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Title

Intensity Modulated Radiotherapy Versus Stereotactic Body Radiotherapy for Prostate Cancer (PACE-B): 2 year Toxicity Results From a Randomised Open-label Phase III Non-inferiority Trial

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Research in context Panel

Evidence before this study

Before this study data supporting stereotactic body radiotherapy was limited to small cohort and phase II studies, and standard prostate radiotherapy was delivered at 2 Gy per fraction over seven and a half weeks. In 2016, due to level one evidence, standard radiotherapy schedule was shortened to four weeks. Subsequent data were found by searching PubMed using the terms ["SBRT" OR "Stereotactic Body Radiotherapy"] AND ["Prostate"[AND ["trial" OR "study"], covering up to 4th November 2021. References of papers found were searched, with the search also supplemented by the authors' knowledge of the field. 9 studies of more than 90 men, reporting late (>3 months after treatment) toxicity outcomes from SBRT to the prostate in phase II or III trials of de novo prostate SBRT, were identified. This included a single randomised phase III study (HYPO-RT-PC trial) and one meta-analysis of multiple phase II studies. Grade 2+ toxicity estimates for ultra-hypofractionation ranged from 1%-16% for gastrointestinal and 3-45% for genitourinary toxicity.

Added value of this study

This is the first published phase III randomised evidence of late toxicity after ultra-hypofractionated stereotactic body radiotherapy, delivered over five fractions, compared with standard fractionation schedules. Overall, this study shows similar gastrointestinal toxicity with ultra-hypofractionation, compared to standard fractionation. Genitourinary toxicity rates are similar between arms for RTOG and patient-reported scales, but worse CTCAE Grade 2+ toxicity is seen after SBRT. Proportions of patients experiencing late grade 3 toxicity appear very low, and rates of Grade 2 toxicity are lower than previously documented for longer schedules. This suggests that, whilst overall toxicity is low regardless of fractionation, using SBRT techniques may increase the risk of moderate, but not severe, genitourinary side effects.

Implications of all the available evidence

Ultrahypofractionated radiotherapy over five fractions appears tolerable, with few serious side effects. The HYPO-RT-PC trial demonstrated that a dose of 42·7 Gy, delivered every other day over 2·5 weeks (6·1Gy/fraction) was non-inferior in terms of failure-free survival compared with conventional fractionation of 78 Gy over 8 weeks (2Gy/fraction) with similar proportions of late toxicity in each group. SBRT in the PACE-B trial was well tolerated with low levels of toxicity; biochemical outcomes are awaited.

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 two year toxicity findings from a randomised trial of conventionally- or moderately-hypofractionated radiotherapy (CRT) versus SBRT.

Methods

PACE is a multi-cohort phase III randomised controlled trial undertaken at 35 hospitals in the UK, Ireland and Canada. In PACE-B, men aged ≥18 years, performance status 0-2, with low/intermediate risk 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 CRT (78Gy/39 fractions (f)/7·8 weeks or 62Gy/20f/4 weeks) or SBRT (36·25Gy/5f/1-2 weeks). Treatment was not masked. Androgen deprivation was not permitted. Co-primary outcomes for this toxicity analysis were Radiation Therapy Oncology Group (RTOG) grade 2+ (G2+) gastrointestinal (GI) and genitourinary (GU) toxicity at 24 months after radiotherapy. Analysis was by treatment received and included all patients with at least 1 fraction of study treatment assessed for late toxicity. Recruitment is complete. Follow-up for oncological outcomes continues. The trial is registered: NCT01584258.

Findings

Between 07/12/2012 and 04/01/2018, 35 centres randomised 874 men (441 CRT; 433 SBRT). Analyses included 430 participants receiving CRT and 414 receiving SBRT assessed for late toxicity. At 24 months, RTOG G2+ GU toxicity was 2·1% (8/381) for CRT and 3·4% (13/384) for SBRT (difference: 1.3% (95% confidence interval -1·3 to -4.0) p=0·39); GI toxicity was 2·9% (11/382) CRT versus 1·6% (6/384) SBRT (difference -1·3% (-3·9 to 1.1); p=0·32). No serious adverse events (defined as RTOG G4+) or treatment-related deaths were reported within the analysis time frame.

