderate, but not severe, genitourinary side-effects.

Implications of all the available evidence

Ultra-hypofractionated radiotherapy over five fractions appears tolerable, with few serious side-effects. SBRT in the PACE-B trial was well tolerated with low levels of toxicity; biochemical outcomes are awaited. Late toxicity with ultra-hypofractionation to 2 years is low and similar to longer schedules. However, a flare of toxicity is seen at around 1 year after SBRT and overall rates of genitourinary toxicity remain higher at 2 years after SBRT than standard prostate radiotherapy.

worse bowel bother are low for both standard and moderately hypofractionated regimens.[5]

During the past decade, there have been multiple innovations that have improved radiotherapy techniques and outcomes, including intensity-modulated radiotherapy (IMRT), volumetric modulated arc therapy (VMAT), better understanding of dosimetric predictors of treatment-related bother, and image-guided radiotherapy. Over the past decade, the evolution of stereotactic body radiotherapy (SBRT) has harnessed these innovations to test ultra-hypofractionated radiotherapy schedules of just five fractions. The PACE study platform is assessing whether five-fraction SBRT is non-inferior to other standard treatments: PACE-A compares SBRT with surgery, PACE-B compares SBRT with control radiotherapy (CRT; conventionally fractionated or moderately hypofractionated radiotherapy), and PACE-C compares SBRT with CRT in higher risk prostate cancer (defined as intermediate and higher National Comprehensive Cancer Network (NCCN) risk prostate cancer, but only with two out of the three possible high risk features) alongside androgen deprivation therapy (ADT).

The primary outcome of PACE-B is freedom from biochemical or clinical failure for men with early prostate cancer. This trial has already shown no significant difference between five fraction SBRT and CRT in short-term toxicity rates.[6] Here, we report clinician-assessed toxicity and patient-reported outcomes up to 2 years after treatment.

See Online for appendix

Methods

Study design and participants

PACE-B is an open-label, multicentre, parallel-group, randomised, controlled, phase 3 trial conducted at 35 hospitals in the UK, Ireland, and Canada (appendix p 4). The study recruited patients with prostate cancer who were intending to have radical radiotherapy as their primary treatment; the full protocol has been previously published.[6]

Eligible patients were men aged 18 years and older who had WHO performance status 0–2, life expectancy of at least 5 years, and histologically-confirmed prostate adenocarcinoma. A minimum of ten biopsy cores taken up to 18 months before randomisation were required, except for those progressing on active surveillance who now required treatment (eg, by virtue of biochemical or MRI progression), in which case the most recent biopsy, even if taken more than 18 months ago, could be used for eligibility. All patients had NCCN low-risk or intermediate-risk disease. Low-risk patients were those with tumours meeting all of the following criteria: clinical or MRI stage of T1c–T2a (according to the TNM 6th edition), N0, M0/X; a Gleason score of 6 or less; and prostate-specific

antigen (PSA) concentration of less than 10 ng/mL. Intermediate-risk patients had at least one of: clinical stage 2b or T2c; Gleason score 3+4 (Gleason 4+3 was excluded); or PSA concentration of 10–20 ng/mL. Distant staging was not mandated. In defining risk stratification, no PSA adjustment was made for 5α-reductase inhibitor use at randomisation. Patients were excluded if they had had previous pelvic radiotherapy, previous treatment for prostate cancer, or bilateral hip prostheses. Treating physicians had discretion to exclude patients for comorbid conditions making radiotherapy inadvisable or technically challenging, such as inflammatory bowel disease or bilateral hip replacements.

Patients were recruited by their clinical teams and provided written, informed consent before enrolment. The protocol is available online. The trial was approved by the London Chelsea Research Ethics Committee (11/LO/1915) in the UK and the relevant institutional review boards in Ireland and Canada, was sponsored by The Royal Marsden NHS Foundation Trust, and was done in accordance with the principles of Good Clinical Practice.

Randomisation and masking

Patients were randomly assigned (1:1) to either CRT or SBRT. Randomisation was done centrally by the Institute of Cancer Research Clinical Trials and Statistics Unit (ICR-CTSU; London, UK) with allocation by computer-generated random permuted blocks (size four and six) stratified by centre and risk group (low or intermediate). Treatment was not masked.

Procedures

Before radiotherapy, three or more prostatic fiducial markers were recommended (but not mandated) for all participants. 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, which was 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 1 cm of seminal vesicles (intermediate-risk patients). For CRT, CTV to planning target volume (PTV) expansion was 5–9 mm isometric, except posteriorly 3–7 mm. For SBRT, CTV to PTV expansion was 4–5 mm isometric, except posteriorly 3–5 mm. Dose constraints were applied to organs at risk and were amended during the trial.[6] The dose constraints used for the majority of patients (604 [71%] of 847) are shown in appendix p 3).

In the CRT group, PTV dose was 78 Gy in 39 daily fractions over 7·8 weeks (ie, 2 Gy per day) or, following protocol amendment on March 24, 2016, 62 Gy in 20 daily fractions (ie, 3·1 Gy per day) over 4 weeks. This change followed publication of the CHHiP trial results supporting moderate hypofractionation,[2] but with a higher dose (62 Gy *vs* 60 Gy) due to a hypothesised interaction with ADT. After the amendment, centres were required to choose one schedule (either 78 Gy in 39 fractions or 62 Gy in 20 fractions) as their CRT treatment for all subsequent patients. The SBRT PTV dose was 36·25 Gy in five fractions to the PTV and 40 Gy to the CTV over 1–2 weeks (ie, daily or alternate days, at centre discretion). CRT was prescribed such that dose to 98% of the PTV (D98%) was at least 74·1 Gy for those receiving 78 Gy in 39 fractions and PTV D98% was at least 58·9 Gy for those receiving 62 Gy in 20 fractions. For SBRT, the dose to 95% of the PTV (D95%) was at least 36·25 Gy with a secondary objective of D95% CTV of at least 40 Gy. Dose heterogeneity was allowed within the SBRT targets such that maximum doses of more than 45 Gy were permitted.

Treatment was mandated to commence within 12 weeks of randomisation, and commencement within 8 weeks was strongly recommended. Daily image-guided radiotherapy of the prostate (fiducials or cone beam CT) was mandatory. No rectal spacing devices were used. For SBRT, continuous intrafractional motion monitoring was permitted, or a re-imaging was required if fraction delivery exceeded 3 min. A radiotherapy quality assurance programme was undertaken for each centre to ensure consistency with trial protocol. Patients had no radiological assessments. Patients had a prostate specific antigen (PSA) blood test taken at 12 weeks, 6 months, 9 months, and 12 months after treatment and annually thereafter.

