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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;
VH, EH, SBu, SBr, MM, JP report grants and payment from Accuray Inc., received by the Institute of Cancer Research via Royal Marsden Trust during the conduct of the study;
EH reports grants from Varian Medical Systems Inc., Astra Zeneca, Janssen-Cilag, Bayer, Roche Products LTD, Merck Sharp & Dohme received by the Institution of Cancer Research over the past 36

months;
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

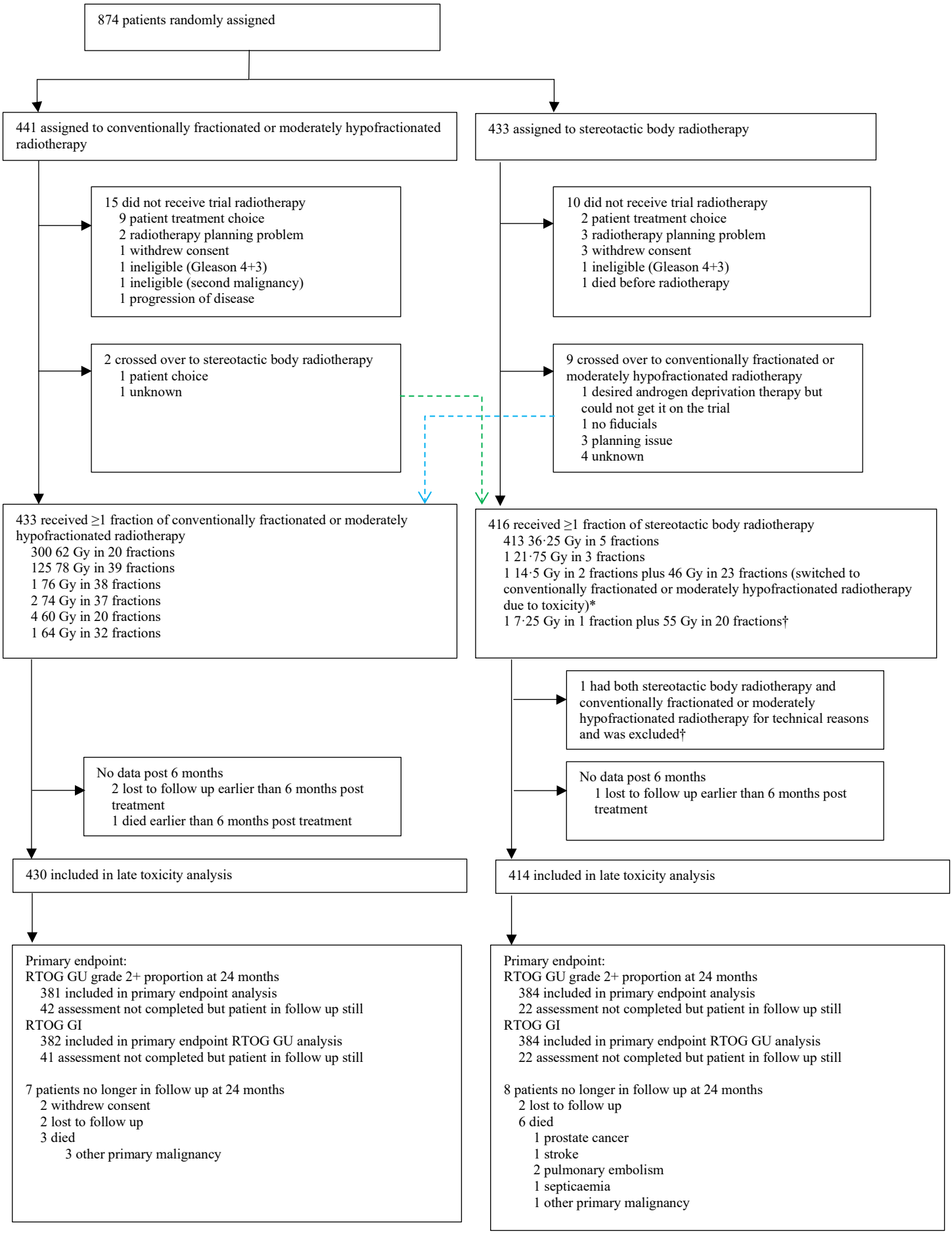
Table 2: Genitourinary (GU) and gastrointestinal (GI) toxicity rates for RTOG and CTCAE scales at 24 months, by treatment received

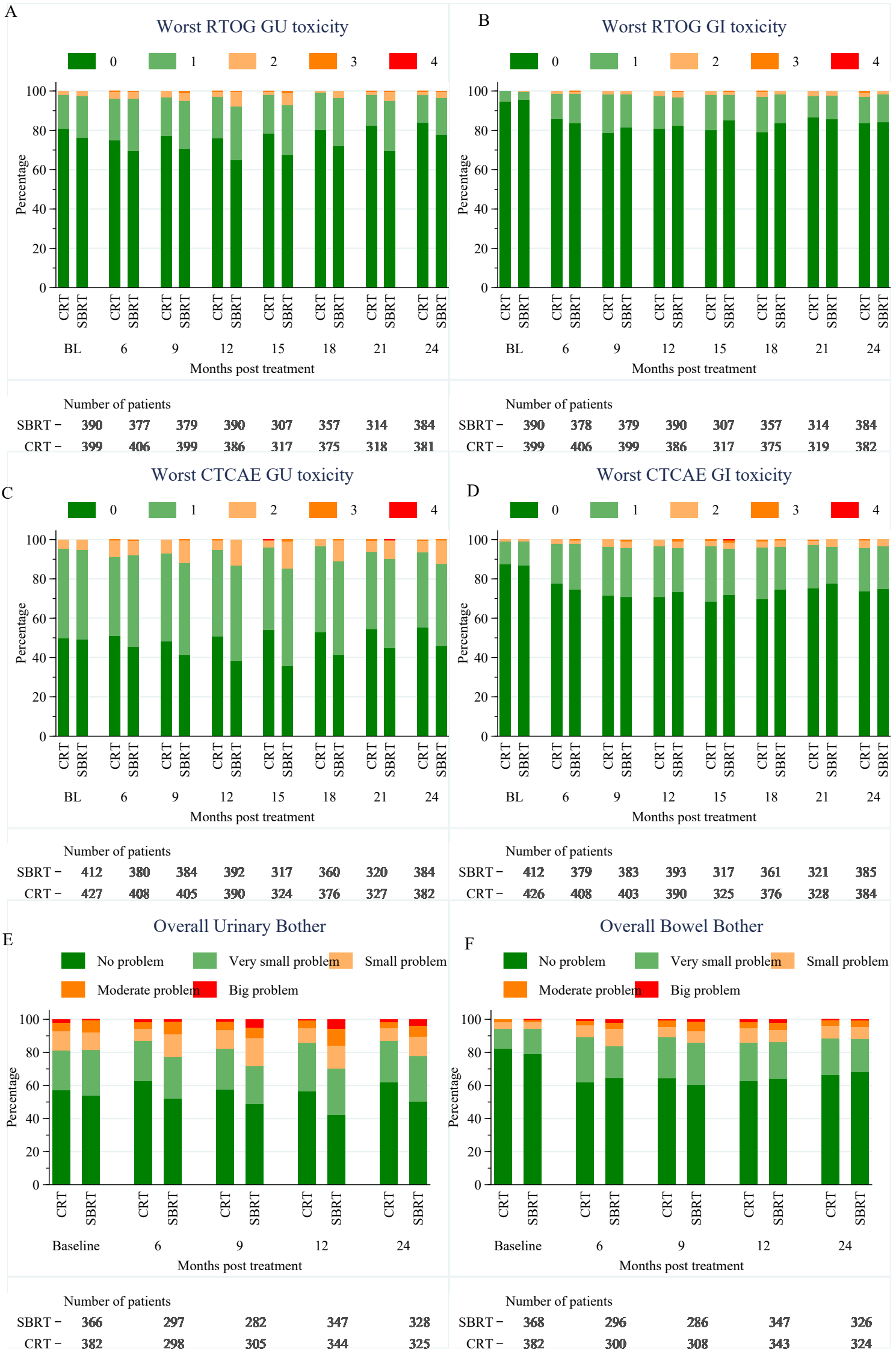
Figure 2: Worst grade RTOG GU (a), RTOG GI (b), CTCAE GU (c), CTCAE GI (d) and EPIC 26 Overall urinary (e) and overall bowel bother (f) between 6 and 24 months