Interpretation

Two-year RTOG toxicity rates are similar for five fraction SBRT and conventional schedules of radiotherapy. Prostate SBRT is safe and associated with low levels of side effects. Biochemical outcomes are awaited.

Funding

Accuray Incorporated.

Main Body

Introduction

Prostate cancer affects nearly 1·5 million men annually.[1] The majority are diagnosed with potentially curable disease and a range of treatments (external beam radiotherapy, surgery, brachytherapy) are available. Radiotherapy for early disease achieves high levels of long term cancer cure with over 90% of men relapse-free at five years after treatment.[2] Radiotherapy schedules have been shortened over the last decade following publication of multiple phase III trials showing non-inferiority of moderate hypofractionation to longer schedules.[2–4] Although some data suggest worse temporary bowel toxicity, all these trials reported low rates of long term side effects, which were similar between arms. Data examining patient-reported quality of life suggest no difference in patient-reported outcomes (PROs) at five years between different schedules, and levels of moderate or worse "bowel bother" are low.[5]

During the last decade there have been multiple innovations which 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. Latterly, 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 tests whether five fraction SBRT is non-inferior to other standard treatments: PACE-A compares SBRT with surgery, PACE-B compares SBRT with standard schedules of radiotherapy (CRT) and PACE-C compares SBRT with standard radiotherapy in higher risk prostate cancer, alongside androgen deprivation therapy (ADT).

The PACE-B trial tests whether SBRT is non-inferior to CRT in terms of 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 PROs to two years.

Methods

Study design and participants

PACE-B is a prospective, phase III, multicentre, parallel-group, randomised controlled trial undertaken at 35 hospitals in the UK, Ireland and Canada. The study recruited patients intending to have radical radiotherapy as their primary treatment; the full protocol has been previously published.[6] 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, sponsored by The Royal Marsden Hospital NHS Foundation Trust, and conducted in accordance with the principles of Good Clinical Practice.

Eligible patients were aged ≥18 years, with World Health Organisation performance status 0-2[7], life expectancy ≥5 years and histologically confirmed prostate adenocarcinoma. All patients had National Comprehensive Cancer Network (NCCN) low or intermediate risk disease.[8] Low risk patients were: cT1c-T2a (TNM 6th edition[9]), N0, M0/X; Gleason score ≤ 6; prostate specific antigen (PSA) <10ng/mL. Intermediate risk patients had at least one of: T2b/T2c; Gleason score 3+4 (Gleason 4+3 was excluded); PSA 10-20ng/mL. Distant staging was not mandated. A minimum ten biopsy cores, ≤18 months before

randomisation, were required, except for those progressing on active surveillance who now required treatment (e.g. by virtue of biochemical or MRI progression), where the last biopsy, even if ≥18 months could be used for eligibility. In defining risk stratification, no PSA adjustment was made for 5-alpha reductase inhibitor use at randomisation. 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.

Protocol link: https://go.icr.ac.uk/paceprotocol

Randomisation and masking

Patients were randomised in 1:1 ratio to either CRT or SBRT. Randomisation was done centrally by the Institute of Cancer Research Clinical Trials and Statistics Unit (ICR-CTSU) with allocation by computer generated random permuted blocks (size 4 and 6) 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, 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). CRT CTV to planning target volume (PTV) expansion was 5-9mm isometric, except posteriorly 3-7mm. 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.[6] The OAR constraints used for the majority of the patients (604/847) are reproduced in Appendix p3. ADT or any other prior treatment for prostate cancer was not permitted.

CRT PTV dose was 78 Gy in 39 daily fractions or, following protocol amendment (March 24th 2016), 62Gy in 20 daily fractions. This change followed publication of the CHHiP trial results supporting moderate hypofractionation,[2] but with a higher dose (62Gy versus 60Gy) due to an hypothesized interaction with ADT. After the amendment, centres were required to choose one schedule (either 78Gy in 39 fractions or 62Gy in 20 fractions) as their control CRT treatment for all subsequent patients. The SBRT PTV dose was 36·25Gy in 5 fractions to the PTV and 40 Gy to the CTV over 1-2 weeks (i.e. daily or alternate days, at centre discretion). CRT was prescribed such that PTV D98% ≥74.1Gy (for those receiving 78 Gy in 39 fractions) and PTV D98% ≥58·9 Gy (for those receiving 62 Gy in 20 fractions). For SBRT the D95% PTV ≥ 36·25 Gy with a secondary objective of D95% CTV ≥ 40 Gy. Dose hetereogeneity was allowed within the SBRT targets such that maximum doses >45 Gy were permitted.