Participants in both groups were assessed at baseline, during the acute toxicity period, and then once every 3 months for the first 2 years and once every 6 months to year 5. Late toxicity (from 6 months) was clinician-reported using the Radiation Therapy Oncology Group (RTOG) genitourinary and gastrointestinal domain scales[7] and Common Terminology Criteria for Adverse Events (CTCAE).[8] Paper questionnaires collected patient-reported outcomes at months 6, 9, 12, and 24, and annually thereafter, using the Expanded Prostate Cancer Index Composite Short Form (EPIC-26),[9] the Vaizey Faecal Incontinence Score,[10] International Prostate Symptom Score (IPSS),[11] and the International Index of Erectile Function 5-question (IIEF-5)[12] score (omitted at month 9). EPIC-26 scores were rescaled to a 0–100-point scale, with higher scores representing better QOL.[13] Minimally clinically important difference in EPIC-26 subdomain scores were: urinary incontinence (8 points), urinary irritative or obstructive (6 points), bowel (5 points), sexual (11 points), and hormonal (5 points).[14] IPSS severity categories were assessed as none (0 points), mild (1–7 points), moderate (8–19 points), and severe (20–35 points).[14] The IIEF-5 total score was calculated and ranged from 1 (most severe erectile dysfunction) to 25 (no erectile dysfunction). The Vaizey total score was calculated and ranged from 0 (no problems with incontinence) to 24 (very severe problems with incontinence).

For the **protocol** see https://go.icr.ac.uk/paceprotocol

Outcomes

The trial's primary endpoint is freedom from biochemical or clinical failure at 5 years, the data for which are not yet mature. For this prespecified late-toxicity analysis, co-primary endpoints were the proportions of patients with RTOG grade 2 or worse genitourinary toxicity and the proportions of patients with RTOG grade 2 or worse gastrointestinal toxicity at 24 months after treatment.

Secondary endpoints were the cumulative incidence of RTOG grade 2 or worse genitourinary and gastrointestinal toxicity up to 24 months; CTCAE grade 2 or worse genitourinary and gastrointestinal toxicity rates at, and cumulative to, 24 months; CTCAE grade 2 or worse erectile dysfunction; and other prespecified CTCAE parameters, including hot flashes, other pain, fatigue, anorexia, weight loss and radiation dermatitis and other CTCAE. Given differential effects on genitourinary and gastrointestinal events, overall rates of any toxicity, another secondary endpoint, are not reported. Secondary endpoints relating to patient-reported outcomes were EPIC-26 composite scores (bowel, urinary, sexual, and hormonal) reported as a score and as the percentage of patients with a minimally clinically important difference in domain-specific QOL. The following were prespecified as other patient-reported outcomes of specific interest: IPSS (total, quality of life, and by category), Vaizey score, and IIEF-5 score.

Recruitment completed to target and follow-up for oncological outcomes continues, and will be published at a later date.

Statistical analysis

The trial is powered for non-inferiority of time to biochemical or clinical failure with a sample size of 858 patients to exclude a hazard ratio (HR) of 1·45, to rule out a 6% difference at 5 years between treatment groups. This sample size was also specified as sufficient (80% power, 5% significance) to exclude a 16% rate of RTOG grade 2 or worse genitourinary or gastrointestinal toxicity with SBRT, assuming this rate was expected to be 10% with CRT, at 2 years after radiotherapy. Analyses are by treatment received, with participants included if they received one or more fractions of CRT or SBRT and were assessed for late toxicity. A statistical analysis plan was written before the analysis. All analyses presented were prespecified unless stated otherwise.

The frequency and percentage of each toxicity grade at each timepoint assessed for genitourinary toxicity, gastrointestinal toxicity, and sexual function are presented graphically in stacked bar charts. The incidence of individual component adverse events are examined. The proportion of patients experiencing grade 2 or worse side-effects are compared between groups using χ^2 tests or Fisher's exact test, as appropriate. We calculated 95% CIs for the difference in proportions at 24 months using the Wilson Score method, including a continuity correction. This method was not prespecified, but was adopted post hoc to allow for low event rates observed; in accordance, a continuity corrected χ^2 test is presented. For specific timepoint analyses, data were attributed to the closest protocol defined timepoint (eg, assessments between 22·5 and 27·0 months were assigned to the 2-year timepoint). To assess the effect of missing data for the primary endpoints (RTOG grade 2 or worse gastrointestinal and genitourinary toxicity at 24 months), a sensitivity analysis was done using last value carried forward. For completeness, this was also done for the corresponding CTCAE analysis; this analysis was not prespecified. Rates of grade 1 or worse and grade 3 or worse toxicity were presented for completeness. For analysis of cumulative incidence of late toxicity, time-to-event methods were used. Time to first incidence of late grade 1 or worse, grade 2 or worse, and grade 3 or worse genitourinary and gastrointestinal toxicity was measured from the completion of radiotherapy, with grade 2 or worse events of primary interest. Patients who were event-free at the time of analysis were censored at their last available toxicity assessment. Cumulative incidence graphs are presented with HRs (including 95% CIs) and log-rank tests used to compare treatment groups. Point estimates are reported using the upper limit of the assessment window (eg, at 27 months for the 2-year estimate). A significance level of 0·025 was used for each of the co-primary endpoints. To reduce the effect of multiple comparisons, a p value less than 0·01 was considered significant for secondary endpoints.

Patient-reported outcome scores were calculated in accordance with the relevant manuals. Descriptive statistics are presented for continuous variables at baseline and 24 months; frequency and percentages are used for categorical data. Statistical comparisons were made at 24 months using Mann-Whitney test for continuous scores, χ^2 trend test for ordinal, and χ^2 test for binary variables. Overall bowel and urinary bother EPIC-26 questions were analysed post-hoc to facilitate comparisons to other trials.

Comparison of participants treated by SBRT using robotic non-coplanar radiotherapy (CyberKnife) with those treated by SBRT using conventional linear accelerator (linac) was prospectively included in the protocol, after amendment 6 (Aug 5, 2014) permitted standard linac SBRT delivery. As analysis of acute toxicity data had suggested a significant difference by delivery platform,[6] we planned this subgroup analysis in the late toxicity analysis, to include comparisons of CTCAE, RTOG, and patient-reported outcomes with significance tests done for comparisons at 2 years. As this is a non-randomised comparison, differences in baseline characteristics were compared using *t* tests for continuous scores, χ^2 trend test for ordinal, and χ^2 test for binary variables. Post-hoc analysis of the association of toxicity with fiducial use is reported for hypothesis generation.