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

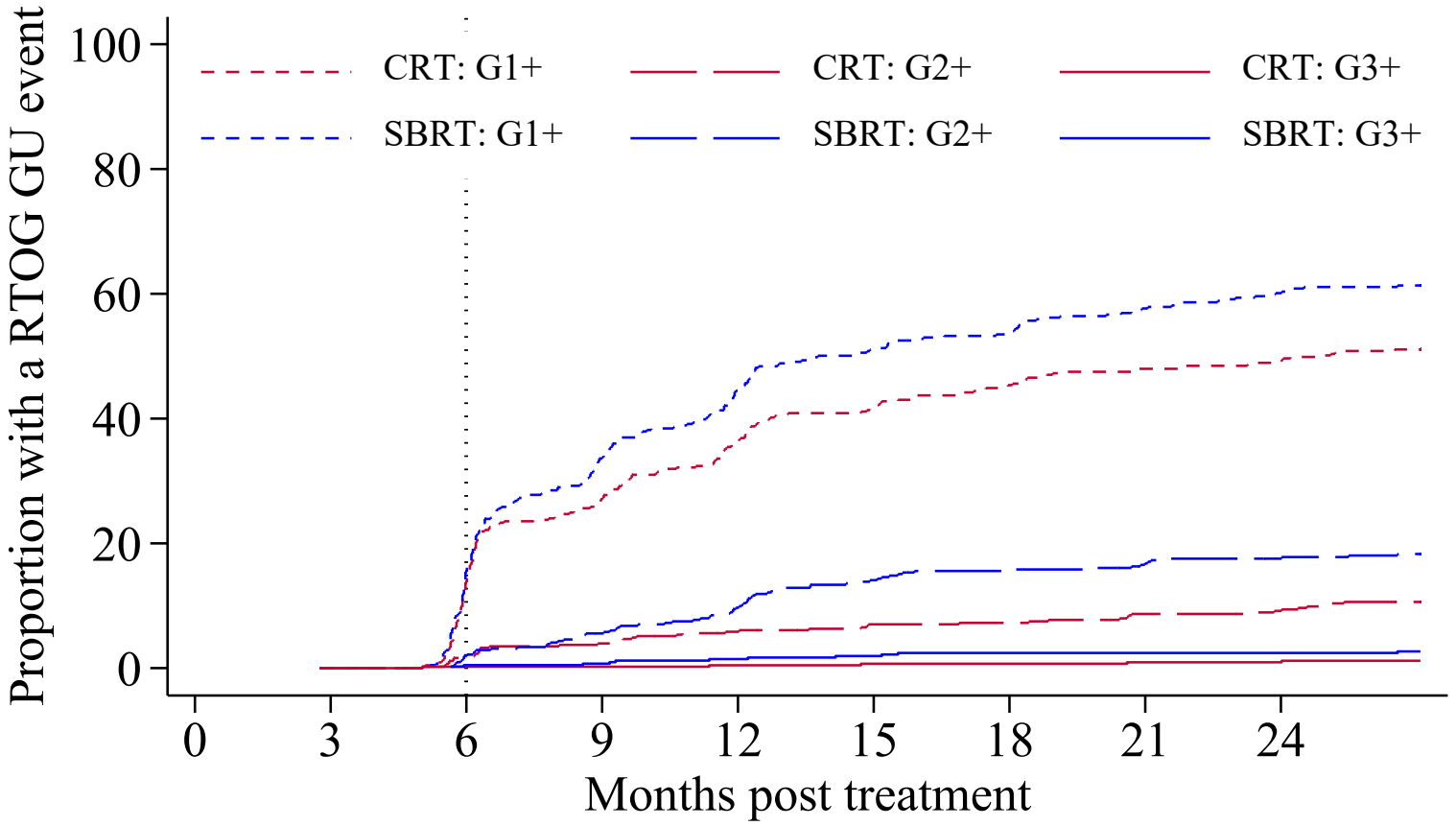
Table 3: RTOG grade 2+ toxicity rates in PACE-B compared to other large randomised trials of hypofractionation

Figure 1: Patient flow through the study
Diagrammatic representation of patient flow through the trial, with reasons stated where possible for any deviation from allocated treatments. Crossovers between treatment arms analysed as treatment received for this late toxicity analysis. Dose-fractionation regimens administered within each arm are shown. Two men received both SBRT and CRT treatments: *included is one patient who received two fractions of SBRT (14·5 Gy) then developed grade 3 toxicity (urosepsis) and switched to CRT (further 46Gy in 23 fractions). †Excluded is one patient who received a single incomplete fraction of SBRT (<7·25 Gy, set-up issues) and switched to CRT (further 55Gy in 20 fractions).


874 patients randomly assigned
441 assigned to conventionally fractionated or moderately hypofractionated radiotherapy
433 assigned to stereotactic body radiotherapy
15 did not receive trial radiotherapy
9 patient treatment choice
2 radiotherapy planning problem
1 withdrew consent
1 ineligible (Gleason 4+3)
1 ineligible (second malignancy)
1 progression of disease
10 did not receive trial radiotherapy
2 patient treatment choice
3 radiotherapy planning problem
3 withdrew consent
1 ineligible (Gleason 4+3)
1 died before radiotherapy
2 crossed over to stereotactic body radiotherapy
1 patient choice
1 unknown
9 crossed over to conventionally fractionated or moderately hypofractionated radiotherapy
1 desired androgen deprivation therapy but could not get it on the trial
1 no fiducials
3 planning issue
4 unknown
433 received ≥1 fraction of conventionally fractionated or moderately hypofractionated radiotherapy
300 62 Gy in 20 fractions
125 78 Gy in 39 fractions
1 76 Gy in 38 fractions
2 74 Gy in 37 fractions
4 60 Gy in 20 fractions
1 64 Gy in 32 fractions
416 received ≥1 fraction of stereotactic body radiotherapy
413 36·25 Gy in 5 fractions
1 21·75 Gy in 3 fractions
1 14·5 Gy in 2 fractions plus 46 Gy in 23 fractions (switched to conventionally fractionated or moderately hypofractionated radiotherapy due to toxicity)*
1 7·25 Gy in 1 fraction plus 55 Gy in 20 fractions†
1 had both stereotactic body radiotherapy and conventionally fractionated or moderately hypofractionated radiotherapy for technical reasons and was excluded†
No data post 6 months
2 lost to follow up earlier than 6 months post treatment
1 died earlier than 6 months post treatment
No data post 6 months
1 lost to follow up earlier than 6 months post treatment
430 included in late toxicity analysis
414 included in late toxicity analysis
Primary endpoint:
RTOG GU grade 2+ proportion at 24 months
381 included in primary endpoint analysis
42 assessment not completed but patient in follow up still
RTOG GI
382 included in primary endpoint RTOG GU analysis
41 assessment not completed but patient in follow up still
7 patients no longer in follow up at 24 months
2 withdrew consent
2 lost to follow up
3 died
3 other primary malignancy
Primary endpoint:
RTOG GU grade 2+ proportion at 24 months
384 included in primary endpoint analysis
22 assessment not completed but patient in follow up still
RTOG GI
384 included in primary endpoint RTOG GU analysis
22 assessment not completed but patient in follow up still
8 patients no longer in follow up at 24 months
2 lost to follow up
6 died
1 prostate cancer
1 stroke
2 pulmonary embolism
1 septicaemia
1 other primary malignancy


A
Worst RTOG GU toxicity
0
1
2
3
4
Percentage
CRT
SBRT
BL
6
9
12
15
18
21
24
Months post treatment
Number of patients
SBRT – 390 377 379 390 307 357 314 384
CRT – 399 406 399 386 317 375 318 381
B
Worst RTOG GI toxicity
Number of patients
SBRT – 390 378 379 390 307 357 314 384
CRT – 399 406 399 386 317 375 319 382
C
Worst CTCAE GU toxicity
Number of patients
SBRT – 412 380 384 392 317 360 320 384
CRT – 427 408 405 390 324 376 327 382
D
Worst CTCAE GI toxicity
Number of patients
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
Baseline
Number of patients
SBRT – 366 297 282 347 328
CRT – 382 298 305 344 325
F
Overall Bowel Bother
Number of patients
SBRT – 368 296 286 347 326
CRT – 382 300 308 343 324