Treatment was mandated to commence within 12 weeks of randomisation, with ≤8 weeks strongly recommended. Daily IGRT to prostate (fiducials or cone beam CT) was mandatory. No rectal spacing devices were used. For SBRT, continuous intra-fractional motion monitoring was permitted or a re-imaging was required if fraction delivery exceeded 3 minutes. A radiotherapy quality assurance programme was undertaken for each centre to ensure consistency with trial protocol.

Participants in both groups were assessed at baseline, during the acute toxicity period and then 3 monthly for the first 2 years and 6 monthly to year 5. Late toxicity (from 6 months) was clinician reported using the Radiation Therapy Oncology Group (RTOG) genitourinary (GU) and gastrointestinal (GI) domain scales[10] and Common Terminology Criteria for Adverse Events (CTCAE).[11] Paper questionnaires collected PROs at months 6, 9, 12 and 24: Expanded Prostate Cancer Index Composite Short Form (EPIC-26),[12] the Vaizey Faecal Incontinence Score,[13] International Prostate Symptom Score (IPSS)[14] and the International Index of Erectile Function 5-question (IIEF-5)[15] score (omitted at month 9).

Outcomes

The trial's primary endpoint is freedom from biochemical or clinical failure, the data for which is not yet mature. For this pre-specified late toxicity analysis, co-primary endpoints are the proportions of patients with RTOG grade 2 or higher (G2+) GU and GI toxicity at 24 months after treatment. Secondary endpoints were cumulative RTOG G2+ GU and GI toxicity to 24 months, CTCAE G2+ GU and GI rates at, and cumulative to, 24 months, CTCAE G2+ erectile function and other pre-specified CTCAE parameters including hot flushes and fatigue CTCAE. Secondary endpoints relating to PROs were EPIC-26 composite scores (urinary incontinence/irritative, urinary obstructive, bowel and sexual domains) reported as a score and as the percentage of patients experiencing a minimally clinically important difference (MCID) in domain-specific quality of life. The following were pre-specified as other PROs of specific interest: IPSS (total, QOL and by category), Vaizey score, bowel bother and IIEF-5 score.

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 of 1·45. This sample size was also specified as sufficient (80% power) to exclude a 16% rate of RTOG G2+ GU and/or GI 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 prior to commencing analysis. All analysis presented were pre-specified unless stated otherwise.

The frequency and percentage of each toxicity grade at each timepoint assessed for GU, GI and sexual function are presented graphically in stacked bar charts. The proportion of patients experiencing G2+ side effects are compared between groups using chi-squared tests or Fisher's exact test, as appropriate. We calculated 95% confidence intervals for the difference in proportions at 24 months using the Wilson Score method including a continuity correction. This method was not pre-specified but was adopted to allow for low event rates observed; in accordance, a continuity corrected chi-square test is presented. For specific timepoint analyses data were attributed to the closest protocol defined timepoint e.g. assessments conducted between 22·5 and 27·0 months were assigned to the 2 year timepoint. To assess the impact of missing data for the primary endpoints, RTOG G2+ GI and GU toxicity at 24 months, a sensitivity analysis was caried using last value carried forward. For completeness this was also performed for the corresponding CTCAE analysis. This analysis was not pre-specified. Given differential effects on GU and GI events, overall rates of any toxicity are not reported. For analysis of cumulative incidence of late toxicity, time-to-event methods were used. Time to first incidence of late G1+, G2+ and G3+ GU and GI toxicity was measured from the completion of radiotherapy, with G2+ events of primary interest. Patients event free at the time of analysis were

censored at their last available toxicity assessment. Cumulative incidence graphs are presented with hazard ratios (HR) (including 95% confidence intervals) and log-rank tests used to compare treatment groups. Point estimates are reported using the upper limit of the assessment window e.g. at 27 months for 2 year estimate. A significance level of 0·025 was used for each of the co-primary endpoints. To reduce the impact of multiple comparisons, a p-value <0·01 was considered significant for secondary endpoints.