Analyses are based on a snapshot of data taken on July 2, 2021, and were done using Stata version 17, with

the exception of 95% CIs for the difference in proportions that were computed using SAS (version 9.4). The Independent Data Monitoring Committee gave approval for release of these results before the release of the trial's primary efficacy endpoint results. The study is registered with ClinicalTrials.gov, NCT01584258.

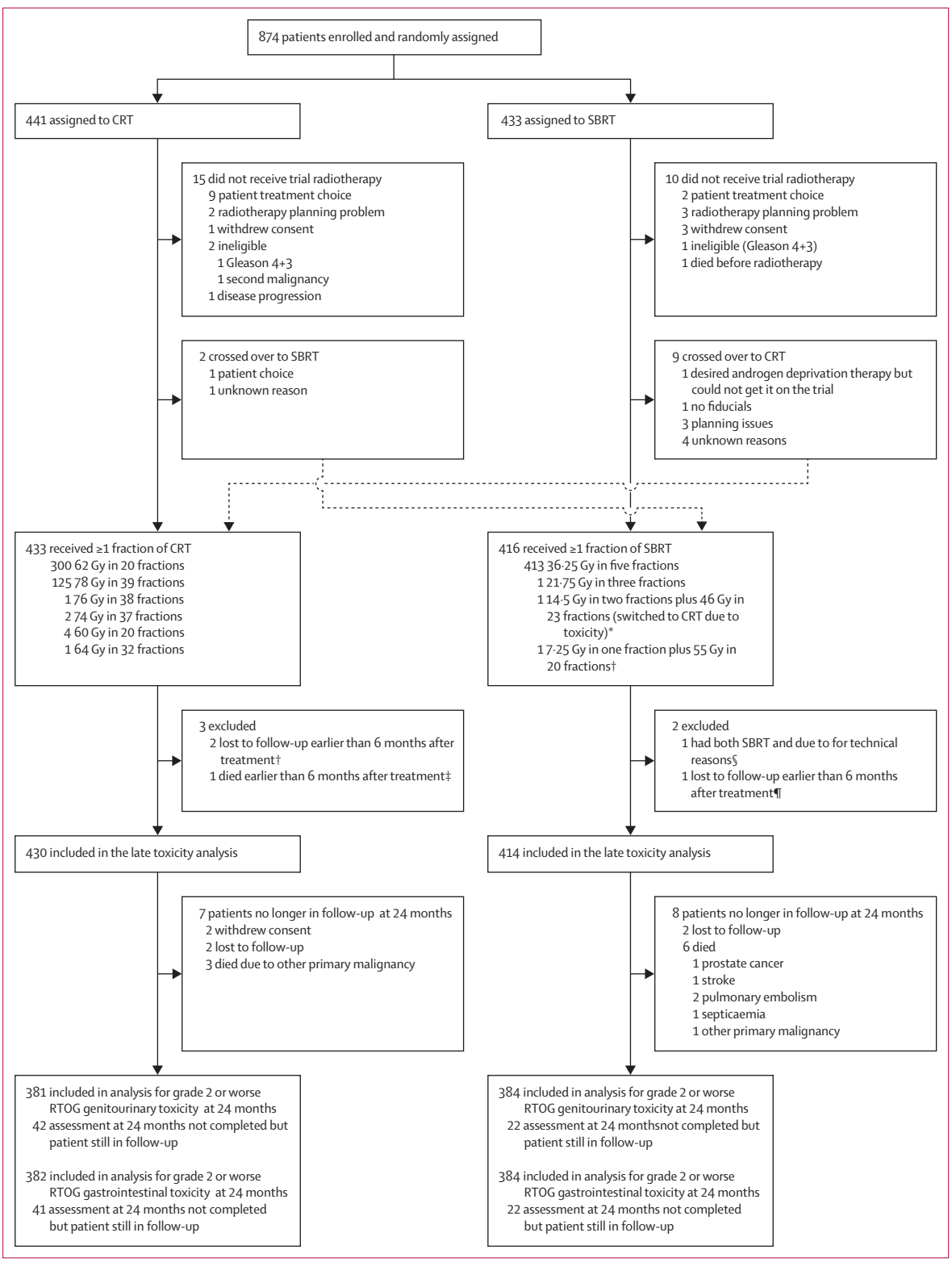


Figure 1: **Trial profile**
Crossovers between treatment groups analysed as treatment received for this late toxicity analysis. RTOG=Radiation Therapy Oncology Group. SBRT=stereotactic body radiotherapy. CRT=control radiotherapy. *Included patient who received two fractions of SBRT (14·5 Gy) then developed grade 3 toxicity (urosepsis) and switched to CRT (further 46 Gy in 23 fractions). †One patient received 62 Gy in 20 fractions and the other received 74 Gy in 37 fractions. ‡Patient received 62 Gy in 20 fractions. §Patient received a single incomplete fraction of SBRT (<7·25 Gy) due to set-up issues and switched to CRT (further 55 Gy in 20 fractions). ¶Patient received 36·25 Gy in five fractions.

	CRT (n=430)	SBRT (n=414)
Age at randomisation (years)	69·7 (65·6–74·0)	69·6 (65·4–73·8)
Race		
Black	24 (6%)	35 (8%)
East Asian	3 (1%)	4 (1%)
Mixed heritage	2 (<1%)	2 (<1%)
South Asian	9 (2%)	19 (5%)
White	386 (90%)	351 (85%)
Other	6 (1%)	3 (1%)
T-stage		
T1c	78 (18%)	77 (19%)
T2a	127 (30%)	103 (25%)
T2b	58 (13%)	80 (19%)
T2c	167 (39%)	151 (36%)
NCCN risk group		
Low	43 (10%)	35 (8%)
Intermediate	387 (90%)	379 (92%)
Gleason score		
3+3	84 (20%)	61 (15%)
3+4	346 (80%)	353 (85%)
Prostate volume		
<40 mL	156 (36%)	165 (40%)
40–79 mL	204 (47%)	174 (42%)
≥80 mL	16 (4%)	21 (5%)
Unknown	54 (13%)	54 (13%)
PSA (ng/mL)*	8·0 (6·3–10·7)	8·0 (5·5–11·0)

Data are n (%) or median (IQR). CRT=control radiotherapy. SBRT=stereotactic body radiotherapy. NCCN=National Comprehensive Cancer Network. PSA=prostate specific antigen. *Four (21%) of the 19 patients on 5α-reductase inhibitors at baseline had a PSA value of 10–20 ng/mL.