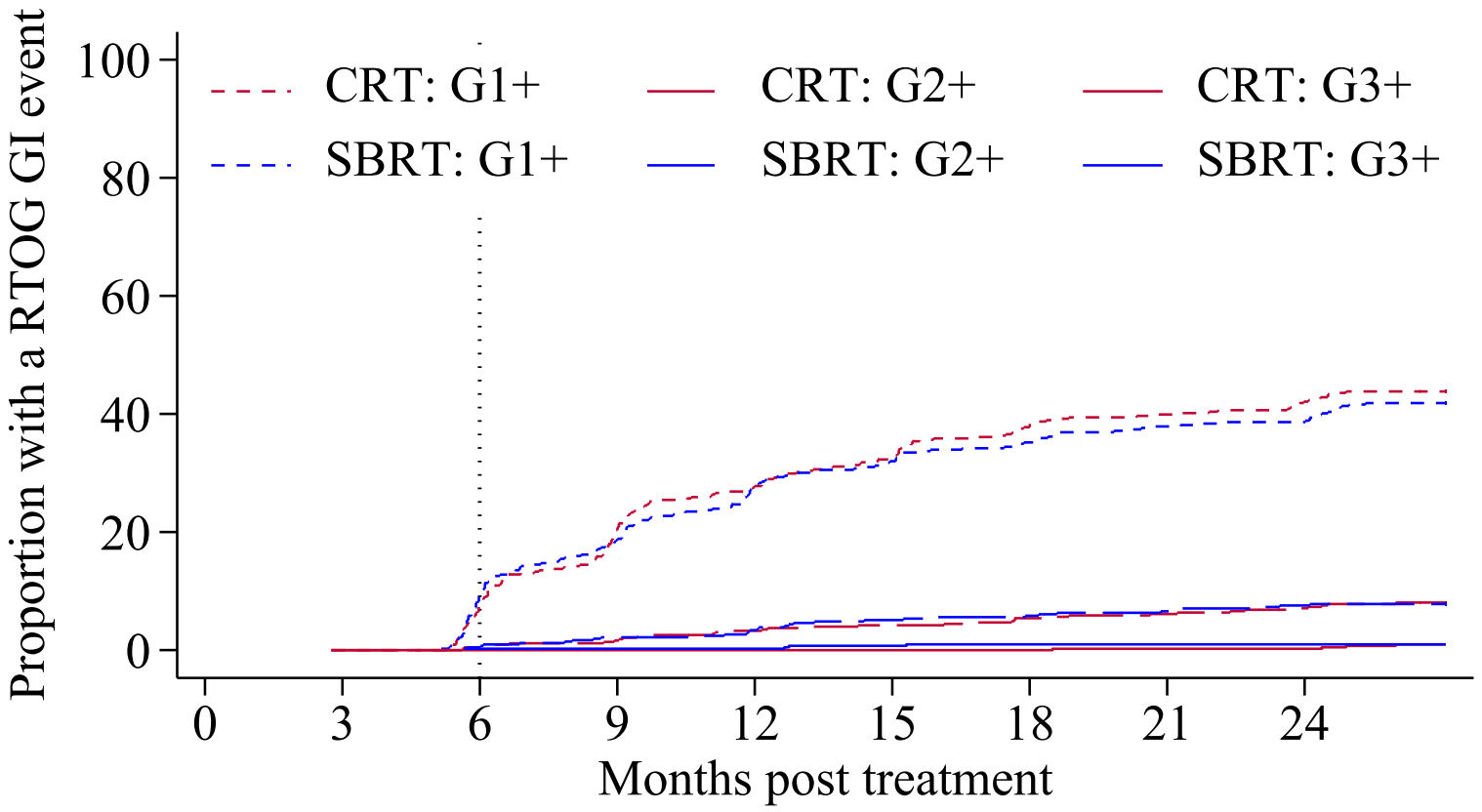
A.



Number at risk (cumulative censored)

SBRT: G3+	414(0)	414(0)	412(0)	409(2)	405(3)	400(6)	397(7)	394(10)	390(14)
CRT: G3+	430(0)	429(1)	428(1)	427(2)	423(5)	419(8)	417(10)	414(12)	409(17)
SBRT: G2+	414(0)	414(0)	406(0)	389(2)	371(3)	350(6)	342(7)	335(10)	329(13)
CRT: G2+	430(0)	429(1)	422(1)	411(2)	400(5)	393(7)	390(9)	382(11)	377(14)
SBRT: G1+	414(0)	414(0)	350(0)	274(1)	229(1)	201(2)	188(3)	173(3)	162(4)
CRT: G1+	430(0)	429(1)	370(1)	313(1)	270(4)	247(5)	231(5)	219(6)	213(7)

B.



Number at risk (cumulative censored)

SBRT: G3+	414(0)	414(0)	413(0)	411(2)	410(3)	405(6)	403(7)	400(10)	396(14)
CRT: G3+	430(0)	429(1)	429(1)	428(2)	425(5)	422(8)	420(10)	416(13)	411(18)
SBRT: G2+	414(0)	414(0)	412(0)	403(2)	398(2)	388(5)	384(6)	378(9)	370(13)
CRT: G2+	430(0)	429(1)	427(1)	421(2)	411(5)	404(8)	397(10)	391(13)	382(18)
SBRT: G1+	414(0)	414(0)	376(0)	335(2)	298(2)	278(4)	264(5)	253(5)	247(8)
CRT: G1+	430(0)	429(1)	396(1)	341(2)	307(4)	284(7)	261(8)	250(10)	237(14)

Table 1: Demographic and clinical characteristics

	CRT (N=430)		SBRT (N=414)		
Age at randomisation (years)	69·7	(65·6, 74·0)	69·6	(65·4, 73·8)	
Ethnic origin					
Black	24	(6)	35	(9)	
East Asian	3	(1)	4	(1)	
Mixed Heritage	2	(1)	2	(1)	
Southern 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	(14)	80	(19)	
T2c	167	(39)	151	(37)	
NCCN risk group					
Low	43	(10)	35	(9)	
Intermediate	387	(90)	379	(92)	
Gleason score					
3+3	84	(20)	61	(15)	
3+4	346	(81)	353	(85)	
Prostate volume					
<40 mL	156	(36)	165	(40)	
40 - <80 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 (inter-quartile range). CRT=control radiotherapy. SBRT=stereotactic body radiotherapy. NCCN= National Comprehensive Cancer Network. PSA=prostate specific antigen.

* Four of the 19 patients on 5-alpha reductase inhibitors at baseline had a PSA value of 10-20 ng/mL·

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

	GU								GI							
Worst Grade	**Worst grade RTOG toxicity**				**Worst grade CTCAE toxicity**				**Worst grade RTOG toxicity**				**Worst grade CTCAE toxicity**			
	CRT (n=430)		**SBRT (n=414)**		**CRT (n=430)**		**SBRT (n=414)**		**CRT (n=430)**		**SBRT (n=414)**		**CRT (n=430)**		**SBRT (n=414)**	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
0	320	(84)	299	(78)	211	(55)	176	(46)	320	(84)	323	(84)	283	(74)	288	(75)
1	53	(14)	72	(19)	146	(38)	161	(42)	51	(13)	55	(14)	85	(22)	84	(22)
2	7	(2)	11	(3)	23	(6)	46	(12)	8	(2)	6	(2)	15	(4)	13	(3)
3	1	(0)	2	(1)	2	(1)	1	(<1)	3	(1)	0	(0)	1	(<1)	0	(0)
4	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)
5	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)
Missing	49		30		48		30		48		30		46		29	
Grade 2+																
Yes	8	(2)	13	(3)	25	(7)	47	(12)	11	(3)	6	(2)	16	(4)	13	(3)
No	373	(98)	371	(97)	357	(94)	337	(88)	371	(97)	378	(98)	368	(96)	372	(97)
p-value (Chi squared)	0.39				0.0096				0.32				0.70			

Percentages are calculated out of non-missing values. CRT=control radiotherapy. SBRT=stereotactic body radiotherapy.
missing includes those no longer in follow up at 24 months