PRO scores were calculated in accordance with the relevant manuals. EPIC-26 scores were rescaled to a 0-100 point scale, with higher scores representing better quality of life (QoL).[16] Minimally clinically important difference (MCID) in EPIC-26 subdomain scores were: urinary incontinence (8 points) urinary obstructive (6 points), bowel (5 points), sexual (11 points), hormonal (5 points).[17] IPSS severity categories were assessed as none (0 points), mild (1-7 points), moderate (8-19 points), severe (20-35 points)[14]. The IIEF-5 total score was calculated and ranged from 1 (most severe) to 25 (no erectile dysfunction). The Vaizey total score was calculated and ranged from 0 (no problems) to 24 (very severe problems with incontinence). 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, Chi-square trend test for ordinal and Chi-square 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 (August 5, 2014) permitted standard linac SBRT delivery. As analysis of acute toxicity data had suggested a statistically significant difference by delivery platform[6] we planned this subgroup analysis in the late toxicity analysis, to include comparisons of CTCAE, RTOG, and PRO 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, Chi-square trend test for ordinal and Chi-square test for binary variables. Post hoc analysis of associated variables such as fiducial use is reported, for hypothesis generation.

Analyses are based on a snapshot of data taken on July 2, 2021 and were conducted using Stata version 17, with the exception of 95% confidence intervals for the difference in proportions which were computed using SAS 9.4. The Independent Data Monitoring Committee gave approval for release of these results, prior to release of the trials's primary endpoint (efficacy) results. The study is prospectively registered (clinicaltrials.gov: NCT01584258).

Role of the funding source

The funder of the study (Accuracy Inc, Sunnyvale, CA) had no role in 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. NvA, EH, VH, MM also had full access to the data.

Results

Between August 7, 2012 and January 4, 2018, 874 men were randomised from 35 centres across the UK, Ireland and Canada (Appendix p4). Four hundred and forty-one men were allocated CRT and 433 SBRT (Figure 1). Patients not completing treatment or not evaluable were excluded from all analyses.

Data completeness was good, with 24 month clinician reported toxicity available for 766/844 (90·8%) patients (RTOG) and 769/884 (91·4%) patients (CTCAE) in the analysis population (Appendix p5). Nine patients died between radiotherapy and the 24 month follow-up timepoint, 3 in the CRT arm and 6 in the SBRT arm. Patients receiving less than the protocol dose were 7/433 (CRT) and 3/413 (SBRT) (Figure 1). Recruitment completed to target; follow-up for oncological outcomes continues.

Demographic and clinical characteristics are presented in Table 1. Concomitant medication use at baseline was similar between groups (Appendix p6). The majority of patients receiving CRT (300/430, 69.8%) received treatment over 4 weeks and the majority receiving SBRT (310/414; 74·9%) received SBRT over 2 weeks. More SBRT patients received fiducial markers (303/414, 73·0%) than CRT (244/430, 57·0%). SBRT was delivered by standard linac for 245/414 (59·2%) patients and by CyberKnife for 169/414 (40·8%) (Appendix p6). Margins used have been previously published[6] confirming that most patients received protocol-compliant margins. The most common margins used were 7mm/5mm posteriorly for CRT and 5mm/3mm for SBRT.

At 2 years incidence of RTOG G2+ GU toxicity was 2·1% (8/381) for CRT and 3·4% (13/384) for SBRT giving a non-significant absolute difference of 1.3% (95% confidence interval (CI) -1·3 to 4·0%, p=0·39; Table 2). There was evidence of increased CTCAE GU G2+ toxicity at 2 years with SBRT absolute difference 5·7% (1·4 to 10·1%), p=0·0096). Pre-specified components of RTOG GU and CTCAE GU endpoints for 24 months are presented in appendix p7-8. Sensitivity analysis results gave similar estimates for absolute differences (RTOG: 1·5%; CTCAE: 4·9%) although the CTCAE difference was not statistically significant at the 1% level (p=0·026, Appendix p9-10). Figure 2 shows clinician assessed toxicity grades at each timepoint, with higher rates of RTOG G2+ GU seen for SBRT at 12-15 months post-treatment (Appendix p11) and a similar pattern was observed for CTCAE G2+ GU (Appendix p12).