Table 1: **Baseline demographics and clinical characteristics**

Role of the funding source

The trial funder, Accuray, 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 before February, 2014. Accuray had no role in data collection, data analysis, data interpretation, or writing of the report.

Results

Between Aug 7, 2012, and Jan 4, 2018, 874 men were enrolled and randomly assigned to CRT (n=441) or SBRT (n=433; figure 1; table 1). Patients who received no fraction of a protocol treatment or who were not evaluable were excluded from all analyses. Additionally, one patient that received both SBRT and CRT was excluded from the analysis. In this analysis, 430 patients were analysed in the CRT group and 414 in the SBRT group; a total of 844 (97%) of 874 randomly assigned patients. Data completeness was good; 24-month clinician-reported toxicity results of patients in the analysis population were available for 766 (91%) of 844 patients using RTOG and 769 (91%) of 844 patients using CTCAE (appendix p 5). Nine patients died between radiotherapy and the 24-month follow-up timepoint; three in the CRT group and six in the SBRT group. Seven (2%) of 433 patients in the CRT group and three (1%) of 413 patients in the SBRT group received less than the protocol dose. No treatment-related deaths were reported.

Concomitant medication use at baseline was similar between groups (appendix p 6). 300 (70%) of 430 patients receiving CRT received treatment over 4 weeks and 310 (75%) of 414 patients receiving SBRT received treatment over 2 weeks. More patients treated with SBRT received fiducial markers (303 [73%] 414) than patients treated with CRT (244 [57%] 430). SBRT was delivered by standard linac for 245 (59%) of 414 patients and by CyberKnife for 169 (41%) of 414 patients (appendix p 6). Most patients received protocol-compliant margins, and these have been previously published.[6] The most common margins used for CRT were 7 mm isotropic (in all directions), except for posteriorly in which the margin was 5 mm and for SBRT was 5 mm isotropic and 3 mm posteriorly.

At 2 years, eight (2%; 95% CI 1·0–4·3) of 381 patients in the CRT group had RTOG grade 2 or worse genitourinary toxicity compared with 13 (3%; 1·9–5·9) of 384 patients in the SBRT group (absolute difference 1·3% [95% CI –1·3 to 4·0]; p=0·39; table 2). There was evidence of increased grade 2 or worse genitourinary toxicity rates according to the CTCAE criteria at 2 years with SBRT (absolute difference 5·7% [95% CI 1·6–9·8]; p=0·010). Prespecified components of RTOG and CTCAE genitourinary toxicity endpoints for 24 months are presented in the appendix (pp 7–8). Sensitivity analysis results gave similar estimates for absolute differences (RTOG 1·5% [95% CI –1·0 to 4·3]; p=0·27 and CTCAE 4·9% [95% CI 0·6 to 9·2]; p=0·026; appendix pp 9–10). Clinician-assessed toxicity grades at each timepoint showed higher rates of grade 2 or worse RTOG genitourinary toxicity for SBRT than CRT at 12–15 months after treatment (figure 2; appendix p 11) and a similar pattern was observed for CTCAE grade 2 or worse genitourinary toxicity (figure 2; appendix p 12). Incidence of grade 2 or worse genitourinary events varied widely between centres, from 0% to 32% in centres recruiting more than five patients (data not shown).

Cumulative grade 2 or worse genitourinary toxicity rates were higher with SBRT than with CRT, as assessed by both RTOG and CTCAE criteria. At 2 years, cumulative incidence rates of RTOG grade 2 or worse genitourinary toxicity were 10·6% (95% CI 8·0–14·0) for CRT (45 events) and 18·3% (14·9–22·4; 75 events) for SBRT (HR 1·80 [95% CI 1·25–2·61]; log-rank p=0·0015; figure 3A). Corresponding figures for CTCAE grade 2 or worse genitourinary cumulative toxicity were 19·8% (95% CI 16·3–23·9; 84 events) for CRT and 32·3% (28·0–37·0; 132 events) for SBRT (HR 1·73 [95% CI 1·32–2·28]; log-rank p=0·0001; appendix p 13).

The most frequently reported CTCAE grade 2 or worse genitourinary toxicity was increased urinary frequency, which peaked 9 months in the CRT group with 18 (5%) of 404 patients reporting increased urinary frequency and at 15 months in the SBRT group, with 30 (10%) of 315 patients reporting this type of event (appendix p 14). The frequency of grade 3 genitourinary toxicity was less than 1% in both treatment groups at all timepoints according to both RTOG and CTCAE criteria, and there was no grade 4 toxicity seen at 24 months (table 2; appendix pp 11–12).

The incidence of grade 2 or worse gastrointestinal toxicities was low, with no significant differences between groups at 2 years: according to RTOG criteria, 11 (3%; 95% CI 1·5–5·3) of 382 patients had a grade 2 or worse toxicity in the CRT group versus six (2%; 0·1–3·5) of 384 patients in the SBRT group (absolute difference –1·3% [95% CI –3·9 to 1·1; p=0·32), and according to CTCAE criteria the absolute difference was –0·8% (–3·8 to 2·2; p=0·70; table 2). Prespecified components of RTOG gastrointestinal and CTCAE gastrointestinal endpoints for 24 months are presented in the appendix (pp 15–16). Sensitivity analysis results gave similar estimates for absolute differences (RTOG –1·1% [95% CI –3·5 to 1·2]; p=0·40 and CTCAE –0·6% [95% CI –3·5 to 2·3]; p=0·81; appendix pp 9–10). Low and similar rates were seen using both assessment criteria at all follow-up timepoints (figure 2; appendix pp 17–18).

There was also no evidence of differences in cumulative gastrointestinal toxicity rates. For RTOG, 2-year cumulative grade 2 or worse incidence rates were 8·1% (95% CI 5·8–11·1; 34 events) for CRT and 7·8% (5·6–10·9; 32 events) for SBRT (HR 0·98 [95% CI 0·60–1·58]; log-rank p=0·92; figure 3B). For CTCAE, 2-year grade 2 or worse cumulative incidence rates of gastrointestinal toxicity were 12·3% (95% CI 9·5–15·8; 52 events) for CRT and 12·5% (9·6–16·1; 51 events) for SBRT (HR=1·02 [0·70–1·51]; log-rank p=0·91; appendix p 19).

No CTCAE gastrointestinal individual element showed any significant difference between CRT and SBRT groups (appendix p 20). Grade 3 or worse gastrointestinal toxicity was low according to both RTOG and CTCAE scales (appendix p 18) and there was no grade 4 or worse gastrointestinal toxicity.