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

Percentage (n)	PACE-B incidence at 2 years post-treatment		HYPO-RT-PC[24] incidence at 5 years post-treatment		CHHiP[2] incidence at 2 years post-treatment		
	62Gy in 20f or 78Gy in 39f	36.25 (40)Gy in 5f	78Gy in 39f	42.7Gy in 7f	57Gy in 19f	60Gy in 20f	74Gy in 37f
Grade 2+ GU toxicity	2 (n=381)	3 (n=384)	5 (n=249)	5 (n=243)	1 (n=962)	2 (n=959)	1 (n=922)
Grade 2+ GI toxicity	3 (n=382)	2 (n=384)	4 (n=249)	1 (n=244)	2 (n=962)	3 (n=959)	4 (n=922)

f=fractions

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

Supplementary material

Contents

Table 1: Dose constraints used in protocol versions 8 and 9 of PACE B (a) for conventionally fractionated radiotherapy (CRT) and (b) for SBRT

a)

Organ at risk	**Dose volume constraints - CRT**			
	Dose (Gy) for 78Gy/39 fractions	Dose (Gy) for 62Gy/20 fractions)	Maximum Volume (% or cc)	
			Mandatory	Optimal
Rectum	30	24	-	80%
	40	32	-	65%
	50	40	60%	50%
	60	48	50%	35%
	65	52	30%	-
	70	56	25%	15%
	75	60	5%*	3%
Bladder	50	40	50%	-
	60	48	25%	-
	74	59	15%	5%
Femoral Heads	50	40	50%	5%
Bowel	50	40	17cc	-
Penile bulb	50	40	-	50%
	60	48	-	10%

b)

Organ at risk	**Dose volume constraints - SBRT**
Rectum	V18.1 Gy <50% (i.e. 50% rectum <18.1 Gy) V29 Gy <20 % (i.e less than 20% rectum receiving 29 Gy) V36 Gy <1cc
Bladder	V18.1 Gy <40% V37 Gy <10cc (optimal V37 Gy<5cc)
Prostatic urethra (if visualized)	V42Gy <50% (optimal , not mandatory)
Femoral head	V14.5 Gy <5%
Penile Bulb	V29.5 Gy <50%
Testicular	Blocking structure
Bowel	V18.1 Gy <5cc V30 Gy <1cc

Table 2: Participating sites and accrual figures

Centre Name	Principal Investigator	Date site open	Number patients recruited
Royal Marsden Hospital, London, UK	Dr Van As	Aug 12	**172**
Mount Vernon Hospital, London, UK	Dr Osler	Jan 13	**114**
James Cook University Hospital, Middlesborough UK	Dr Van der Voet	20 Oct 15	**110**
Odette Cancer Centre, Toronto, Canada	Dr Chu	10 Feb 16	**83**
Churchill Hospital, Oxford, UK	Dr Camilleri	12 Oct 15	**41**
Queen Elizabeth Hospital, Birmingham, UK	Dr Ford	13 Nov 15	**36**
Leicester Royal Infirmary, Leicester, UK	Dr Kancherla	25 Jul 16	**34**
Freeman Hospital, Newcastle, UK	Dr Frew	21 Oct 15	**30**
University Hospital Coventry & Warwickshire, Coventry, UK	Dr Chan	03 Dec 15	**30**
Clatterbridge Cancer Centre, Liverpool, UK	Dr Tolan	24 May 16	**25**
Juravinski Cancer Centre, Hamilton, Canada	Dr Dayes	27 Jan 17	**24**
Belfast City Hospital, Belfast, UK	Dr Jain	21 Oct 15	**21**
St Bartholomew's Hospital, London, UK	Dr Wells	23 Aug 16	**17**
Hôspital Charles-LeMoyne, Quebec, Canada	Dr Lymberiou	23 May 17	**14**
Addenbrooke's Hospital, Cambridge, UK	Dr Martin	13 Jan 16	**13**
Nottingham City Hospital, Nottingham, UK	Dr Saunders	21 Jun 16	**11**
Royal Free Hospital, London, UK	Dr Vilarino-Varela	18 Jan 17	**11**
Hôspital Maisonneuve-Rosemont, Montreal, Canada	Dr Vavassis	14 Sep 17	**11**
Walker Family Cancer Centre, St Catharines, Canada	Dr Tsakiridis	03 Apr 17	**9**
Hinchingbrooke Hospital, Huntingdon, UK	Dr Russell	20 Jan 16	**7**
Northeast Cancer Centre. Greater Sudbury, Canada	Dr Carlson	19 Oct 16	**7**
London Health Sciences Centre, Ottawa, Canada	Dr Rodrigues	11 Aug 17	**7**
Velindre Cancer Centre, Cardiff, UK	Dr Tanguay	28 Jun 17	**6**
Sunderland Royal Hospital, Sunderland, UK	Dr Iqbal	03 Jun 16	**5**
Charing Cross Hospital, London, UK	Mr Winkler	13 Sep 16	**5**
Ottawa Hospital, Ottawa, Canada	Dr Morgan	23 Aug 17	**5**
Beacon Hospital, Dublin, Ireland	Dr Mihai	03 Mar 17	**4**
Lakeridge Health, Oshawa, Canada	Dr Li	09 Mar 17	**4**
Weston Park Hospital, Sheffield, UK	Dr Din	16 Aug 17	**4**
Lincoln County Hospital, Lincoln, UK	Dr Panades	14 Mar 17	**3**
Norfolk & Norwich University Hospital, Norwich, UK	Dr Wade	01 Jun 17	**3**
West Suffolk Hospital, Bury St Edmunds, UK	Dr Martin	21 Jun 16	**2**
St Luke's Research Oncology Network, Dublin, Ireland and Cancer Trials Ireland	Dr Armstrong	18 Aug 17	**2**
Pilgrim Hospital, Bostson, UK	Dr Panades	30 Mar 17	**1**
Glan Clwyd, Ryhl, UK	Dr Oommen	07 Aug 17	**1**
University College London Hospital, London, UK	Dr Mitra	03 Mar 17	**0**
The Beatson West of Scotland Cancer Centre, Glasgow, UK	Dr Dodds	04 Oct 17	**0**
		Total	**874**

Table 3: Completeness of RTOG data between 6 and 24 months

RTOG Assessment performed	Treatment received				Total (N=844)	
	CRT (N=430)		SBRT (N=414)			
	n	%	n	%	n	%
Baseline	399	93	390	94	789	94
6 month	406	94	378	91	784	93
9 month	399	93	379	92	778	92
12 month	386	90	390	94	776	92
15 month	317	74	309	75	626	74
18 month	375	87	357	86	732	87
21 month	319	74	314	76	633	75
24 month	382	89	384	93	766	91

Note: data indicates the assessment was done, however in some cases individual pre-specified terms may not have been assessed.

Table 4: Completeness of CTCAE data between 6 and 24 months

CTCAE Assessment performed	Treatment received				Total (N=844)	
	CRT (N=430)		SBRT (N=414)			
	n	%	n	%	n	%
Baseline	427	99	412	100	839	99
6 month	408	95	380	93	788	93
9 month	405	94	384	93	789	96
12 month	390	91	393	95	783	93
15 month	325	76	317	77	643	76
18 month	376	87	361	87	737	87
21 month	328	76	321	78	649	77
24 month	384	89	385	93	769	91

Note: data indicates the assessment was done, however in some cases individual pre-specified terms may not have been assessed.

CTCAE GU and GI domain definitions

Specific CTCAE items in the genitourinary composite are bladder spasm, cystitis, haematuria, prostatic obstruction, urinary frequency, urinary incontinence, urinary retention, urinary urgency, urethral stricture, and gastrointestinal unspecified

Specific CTCAE items in the gastrointestinal composite are anal pain, colitis, constipation, diarrhoea, diverticulitis, faecal incontinence, fistula, gastrointestinal pain, haemorrhoids, gastrointestinal haemorrhage, proctitis, rectal pain, rectal prolapse, and gastrointestinal unspecified

Table 5: Concomitant medications used at baseline by treatment received

Concomitant medication at randomsiation	CRT (N=430)		SBRT (N=414)		Total (N=844)	
	n	%	n	%	n	%
Alpha blockers						
Yes	70	16	70	17	140	17
No	356	83	341	82	697	83
Unknown	4	1	3	1	7	1
Aspirin						
Yes	76	18	69	17	145	17
No	350	81	341	82	691	82
Unknown	4	1	4	1	8	1
Statin						
Yes	158	37	132	32	290	34
No	268	62	277	67	545	65
Unknown	4	1	5	1	9	1
Anticholinergic for bladder symptoms						
Yes	14	3	10	2	24	3
No	413	96	400	97	813	96
Unknown	3	1	4	1	7	1