Cumulative G2+ GU toxicity rates were higher with SBRT on both RTOG and CTCAE assessment. At 2 years cumulative incidence rates of RTOG G2+ GU toxicity were 10·6% (95% CI: 8·0% to 14·0%, 45 events) for CRT and 18·3% for SBRT (95% CI: 14·9% to 22·4%, 75 events) with HR 1·80 (95% CI: 1·25–2·61, logrank p=0·0015) (Figure 3a). Corresponding figures for CTCAE G2+ GU cumulative toxicity were 19·8% (95% CI: 16·3% to 23·9%, 84 events) for CRT and 32.3% (28·0% to 37·0%, 132 events) for SBRT; HR=1·73 (1·32 to 2·28), logrank p=0·0001) (Appendix p13). The most frequently reported CTCAE GU G2+ toxicity was urinary frequency which peaked at 4·5% (18/404) at 9 months for CRT and at 9·5% (30/315) at 15 months for SBRT (Appendix p14). The frequency of grade 3 GU toxicity was less than 1% in both treatment groups at all timepoints (RTOG and CTCAE) and there was no grade 4 toxicity seen at 24 months (Table 2 and Appendix p11-12).

The incidence of G2+ GI toxicities was low with no significant differences between groups at 2 years: RTOG: CRT 2·9% (11/382) vs SBRT 1·6% (6/384); absolute difference -1·3% (95% CI: -3·9 to 1.1%) p=0·32; CTCAE: absolute difference -0·8% (-3·8 to 2·2%), p=0·70 (Table 2). Pre-specified components of RTOG GI and CTCAE GI endpoints for 24 months are presented in appendix p15-16. Sensitivity analysis results gave similar estimates for absolute differences (RTOG: -1·1%; CTCAE: -0·6%; Appendix p9-10). Low and similar rates were seen using both assessment criteria at all follow-up time points (Figure 2; Appendix p17-18).

There was also no evidence of differences in cumulative GI toxicity rates. For RTOG, 2 year cumulative G2+ 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 (0·60-1·58) logrank p=0·92 (Figure 3b). For CTCAE, 2 year G2+ GI cumulative incidence rates were 12·3% (95% CI: 9·5-15·8, 52 events) for CRT and 12·5% (9·6-16·1, 51 events); HR=1·02 (0·70-1·51, logrank p=0·91) (Appendix p19). No CTCAE GI individual element showed any significant

difference between CRT and SBRT groups (Appendix p20). Grade 3+ GI toxicity was low on RTOG and CTCAE scales (Appendix p18) and there was no Grade 4+ GI toxicity.

Pre-specified non GI/GU CTCAE endpoints for 24 months are presented in appendix p21 There were no apparent differences in CTCAE erectile dysfunction between CRT and SBRT groups (Appendix p22) nor in G2+ rates of other CTCAE toxicities recorded (Appendix p23). No treatment related deaths were reported.

Median EPIC-26 scores for urinary incontinence, urinary irritative-obstructive, bowel, sexual and hormonal composite scales showed no statistically significant differences at 2 years (Appendix p24). However, the proportion of patients experiencing MCID detriment was worse for urinary incontinence (22·5% (62/275) CRT, 32·3% (85/263) SBRT; p=0·011) and urinary irritative-obstruction (CRT 26·4% (70/265) CRT, 32.8% (79/241) SBRT; p= 0·12) and better for bowel function (34·4% (93/270) CRT, 24.02% (64/267 SBRT; p=0·0076) for patients receiving SBRT (Appendix p25). More patients achieved an improvement in urinary QOL after treatment compared to bowel QOL (Appendix p26-27). Overall urinary bother was lower at 2 years post-treatment in those receiving CRT compared to SBRT; moderate/big problem with urinary function seen in 5·2% (17/325) after CRT compared with 10·4% (34/328) after SBRT, p=0·014 (Figure 2e, Appendix p27). Bowel bother at 2 years was low in both groups; moderate/severe bowel bother seen in 3·7% (12/324) CRT and 4·6% (15/326) SBRT, p=0·57 (Figure 2f, Appendix p27).