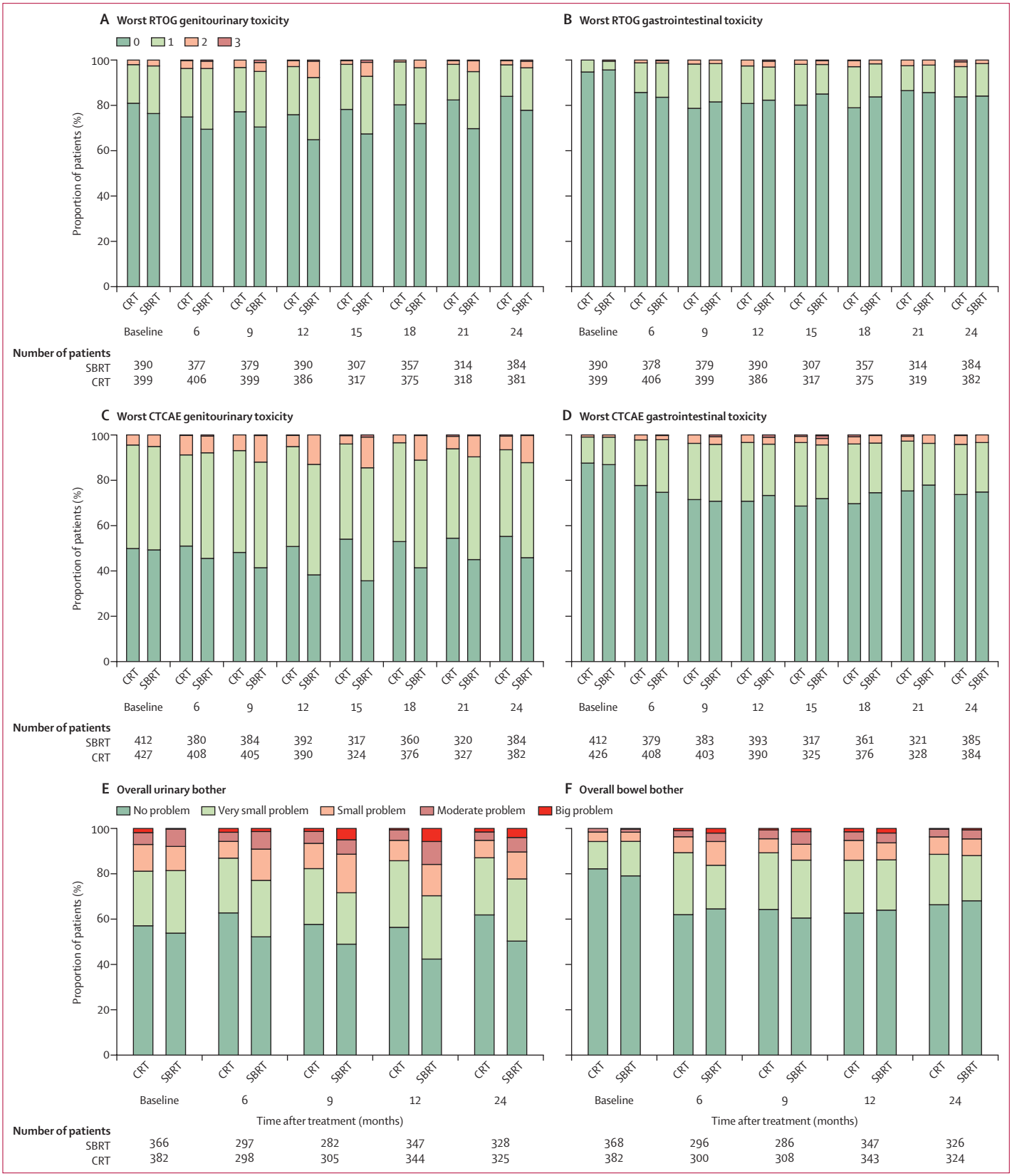
Prespecified CTCAE 24-month endpoints not relating to genitourinary or gastrointestinal toxicity are presented in the appendix (p 21). There were no apparent differences in CTCAE erectile dysfunction between CRT and SBRT groups or in grade 2 or worse rates of other CTCAE toxicities recorded (appendix pp 22–23).

Median EPIC-26 scores for urinary incontinence, irritative or obstructive urinary symptoms, bowel, sexual, and hormonal composite scales showed no significant differences at 2 years between CRT and SBRT (appendix p 24). However, there was a higher, but not significantly different, proportion of patients who had a minimally clinically important difference in urinary incontinence in the SBRT group than in the CRT group (p=0·011) and in urinary irritative-obstruction in the SBRT group than in the CRT (p=0·12; appendix p 25). There was a higher

	CRT (n=430)	SBRT (n=414)	p value*
Genitourinary RTOG			
0	320 (84%)	299 (78%)	..
1	53 (14%)	72 (19%)	..
2	7 (2%)	11 (3%)	..
3	1 (<1%)	2 (<1%)	..
4	0	0	..
5	0	0	..
Missing data	49	30	..
Genitourinary RTOG grade ≥2			0·39
Yes	8 (2%)	13 (3%)	..
No	373 (98%)	371 (97%)	..
Genitourinary CTCAE			
0	211 (55%)	176 (46%)	..
1	146 (38%)	161 (42%)	..
2	23 (6%)	46 (12%)	..
3	2 (<1%)	1 (<1%)	..
4	0	0	..
5	0	0	..
Missing	48	30	..
Genitourinary CTCAE grade ≥2			0·010
Yes	25 (7%)	47 (12%)	..
No	357 (93%)	337 (88%)	..
Gastrointestinal RTOG			
0	320 (84%)	323 (84%)	..
1	51 (13%)	55 (14%)	..
2	8 (2%)	6 (2%)	..
3	3 (1%)	0	..
4	0	0	..
5	0	0	..
Missing	48	30	..
Gastrointestinal RTOG grade ≥2			0·32
Yes	11 (3%)	6 (2%)	..
No	371 (97%)	378 (98%)	..
Gastrointestinal CTCAE			
0	283 (74%)	288 (75%)	..
1	85 (22%)	84 (22%)	..
2	15 (4%)	13 (3%)	..
3	1 (<1%)	0	..
4	0	0	..
5	0	0	..
Missing	46	29	..
Gastrointestinal CTCAE grade ≥2			0·70
Yes	16 (4%)	13 (3%)	..
No	368 (96%)	372 (97%)	..