Table 6: Radiotherapy treatment delivery

Treatment Characteristic	CRT (N=430)		SBRT (N=414)		Total (N=844)	
	n	%	n	%	n	%
Fiducial markers inserted?						
Yes	244	57	303	73	547	65
No	186	43	111	27	297	35
Planned RT technique						
Static field IMRT	91	21	1*	0	92	11
VMAT	320	74	241	58	561	67
Cyberknife	0	0	169	41	169	20
Other	19	4	3	1	22	3
Overall treatment time						
1 week	0	0	87	21	87	10
2 weeks	0	0	310	75	310	37
3 weeks	0	0	17	4	17	2
4 weeks	135	31	0	0	135	16
5 weeks	165	38	0	0	165	10
6 weeks	2	1	0	0	2	<1
7 weeks	1	<1	0	0	1	<1
8 weeks	59	14	0	0	59	7
9 weeks	68	16	0	0	68	8

* patient randomised to CRT but received SBRT

Table 7a. Grades for pre-specified RTOG GU terms at 24 months

RTOG Grade At 24 months	Cystitis				Haematuria				Urethral stricture post operative			
	CRT		SBRT		CRT		SBRT		CRT		SBRT	
	n	%	n	%	n	%	n	%	n	%	n	%
0	368	97	359	93	373	98	376	98	376	99	372	97
1	13	3	22	6	5	1	6	2	3	1	9	2
2	0	0	3	1	2	1	2	1	1	0	2	1
3	0	0	0	0	1	0	0	0	0	0	1	0
4	0	0	0	0	0	0	0	0	0	0	0	0
missing	49		30		49		30		50		30	
Grade 2+												
Yes	0	0	3	1	3	1	2	1	1	0	3	1
No	381	100	381	99	378	99	382	99	379	100	381	99

Table 7b. Grades for non pre-specified RTOG GU terms at 24 months

RTOG Grade At 24 months	Incontinence				Retention				Frequency				Nocturia				Pain				Urgency				Other			
	CRT		SBRT		CRT		SBRT		CRT		SBRT		CRT		SBRT		CRT		SBRT		CRT		SBRT		CRT		SBRT	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
0	379	99	374	97	379	99	381	99	379	99	375	98	357	94	366	95	380	100	381	99	371	97	369	96	380	100	383	100
1	2	1	8	2	1	0	0	0	2	1	8	2	22	6	18	5	1	0	3	1	9	2	12	3	1	0	1	0
2	0	0	2	1	1	0	2	1	0	0	1	0	2	1	0	0	0	0	0	0	1	0	3	1	0	0	0	0
3	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	49		30		49		30		49		30		49		30		49		30		49		30		49		30	
Grade 2+																												
Yes	0	0	2	1	1	0	3	1	0	0	1	0	2	1	0	0	0	0	0	0	1	0	3	1	0	0	0	0
No	381	100	382	99	380	100	381	99	381	100	383	100	379	99	384	100	381	100	384	100	380	100	381	99	381	100	384	100

Table 7c. Grades for pre-specified CTCAE GU terms at 24 months

CTCAE Grade At 24 months	Haematuria				Pain/Dysuria				Frequency				Incontinence				Urgency				Urinary retention			
	CRT		SBRT		CRT		SBRT		CRT		SBRT		CRT		SBRT		CRT		SBRT		CRT		SBRT	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
0	374	98	373	97	363	95	348	91	264	69	240	63	340	89	321	84	287	75	257	68	348	91	345	90
1	5	1	10	3	19	5	31	8	111	29	119	31	39	10	51	13	86	23	111	29	22	6	27	7
2	2	1	1	0	0	0	3	1	7	2	22	6	2	1	10	3	8	2	12	3	11	3	10	3
3	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
missing	48		30		48		31		48		33		49		32		49		34		48		32	
Grade 2+																								
Yes	3	1	1	0	0	0	4	1	7	2	22	6	2	1	10	3	8	2	12	3	12	3	10	3
No	379	99	383	100	382	100	379	99	375	98	359	94	379	99	372	97	373	98	368	97	370	97	372	97

Table 8a: Visit used in 24 month sensitivity analysis of GU endpoints

	RTOG GU				CTCAE GU			
	CRT		SBRT		CRT		SBRT	
Assessment visit (months)	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
6	2*	1	1	<1	2*	1	1	<1
9	3	1	2	1	4	1	2	1
12	7	2	4	1	7	2	4	1
15	2	1	3	1	1	<1	3	1
18	10	2	6	1	9	2	8	2
21	25	6	14	3	25	6	12	3
24	381	89	384	93	382	89	384	93
Total	430	100	414	100	430	100	414	100

*for one patient their 12 week visit was used as they didn't have any toxicity assessment and died within 7 months of radiotherapy

Table 8b: Visit used in 24 month sensitivity analysis for GI endpoints

	RTOG GI				CTCAE GI			
	CRT		SBRT		CRT		SBRT	
Assessment visit (months)	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
6	2*	1	1	<1	2*	1	1	<1
9	3	1	2	1	3	1	2	1
12	7	2	4	1	7	2	4	1
15	2	1	3	1	2	1	2	1
18	9	2	6	1	8	2	8	2
21	25	6	14	3	24	6	12	3
24	382	89	384	93	384	89	385	93
Total	430	100	414	100	430	100	414	100

*for one patient their 12 week visit was used as they didn't have any toxicity assessment and died within 7 months of radiotherapy

Table 8c: 24 month sensitivity analysis - GU

Worst Grade	GU							
	Worst grade RTOG toxicity				Worst grade CTCAE toxicity			
	CRT (n=430)		SBRT (n=414)		CRT (n=430)		SBRT (n=414)	
	n	%	n	%	n	%	n	%
0	358	83	316	76	238	55	187	45
1	62	14	82	20	158	37	174	42
2	8	2	14	3	30	7	52	13
3	2	1	2	1	4	1	1	<1
4	0	0	0	0	0	0	0	0
Missing	0		0		0		0	
Grade 2+								
Yes	420	97.7	398	96.1	396	92.1	361	87.2
No	10	2.3	16	3.9	34	7.9	53	12.8
Difference in proportion (SBRT-CRT)	1.5				4.9			
95% CI for proportion	-1.0 to 4.3				0.6 to 9.2			
p-value (Continuity Adj. Chi-Square)	0.27				0.026			

Table 8d: 24 month sensitivity analysis - GI

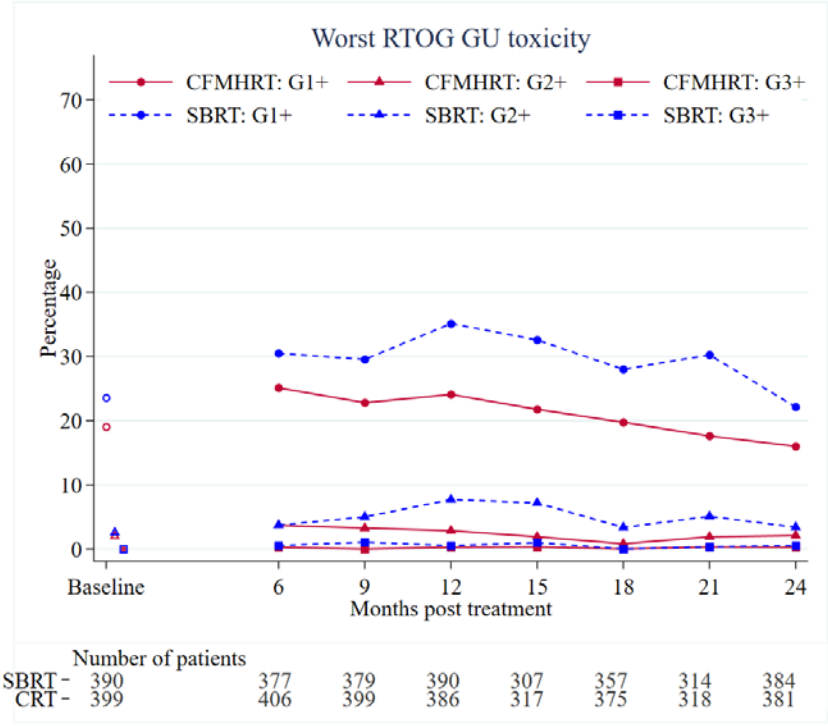
Worst Grade	GI							
	Worst grade RTOG toxicity				Worst grade CTCAE toxicity			
	CRT (n=430)		SBRT (n=414)		CRT (n=430)		SBRT (n=414)	
	n	%	n	%	n	%	n	%
0	363	84	348	84.1	316	74	307	74
1	55	13	59	14.3	96	22	92	22
2	9	2	7	2	17	4	15	4
3	3	1	0	0	1	<1	0	0
4	0	0	0	0	0	0	0	0
Missing	0		0		0		0	
Grade 2+								
Yes	12	2.8	7	1.7	18	4.2	15	3.6
No	418	97.2	407	98.4	412	95.8	399	96.4
Difference in proportion (SBRT-CRT)	-1.1				-0.6			
95% CI for proportion	-3.5 to 1.2				-3.5 to 2.3			
p-value (Continuity Adj. Chi-Square)	0.40				0.81			