Statistically significant but not clinically relevant differences were seen between CRT and SBRT for IPSS total and IPSS Qol scores at 2 years (Appendix p28-29). The proportion of patients with a severe IPSS score was similar at 24 months (5·0% (15/301) vs 6·1% (18/293)) (Appendix p30).

IIEF-5 scores were similar between treatment groups at baseline and at 2 years, although the median score in both groups decreased (4 points, both groups) between timepoints (Appendix p31). Vaizey scores indicated low levels of bowel incontinence at 24 months in both groups (Appendix p31).

Baseline characteristics differed between participants receiving SBRT on a CyberKnife (SBRT-CK) and those receiving SBRT on a conventional linac (SBRT-CL) (Appendix p32). T1 disease (11.2% vs 23.8%, p=0.00097), Gleason 3+4 (78.8% vs. 89.8%, p=0.0020) and intermediate risk disease (87.6% vs 94.3%, p=0.017) were less frequent in SBRT-CK patients than SBRT-CL patients. A lower proportion of SBRT-CK patients were on alpha blocker at baseline (10.6% vs 21.3%; p=0.0046) although baseline IPSS scores were similar. Aspirin use (p=0.0005) and statin use (p=0.00046) was less frequent at randomisation in SBRT-CK patients.

There were no differences seen between SBRT-CK and SBRT-CL groups for RTOG GU and RTOG GI toxicity (Appendix p33 and p35). CTCAE GU G2+ toxicity at 2 years was seen less frequently with SBRT-CK than SBRT-CL; 5·8 % (9/154) vs 16·5% (35/212) (p=0·0020; Appendix p34 and p36); the corresponding rate for CRT was 6.5% (25/384). The rate of CTCAE GI G2+ toxicity at 2 years was 0.6%; (1/155) for SBRT-CK and 5.2% (11/212) SBRT-CL , not statistically significant (p=0·016; Appendix p34 and p36)).

The differences seen in CTCAE GU 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 p37). We noted that the incidence of G2+ GU events varied widely between centres, from 0% to 32%, for centres recruiting >5 patients. Overall the rate of CTCAE GU G2+ toxicity was similar for those receiving fiducial image guidance (9·8%; 49/500) vs those

receiving non-fiducial image guidance (8·6%; 23/266) (Appendix p40). However, the highest incidence of CTCAE GU G2+ events was seen for those receiving SBRT-CL with fiducials (24·0%; 30/125), higher than SBRT-CL without fiducials (7·6%; 8/105). (Appendix p40).

There was a difference observed in sexual function between SBRT-CL and SBRT-Cyberknife on the CTCAE scale (consistent across grades 1-3) (Appendix p40) but was not supported by the EPIC-26 and IIEF-5 PROs; proportion of patients experiencing a decrease in EPIC-26 sexual composite score achieving MCID at 24 months was 41·4% (65/157) for SBRT-CL and 46·2% (48/104) for SBRT-CyberKnife, p=0·45) (Appendix p41); median IIEF-5 scores at 24 months were similar (p=0·21; Appendix p41).

In terms of other PROs, although the percentage of patients experiencing a decrease in GU QoL on the EPIC-26 scale at 24 months post-treatment was lower for SBRT-CK this difference was not significant (urinary incontinence QoL detriment seen in 24·5% (24/98) SBRT-CK versus 37·0% (61/165) SBRT-CL; p=0·036). No significant difference was seen in bowel, sexual or urinary irritative-obstructive composite scores between platforms (Appendix p41-42;). Overall urinary bother was similar between SBRT-CK and SBRT-CL (Appendix p42). IPSS scores (total and QOL) were not significantly different between platforms at baseline or at 24 months (Appendix p43).