Percentages are calculated out of non-missing values. No grade 4 or 5 events were recorded. CRT=control radiotherapy. CTCAE=Common Terminology Criteria for Adverse Events. RTOG=Radiation Therapy Oncology Group. SBRT=stereotactic body radiotherapy. Missing includes those no longer in follow-up at 24 months. *χ^2 test.

Table 2: **Worst genitourinary and gastrointestinal toxicity rates (grade 2 or worse) for RTOG and CTCAE scales at 24 months, by treatment received**


A Worst RTOG genitourinary toxicity
0 1 2 3
Proportion of patients (%)
B Worst RTOG gastrointestinal toxicity
CRT SBRT
Baseline 6 9 12 15 18 21 24
Number of patients
SBRT 390 377 379 390 307 357 314 384
CRT 399 406 399 386 317 375 318 381
SBRT 390 378 379 390 307 357 314 384
CRT 399 406 399 386 317 375 319 382
C Worst CTCAE genitourinary toxicity
D Worst CTCAE gastrointestinal toxicity
SBRT 412 380 384 392 317 360 320 384
CRT 427 408 405 390 324 376 327 382
SBRT 412 379 383 393 317 361 321 385
CRT 426 408 403 390 325 376 328 384
E Overall urinary bother
No problem Very small problem Small problem Moderate problem Big problem
F Overall bowel bother
Time after treatment (months)
SBRT 366 297 282 347 328
CRT 382 298 305 344 325
SBRT 368 296 286 347 326
CRT 382 300 308 343 324

proportion of patients who had a minimally clinically important difference in the bowel domain in the CRT group (p=0·0076; appendix p 25). More patients achieved an improvement in urinary QOL after treatment than bowel QOL (appendix pp 26–27). Overall, urinary bother was lower at 2 years after treatment in patients receiving CRT than in patients receiving SBRT, although these differences were not significant; moderate or severe problems with urinary function were reported by 17 (5%) of 325 patients in the CRT group compared with 34 (10%) of 328 patients in the after SBRT group (p=0·014; figure 2; appendix p 27). Bowel bother at 2 years was low in both groups; moderate or severe bowel bother were reported by 12 (4%) of 324 patients in the CRT group and 15 (5%) of 326 people in the SBRT group (p=0·57; figure 2F; appendix p 27).

Significant, but not clinically relevant, differences were seen between CRT and SBRT for IPSS total and IPSS QOL scores at 2 years (appendix pp 28–29). The proportion of patients with a severe IPSS score was similar at 24 months (15 [5·0%] of 301 patients *vs* 18 [6%] of 293; appendix p 30). IIEF-5 scores were similar between treatment groups at baseline and at 2 years, although the median score in both groups decreased by 4 points in both groups between baseline and 24 months (appendix p 31). Vaizey scores indicated a low degree of bowel incontinence at 24 months in both groups (appendix p 31).

Baseline characteristics differed between participants receiving SBRT on a CyberKnife (SBRT-CK) and those receiving SBRT on a conventional linac (SBRT-CL; appendix p 32). The following characteristics were less frequent in SBRT-CK patients than SBRT-CL patients: T1 disease, Gleason 3+4, and intermediate risk disease. A lower proportion of SBRT-CK patients were on α blocker at baseline than SBRT-CL patients, although baseline IPSS scores were similar. Aspirin use and statin use was less frequent at randomisation in SBRT-CK patients than SBRT-CL patients.

In analyses by delivery platform, we found no differences between SBRT-CK and SBRT-CL groups for RTOG genitourinary and RTOG gastrointestinal toxicity (appendix pp 33, 35). CTCAE genitourinary grade 2 or worse toxicity at 2 years was less frequent in patients treated with SBRT-CK than patients treated with SBRT-CL (nine [6%] of 154 patients *vs* 35 [17%] of 212 patients; p=0·0020; appendix pp 34, 36); the corresponding rate for CRT was 25 (7%) of 382 patients (table 2). CTCAE grade 2 or worse gastrointestinal toxicity at 2 years was seen in one (1%) of 155 patients treated with SBRT-CK and 11 (5%) of 212 patients treated with SBRT-CL (p=0·016; appendix pp 34, 36, 38).

The differences seen in CTCAE genitourinary toxicity between the CyberKnife and conventional linac platforms seemed to be driven by the dysuria, incontinence, and retention CTCAE elements, but small numbers precluded formal statistical analysis (appendix p 37). Incidence of grade 2 or worse genitourinary events varied