Table 9 Worst GU RTOG toxicity from 6-21 months post treatment

Worst Grade	Baseline[1]				6 months				9 months				12 months				15 months				18 months				21 months			
	CRT		SBRT		CRT		SBRT		CRT		SBRT		CRT		SBRT		CRT		SBRT		CRT		SBRT		CRT		SBRT	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
RTOG GU																												
0	323	(81)	298	(76)	304	(75)	262	(70)	308	(77)	267	(70)	293	(76)	253	(65)	248	(78)	207	(67)	301	(80)	257	(72)	262	(82)	219	(70)
1	68	(17)	82	(21)	87	(21)	101	(27)	78	(20)	93	(25)	82	(21)	107	(27)	63	(20)	78	(25)	71	(19)	88	(25)	50	(16)	79	(25)
2	8	(2)	10	(3)	14	(3)	12	(3)	13	(3)	15	(4)	10	(3)	28	(7)	5	(2)	19	(6)	3	(1)	12	(3)	5	(2)	15	(5)
3	0	(0)	0	(0)	1	(<1)	2	(1)	0	(0)	4	(1)	1	(0)	2	(1)	1	(<1)	3	(1)	0	(0)	0	(0)	1	(<1)	1	(<1)
4	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)
missing	31		24		24		37		31		35		44		24		113		107		55		57		112		100	31
Grade 2+																												
Yes	8	(2)	10	(3)	15	(4)	14	(4)	13	(3)	19	(5)	11	(3)	30	(8)	6	(2)	22	(7)	3	(1)	12	(3)	6	(2)	16	(5)
No	391	(98)	380	(97)	391	(96)	363	(96)	386	(97)	360	(95)	375	(97)	360	(92)	311	(98)	285	(93)	372	(99)	345	(97)	312	(98)	298	(95)
p-value[2] Chi squared or Fisher's exact					0.60				0.99				0.0026				0.0015				0.015				0.028			

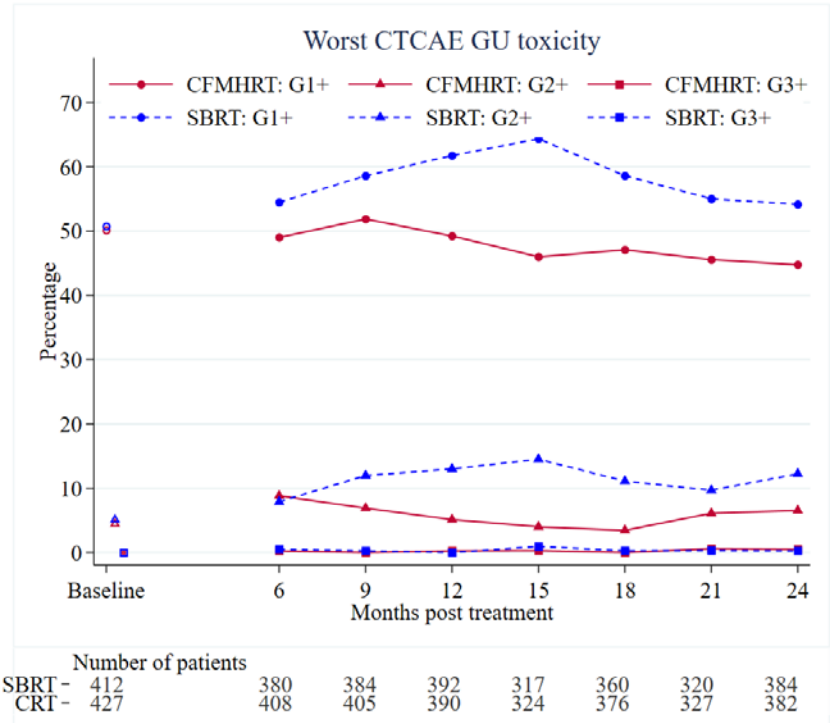
1. Baseline added for completeness
2. Fisher's exact test used where numbers in cells is ≤ 5
missing includes those not longer in follow up at visit

Figure 1: Incidence of RTOG GU toxicity between 6 and 24 months post-radiotherapy.



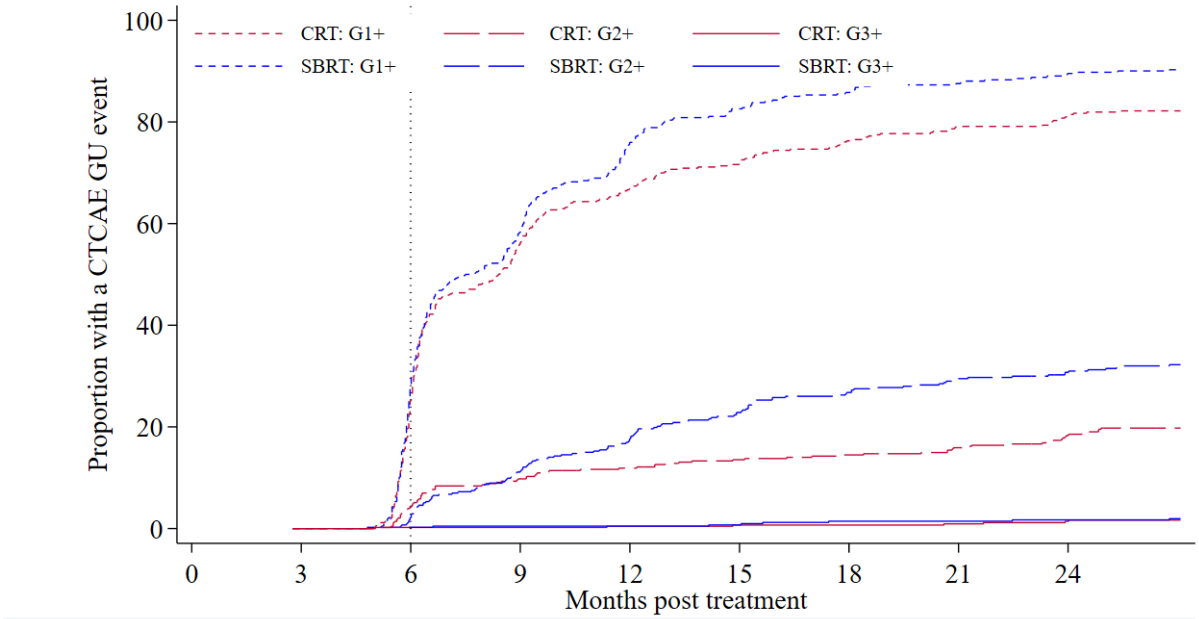
Grade 1+=grade 1 or worse adverse event. Grade 2+=grade 2 or worse adverse event. Grade 3+=grade 3 or worse adverse event.

Figure 2: Incidence of CTCAE GU toxicity between 6 and 24 months post-radiotherapy.



Grade 1+=grade 1 or worse adverse event. Grade 2+=grade 2 or worse adverse event. Grade 3+=grade 3 or worse adverse event.

Figure 3: Time to occurrence of Grades 1-3 CTCAE GU toxicity



Number at risk (cumulative censored)

SBRT: G3+	414(0)	414(0)	413(0)	410(2)	409(3)	405(6)	401(7)	398(10)	393(14)
CRT: G3+	430(0)	429(1)	428(1)	427(2)	422(6)	418(9)	418(9)	415(11)	407(17)
SBRT: G2+	414(0)	414(0)	405(0)	366(2)	338(3)	314(6)	297(7)	284(9)	275(13)
CRT: G2+	430(0)	429(1)	410(1)	387(1)	374(5)	365(7)	361(7)	353(9)	338(14)
SBRT: G1+	414(0)	414(0)	296(0)	172(1)	99(1)	71(2)	57(3)	50(3)	42(3)
CRT: G1+	430(0)	429(1)	321(1)	189(1)	141(2)	121(2)	101(2)	89(2)	81(2)

Figure 4: Incidence of individual CTCAE GU toxicities of grade 2 or higher between 6 and 24 months post-radiotherapy.