There was no significant difference seen in physician-reported toxicity for CRT delivered in a CyberKnife centre vs CRT delivered in a conventional linac centre (Appendix p35-36). Rates of CTCAE G2+ GU events were 4.1% (7/172) after CRT delivered in a centre with a CyberKnife vs 8.8% (18/205) after CRT delivered in a centre without a Cyberknife; Appendix p36). Concerning the main analysis of CRT versus SBRT, but examined solely in Cyberknife centres, there was no difference in CTCAE G2+ GU toxicity; 4·1 % (7/172) CRT vs 5·8% (9/154) SBRT (p=0·46; Appendix p36).

Discussion

PACE-B is the first randomised trial to compare 5-fraction SBRT and conventional radiotherapy (2 or 3 Gy per fraction). We have shown that toxicity rates with modern radiotherapy are low in both groups. The co-primary endpoints of this analysis (RTOG GI and GU toxicity) are not different between groups. However, CTCAE GU toxicity is higher after SBRT suggesting that in this study CTCAE is a more sensitive measure of physician-reported outcomes than RTOG. This finding may be driven by investigators' interpretation of the scales or variance in prescribing practice. However, patient-reported GU outcomes were not significantly worse after SBRT but bowel function was significantly better after SBRT compared to after CRT. Studies have shown that patient-reported toxicity remains stable between 2 and 5 years after treatment[18] indicating these conclusions are likely to be robust over time.

The reasons for higher physician-reported GU toxicity after SBRT are complex and may include differing thresholds for prescribing in response to borderline side effects, as treatment allocation was not blinded. Data suggesting that the alpha/beta ratio for late GI side effects is higher[19] and for GU side effects is lower (around 0·5-2Gy)[20] may also offer an explanation for these findings, as this diminishes the relative therapeutic gain from hypofractionation. It may be that as we progressively hypofractionate we spare GI toxicity but biologically dose escalate equally to both tumour and GU structures. These structures are not well elucidated, with some hypothesizing that bladder trigone[21] and others hypothesizing that urethra[22] is the critical structure. The apparent 'bounce' in GU toxicity seen here and in multiple other SBRT series was absent in one study, which severely constrained the

urethral dose.[23] With better knowledge of GU toxicity determinants, dosimetric constraints and better patient selection may reduce GU 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 these patients experience worse toxicity.

We may also learn more by investigating the apparent difference in toxicity rates when SBRT is delivered in a CyberKnife centre compared to a standard linear accelerator centre. There are many confounders to this non-randomised comparison: the CyberKnife centres were large volume, academic centres who 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 alpha-blocker use at baseline. CyberKnife incorporates many different aspects of delivery including fiducial tracking, long treatment times and non-coplanar beam delivery, which may play a role. 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" experienced by the patient did not mirror the difference in physician-reported toxicity rates. As we move to using PROs as our primary endpoint of interest, differences in physician-reported side effects become less relevant.

Rates of toxicity seen in PACE-B are comparable to other recent large randomised trials (Table 3). The increase in GU toxicity seen with SBRT is consistent with the HYPO-RT-PC trial, where cumulative RTOG G2+ toxicity was seen in 13·2% in the ultra-hypofractionated group and 9·4% in the standard group, driven by a toxicity 'bounce' at around 12 months [24]. In PACE, a higher than standard dose was given in 20 fractions – 62Gy rather than 60Gy. At the time the study was amended to include moderate hypofractionated radiotherapy as a control, 62Gy was modelled to be equivalent to 78Gy (as 60Gy was similar to 74Gy in CHHiP). Subsequent data from the PROFIT trial, however, showed non-inferiority of 60Gy in 20 fractions to 78Gy in 39 fractions.[25]

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, documenting a drop in IIEF-5 score due to radiotherapy alone, in both arms. Whilst consistent with current practice, one limitation is that margins were not identical for CRT and SBRT and, on average, were 2mm smaller for SBRT. This smaller margin may have contributed to lower toxicity rates with SBRT and is a limitation in interpretating the randomised comparison. The study was not blinded either for patient or physician, which is also a limitation.