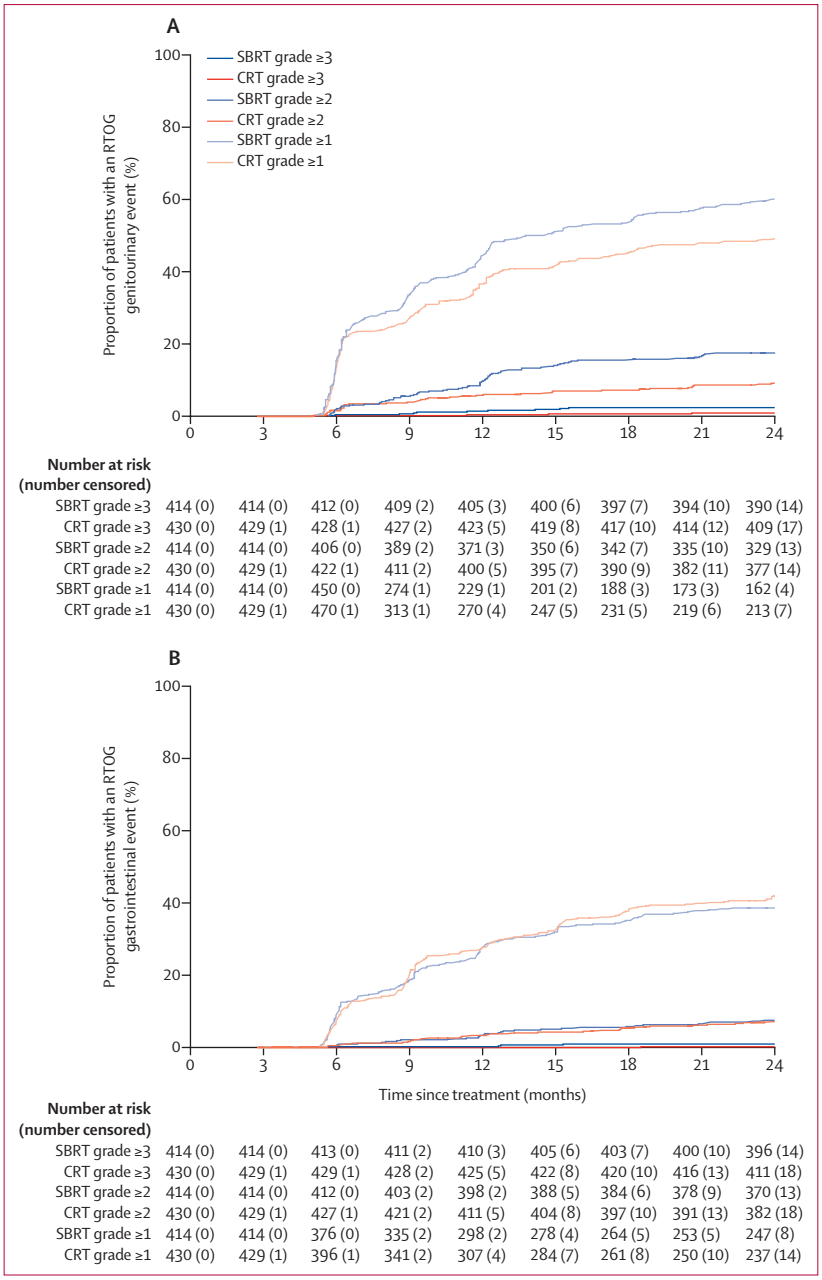


Figure 3: **Time to occurrence of first RTOG genitourinary toxicity event (A) and first RTOG gastrointestinal toxicity event (B) between 6 and 24 months after radiotherapy**

Figure 2: **Worst grade RTOG genitourinary (A), RTOG gastrointestinal (B), CTCAE genitourinary (C), and CTCAE gastrointestinal (C); and EPIC-26 overall urinary bother (E) and overall bowel bother (F) between 6 and 24 months after radiotherapy**

RTOG=Radiation Therapy Oncology Group. CTCAE=Common Terminology Criteria for Adverse Events. EPIC-26= Expanded Prostate Cancer Index Composite Short Form. CRT=control radiotherapy. SBRT=stereotactic body radiotherapy. No grade 4 or worse toxicities were recorded.

widely between centres, from 0% to 32% in centres recruiting more than five patients. Post-hoc analysis looking at fiducial use found that overall the rate of CTCAE genitourinary grade 2 or worse toxicity was similar for those receiving fiducial image guidance than those receiving non-fiducial image guidance (appendix p 40). However, the highest incidence of CTCAE grade 2 or worse genitourinary events was seen for those receiving SBRT-CL with fiducials, higher than SBRT-CL without fiducials (appendix p 40).

There was a difference observed in sexual function between SBRT-CL and SBRT-CK on the CTCAE scale (consistent across grades 1–3; appendix p 40) but this was not supported by the EPIC-26 and IIEF-5 patient-reported outcomes; the proportion of patients who had a decrease in EPIC-26 sexual composite score and a minimally clinically important difference at 24 months was 65 (41%) of 157 patients receiving SBRT-CL and 48 (46%) of 104 patients receiving SBRT-CK (p=0·45; appendix p 41); median IIEF-5 scores at 24 months were similar (p=0·21; appendix p 41).

In terms of other patient-reported outcomes, although the percentage of patients experiencing a decrease in genitourinary composite score on the EPIC-26 scale at 24 months after treatment was lower for SBRT-CK than SBRT-CL, this difference was not significant (a decrease in urinary incontinence composite score was seen in 24 [25%] of 98 patients in the SBRT-CK group *vs* 61 [37%] of 165 patients in the SBRT-CL group; p=0·036; appendix p 41). No significant difference was seen in composite scores of bowel, sexual, or urinary irritative or obstructive symptoms between delivery platforms (appendix pp 41, 42). Overall, urinary bother was similar between SBRT-CK and SBRT-CL groups (appendix p 42). IPSS scores (total and composite score) were not significantly different between delivery platforms at baseline or at 24 months (appendix p 43).

There was no significant difference seen in physician-reported toxicity for CRT delivered in a CyberKnife centre versus CRT delivered in a conventional linac centre (appendix pp 35, 36). CTCAE grade 2 or worse genitourinary events were seen in seven (4%) of 172 patients receiving CRT delivered in a centre with a CyberKnife versus 18 (9%) of 205 patients receiving CRT delivered in a centre without a Cyberknife; (appendix p 36). Concerning the main analysis of CRT versus SBRT, but examined solely in Cyberknife centres, there was no difference in CTCAE grade 2 genitourinary toxicity (seven [4%] of 172 patients receiving CRT *vs* nine [6%] of 154 patients receiving SBRT; p=0·46; appendix p 36).

Discussion

To our knowledge, PACE-B is the first randomised trial to compare five-fraction SBRT and conventional radiotherapy (2 or 3 Gy per fraction). We have shown that toxicity rates with modern radiotherapy were low in both groups. The co-primary endpoints of this analysis (RTOG gastrointestinal and genitourinary toxicity of grade 2 or worse 24 months after treatment) were not different between groups. However, CTCAE genitourinary toxicity (secondary endpoint) was higher after SBRT, suggesting that, in this study, CTCAE is a more sensitive measure of physician-reported outcomes than RTOG. This finding could be driven by investigators' interpretation of the scales or variance in prescribing practice. However, patient-reported genitourinary outcomes were not significantly worse after SBRT but bowel function was significantly better after SBRT than after CRT. Studies have shown that patient-reported toxicity remains stable between 2 and 5 years after treatment,[15] indicating these conclusions are probably robust over time.

The reasons for higher physician-reported genitourinary toxicity after SBRT than CRT are complex and might include differing thresholds for prescribing in response to borderline side-effects, as treatment allocation was not masked. Data suggesting that the α/β ratio for late gastrointestinal side-effects is higher[16] and for genitourinary side-effects is lower (around 0·5–2 Gy)[17] could also offer an explanation for these findings, because a low α/β ratio for normal tissues diminishes the relative therapeutic gain from hypofractionation. It could be that, as we progressively hypofractionate, we spare gastrointestinal toxicity but biologically dose escalate equally to both tumour and genitourinary structures. These structures are not well elucidated, with some hypothesising that bladder trigone[18] and others hypothesising that urethra[19] is the crucial structure. The apparent increase in genitourinary toxicity seen here and in multiple other SBRT series was absent in one study, which severely constrained the urethral dose.[20] With better knowledge of genitourinary toxicity determinants, dosimetric constraints and better patient selection could reduce genitourinary toxicity after SBRT. For example, a small number of patients in PACE had a high IPSS score (>19) at baseline and further analysis will be important to determine if patients treated with SBRT have worse toxicity than patients treated with CRT.