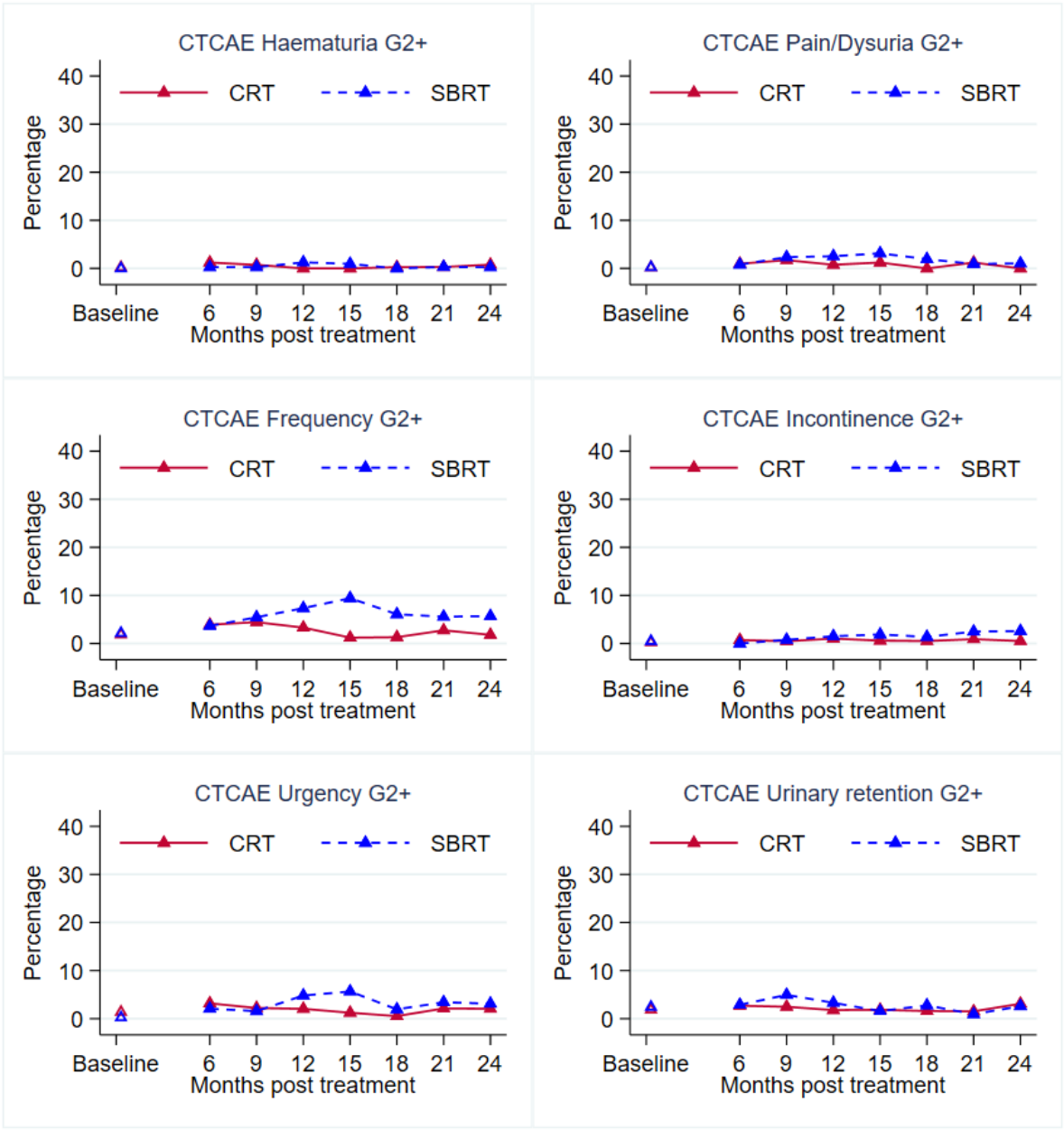


Table 10a. Grades for pre-specified RTOG GI terms at 24 months

RTOG Grade At 24 months	Proctitis				Diarrhoea				rectal stricture				Rectal ulcer				Bowel obstruction			
	CRT		SBRT		CRT		SBRT		CRT		SBRT		CRT		SBRT		CRT		SBRT	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
0	349	91	352	92	358	94	364	95	378	99	381	100	378	99	383	100	379	99	383	100
1	28	7	29	8	19	5	17	4	2	1	1	0	3	1	0	0	2	1	0	0
2	4	1	3	1	4	1	3	1	0	0	0	0	0	0	0	0	0	0	0	0
3	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
missing	48		30		49		30		50		32		49		31		49		31	
Grade 2+																				
Yes	5	1	3	1	4	1	3	1	0	0	0	0	0	0	0	0	0	0	0	0
No	377	99	381	99	377	99	381	99	380	100	382	100	381	100	383	100	381	100	383	100

Table 10b. Grades for non pre-specified RTOG GI terms at 24 months

RTOG Grade At 24 months	GI bleeding				Other GI			
	CRT		SBRT		CRT		SBRT	
	n	%	n	%	n	%	n	%
0	374	98	381	99	371	97	377	98
1	4	1	3	1	10	3	7	2
2	3	1	0	0	0	0	0	0
3	1	0	0	0	1	0	0	0
4	0	0	0	0	0	0	0	0
missing	48		30		48		30	
Grade 2+								
Yes	4	1	0	0	1	0	0	0
No	378	99	384	100	381	100	384	100

Table 10c. Grades for pre-specified CTCAE GI terms at 24 months

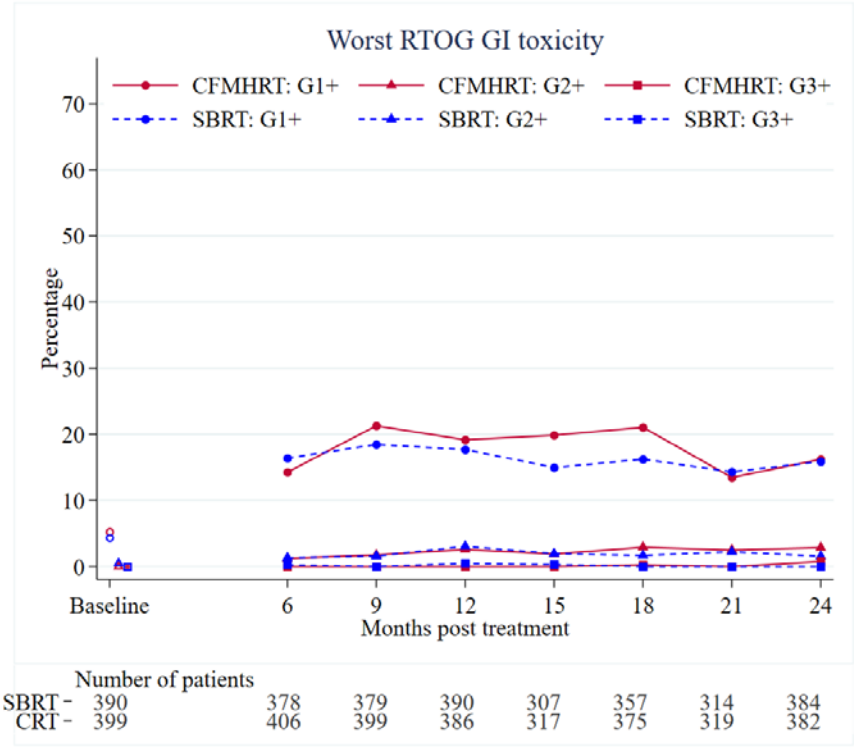
CTCAE Grade At 24 months	Colitis				Fistula				Haemorrhage				Constipation				Nausea				Rectal pain				Diarrhoea				Proctitis			
	CRT		SBRT		CRT		SBRT		CRT		SBRT		CRT		SBRT		CRT		SBRT		CRT		SBRT		CRT		SBRT		CRT		SBRT	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
0	379	99	376	98	372	100	377	100	337	88	355	92	353	92	359	93	372	98	382	99	372	97	374	97	360	94	364	95	352	92	356	92
1	5	1	9	2	1	<1	0	0	40	10	28	7	26	7	21	5	7	2	2	1	10	3	10	3	19	5	17	4	27	7	25	6
2	0	0	0	0	0	0	0	0	6	2	1	<1	4	1	4	1	0	0	0	0	1	<1	0	0	4	1	4	1	5	1	4	1
3	0	0	0	0	0	0	0	0	1	<1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
missing	46		29		57		37		46		30		47		30		51		30		47		30		47		29		46		29	
Grade 2+																																
Yes	0	0	0	0	0	0	0	0	7	2	1	<1	4	1	4	1	0	0	0	0	1	<1	0	0	4	1	4	1	5	1	4	1
No	384	100	385	100	373	100	377	100	377	98	383	100	379	99	380	99	379	100	384	100	382	100	384	100	379	99	381	99	379	99	381	99