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

The low toxicity rates seen in PACE-B encourage further study of SBRT. Patients with intermediate/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 5-fraction nodal irradiation, compared to treating the prostate alone. Focal intra-prostatic boosts have been shown to improve biochemical control with conventional fractionation[26] but it remains to be tested whether the same effect can be seen alongside the biological dose-escalation of 5 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 5 fractions, currently the subject of several clinical trials.[27,28]

Conclusion

To our knowledge, PACE-B is the first phase III trial reporting late toxicity results after randomising patients between five fraction SBRT and conventional radiotherapy. Toxicity was low and similar for both groups on the RTOG and patient-reported scales. The CTCAE scale shows higher GU toxicity for 5 fractions compared to longer courses. Patient reported outcomes suggest bowel quality of life is better and bladder quality of life is worse after SBRT, compared to CRT. SBRT for localised prostate cancer appears to be feasible with low toxicity levels, similar to longer radiotherapy schedules.

Contributions

NvA is the Chief Investigator. EH was the methodological lead. AT, CG, EH, PO, NvA led the study design. AT, CC, CG, EH, PO, NvA developed the protocol. AT, PO, HvdV, AL, WC, DF, ST, SJ, AM, JS, PC, KK, JF, AC, ID, DH, AD, NvA, JA recruited participants. AT, PO, HvdV, AL, WC, DF, ST, SJ, AM, JS, PC, KK, JF, AC, ID, DH, SBr, CC, SBu, AD, CG, KM, NvA undertook data collection. AT, PO, AL, WC, DF, ST, SJ, AM, JS, SBr, CC, SBu, AD, CG, VH, KM, ON, EH, 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. AT, EH, MM and VH accessed and verified the underlying data. EH oversaw statistical analysis done by MM and VH. AT, EH, NvA provided data interpretation. ON leads the PACE Physics Quality Assurance Group for RTQA. SBu provided senior trial management oversight. SBr conducted central study management at ICR-CTSU. AT, MM, EH, NvA led manuscript writing; all other authors contributed to and reviewed the manuscript. All authors had access to data reported in this study. NvA, AT and EH had the final responsibility for the decision to submit for publication.

Declaration of interests

DB reports other from Cancer Research UK, during the conduct of the study;
AT reports funding from Accuray Inc., Varian Medical Systems Inc., and The Royal Marsden Cancer Charity for the funding of the PACE trials;
NvA reports funding from Accuray Inc. and Varian Medical Systems Inc.,;
AT reports personal fees from Elekta, Janssen and Accuray. AT reports grants from the JP Moulton charity, Prostate Cancer UK, Elekta (including as part of the MR Linac consortium), Accurayand Cancer Research UK over the past 36 months;
AT reports she is on the Editorial Board for the International Journal of Radiation Oncology Biology;
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PC reports personal payments from ViewRay, Roche Products LTD, Merck and GenesisCareUK over the past 36 months;
DF reports personal payments from Janssen, Pfizer and BMS over the past 36 months;
SJ reports grants from Boston Scientific and personal payments from Boston Scientific, Astra Zeneca, Novartis, Janssen, Bayer, and Astrellas over the past 36 months;
AL reports that his is the unpaid Founder and Chair of Prostate Cure Foundation and that part of his income is fee-for-service for SBRT and external beam radiation;
AM reports grants from GenesisCareUK over the past 36 months;
KM reports funding from Accuray Inc. for her research post at Royal Marsden Hospital.

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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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Main Table and Figure titles

Table 1: Demographic and clinical characteristics

Figure 1: Patient flow through the study

Table 2: Genitourinary (GU) and gastrointestinal (GI) toxicity rates for RTOG and CTCAE scales at 24 months, by treatment received

Figure 2: Worst grade RTOG GU (a), RTOG GI (b), CTCAE GU (c), CTCAE GI (d) and EPIC 26 Overall urinary (e) and overall bowel bother (f) between 6 and 24 months

Figure 3: Time to occurrence of first grade 1+, 2+ and 3+ RTOG GU (a) and grade 1+, 2+ and 3+ RTOG GI (b) toxicity between 6 and 24 months post-radiotherapy

Table 3: RTOG grade 2+ toxicity rates in PACE-B compared to other large randomised trials of hypofractionation