We could also learn more by investigating the apparent difference in toxicity rates when SBRT is delivered in a CyberKnife centre compared with a standard linear accelerator centre. There are many confounders to this non-randomised comparison: the CyberKnife centres were large volume, academic centres, and were early-adopters of SBRT. More CyberKnife patients had low-risk disease (therefore target volume included less seminal vesicle) and had a lower rate of α-blocker use at baseline than patients with linac as the delivery platform. CyberKnife incorporates many different aspects of delivery including fiducial tracking, long treatment times, and non-coplanar beam delivery, which could alter toxicity rates. A more detailed analysis to include adjustment for observed differences in baseline characteristics and for dosimetry is planned.

It is reassuring that the urinary bother reported by the patient did not mirror the difference in physician-reported toxicity rates. As we move to using patient-reported outcomes as our primary endpoint of interest, the relevance of differences in physician-reported side-effects decreases. Rates of toxicity seen in PACE-B are comparable with other recent large randomised trials: rates of RTOG grade 2 or worse genitourinary toxicity after treatment were 5% in HYPO-RT-PC at 5 years after treatment[21] and 1–2% at 2 years after treatment in the CHHIP trial[2] compared with 2–3% in PACE B. Rates of RTOG grade 2 or worse gastrointestinal toxicity after treatment were 1–4% in HYPO-RT-PC at 5 years after treatment[21] and 2–4% at 2 years after treatment in the CHHiP trial.[2] The increase in genitourinary toxicity seen with SBRT is consistent with the HYPO-RT-PC trial, in which cumulative RTOG grade 2 or worse toxicity was seen in 13·2% of patients in the ultra-hypofractionated group and 9·4% of patients in the standard group at 2 years, driven by a toxicity increase at around 12 months.[21] In PACE, a higher than standard dose was given in 20 fractions (62 Gy rather than 60 Gy). At the time the study was amended to include moderate hypofractionated radiotherapy as a control, 62 Gy was modelled to be equivalent to 78 Gy (as 60 Gy was similar to 74 Gy in CHHiP). Subsequent data from the PROFIT trial, however, showed non-inferiority of 60 Gy in 20 fractions to 78 Gy in 39 fractions.[22]

Strengths of this study include that it provides level one evidence supporting the safety of SBRT, based on a large number of patients. Data completeness is high, ensuring conclusions are robust. Patients were recruited from 35 centres across three countries, incorporating a range of investigators. The trial allowed a variety of treatment platforms and varying image-guidance techniques, making the conclusions widely applicable. We see this heterogeneity as a strength, reflecting real-world practice and allowing exploration of toxicity determinants. The trial also benchmarks sexual function in a population treated with radiotherapy but not ADT, showing a decrease in IIEF-5 score due to radiotherapy alone, in both groups. Although consistent with current practice, one limitation is that margins were not identical for CRT and SBRT and, on average, were 2 mm smaller for SBRT. This smaller margin might have contributed to lower toxicity rates with SBRT than CRT and is a limitation in interpreting the randomised comparison. The study was not masked for either patient or physician, which is also a limitation.

We have included some non-randomised comparisons, which are limited by being inherently prone to high risk of bias and confounding, particularly as there was imbalance between the SBRT-CK and SBRT-CL groups at baseline with respect to α-blocker use and risk group. These comparisons should be considered hypothesis-generating and yet are unlikely to be subsequently studied in a randomised setting. Although this is a large study, the low rates of toxicity mean that the relationships between patient and toxicity and between technical factors and toxicity are hard to show conclusively.

The low toxicity rates seen in PACE-B encourage further study of SBRT. Patients with intermediate-risk or high-risk prostate cancer are currently being studied in PACE-C, which has completed accrual and will enable further comparative analysis of toxicity outcomes. The follow-on PACE-NODES trial will open in 2022, testing the feasibility and efficacy of five-fraction nodal irradiation, compared with treating the prostate alone. Focal intraprostatic boosts have been shown to improve biochemical control with conventional fractionation[23] but it remains to be tested whether the same effect can be seen alongside the biological dose-escalation of five fractions. Finally, if the PACE-B trial shows equivalent efficacy then this encourages us to ask whether we can safely cure prostate cancer in less than five fractions, a question that is currently the subject of several clinical trials.[24,25]

To our knowledge, PACE-B is the first phase 3 trial reporting late toxicity results after random assignment of patients to five fraction SBRT or conventional radiotherapy. Toxicity was low and similar for both groups on the RTOG and patient-reported scales. The CTCAE scale shows higher genitourinary toxicity for five fractions than it does for longer courses. Patient-reported outcomes suggest bowel QOL is better and bladder QOL is worse after SBRT, compared with CRT. SBRT for localised prostate cancer appears to be feasible with low rates of toxicity, similar to longer radiotherapy schedules.

Contributors

NvA is the chief investigator. EH was the methodological lead. ACT, EH, PO, and NvA led the study design. ACT, EH, PO, and NvA developed the protocol. ACT, PO, HvdV, AL, WC, DF, ST, SJ, AM, JS, PC, KK, JF, AC, ISD, DH, AD, NvA, and JA recruited participants. ACT, PO, HvdV, AL, WC, DF, ST, SJ, AM, JS, PC, KK, JF, AC, ISD, DH, SBr, SBu, AD, KM, DHB, and NvA collected the data. ACT, PO, AL, WC, DF, ST, SJ, AM, JS, SBr, SBu, AD, VH, KM, ON, EH, DHB, and NvA are members of the PACE Trial Management Group, which contributed to study design, was responsible for oversight throughout the trial, and contributed to data interpretation. ACT, EH, MM, and VH accessed and verified the underlying data. EH oversaw statistical analysis done by MM and VH. ACT, EH, and NvA provided data interpretation. ON leads the PACE Physics Quality Assurance Group for the UK National Cancer Research Institute Radiotherapy Trials Quality Assurance group (RTTQA). SBu provided senior trial management oversight. JP had oversight of data management. SBr did central study management at the Institute of Cancer Research Clinical Trials and Statistics Unit (ICR-CTSU). ACT, MM, EH, and NvA led manuscript writing; all other authors contributed to and reviewed the manuscript. All authors had access to data reported in this study. All authors had the final responsibility for the decision to submit for publication.

Declaration of interests

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Data sharing

The ICR-CTSU supports the wider dissemination of information from its research and increased cooperation between investigators. Trial data are collected, managed, stored, shared, and archived according to ICR-CTSU Standard Operating Procedures 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 that 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 could lead to deductive disclosures will be removed in line with Cancer Research UK Data Sharing Guidelines.

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