Table 11b Worst GI RTOG toxicity from 6 to 21 months post treatment

Worst Grade	Baseline[1]				6 months				9 months				12 months				15 months				18 months				21 months			
	CRT		SBRT		CRT		SBRT		CRT		SBRT		CRT		SBRT		CRT		SBRT		CRT		SBRT		CRT		SBRT	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
RTOG GI																												
0	378	(95)	373	(96)	348	(86)	316	(84)	314	(79)	309	(82)	312	(81)	321	(82)	254	(80)	261	(85)	296	(79)	299	(84)	276	(87)	269	(86)
1	21	(5)	15	(4)	53	(13)	57	(15)	78	(20)	64	(17)	64	(17)	57	(15)	57	(18)	40	(13)	68	(18)	52	(15)	35	(11)	38	(12)
2	0	(0)	2	(1)	5	(1)	4	(1)	7	(2)	6	(2)	10	(3)	10	(3)	6	(2)	5	(2)	10	(3)	6	(2)	8	(3)	7	(2)
3	0	(0)	0	(0)	0	(0)	1	(<1)	0	(0)	0	(0)	0	(0)	2	(1)	0	(0)	1	(<1)	1	(<1)	0	(0)	0	(0)	0	(0)
4	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)
5	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)
missing	31		26		29		41		38		41		54		36		119		113		66		63		119		107	
Grade 2+																												
Yes	0	(0)	2	(1)	5	(1)	5	(1)	7	(2)	6	(2)	10	(3)	12	(3)	6	(2)	6	(2)	11	(3)	6	(2)	8	(3)	7	(2)
No	399	(100)	388	(100)	401	(99)	373	(99)	392	(98)	373	(98)	376	(97)	378	(97)	311	(98)	301	(98)	364	(97)	351	(98)	311	(98)	307	(98)
p-value[2]																												
Chi squared or									0.85				0.68				0.95				0.26				0.82			
Fisher's exact					1.00																							

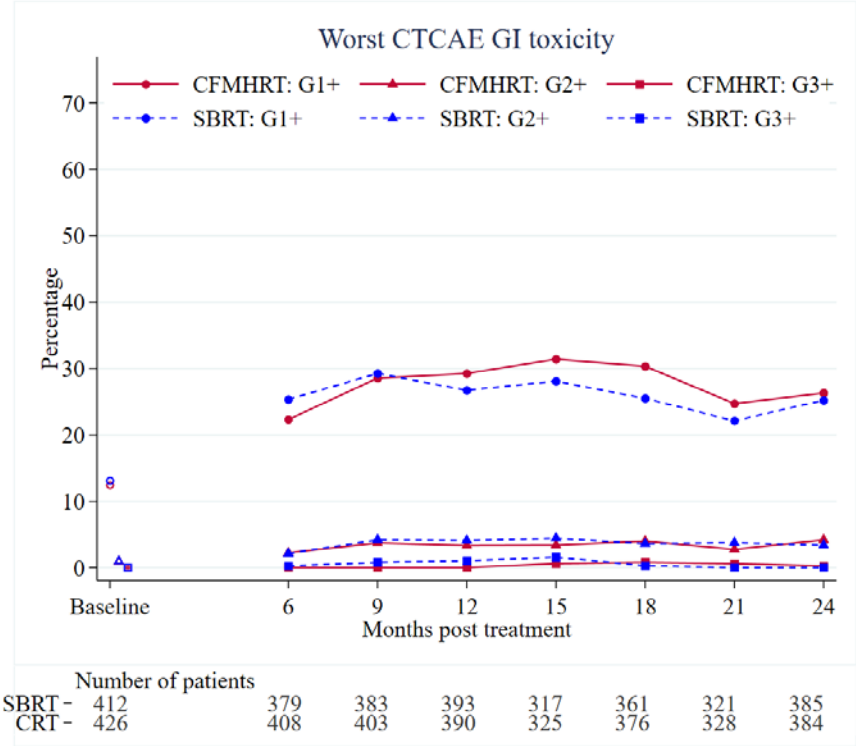
1. Baseline added for completeness
2. Fisher's exact test used where numbers in cells is ≤ 5
missing includes those no longer in follow up at visit

Figure 5: Incidence of RTOG GI toxicity between 6 and 24 months post-radiotherapy.



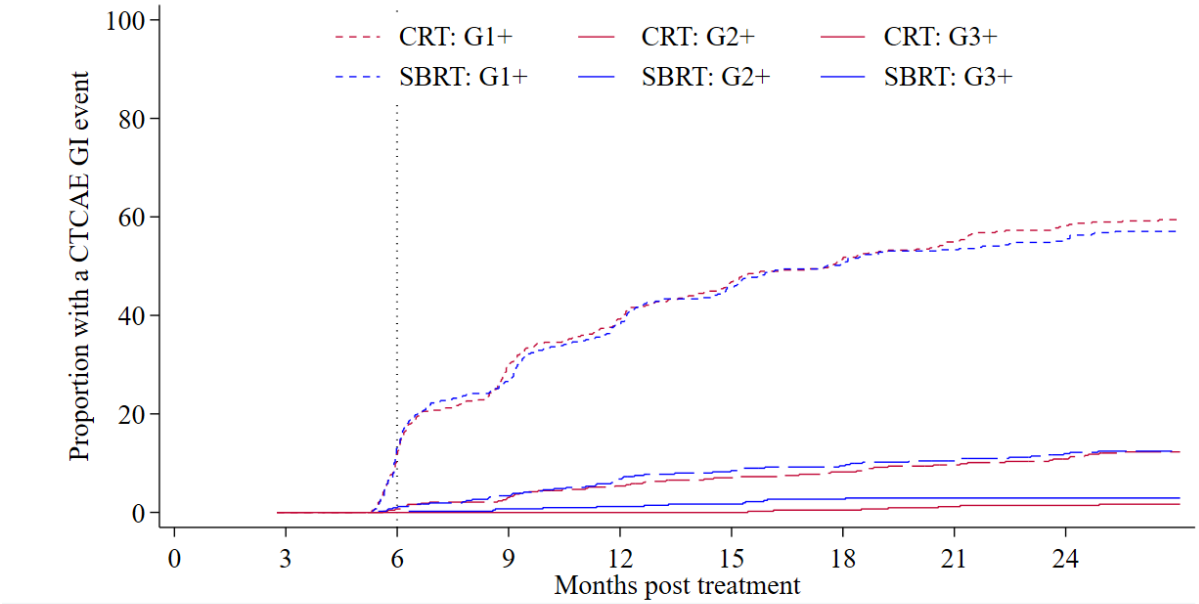
G1+=grade 1 or worse adverse event. G2+=grade 2 or worse adverse event. G3+=grade 3 or worse adverse event.

Figure 6: Incidence of CTCAE GI toxicity between 6 and 24 months post-radiotherapy



G1+=grade 1 or worse adverse event. G2+=grade 2 or worse adverse event. G3+=grade 3 or worse adverse event.

Figure 7: Time to occurrence of grades 1-3 CTCAE GI toxicity between 6 and 24 months post-radiotherapy



Number at risk (cumulative censored)

SBRT: G3+ −	414(0)	414(0)	414(0)	409(2)	406(3)	401(6)	396(7)	392(10)	388(14)
CRT: G3+ −	430(0)	429(1)	429(1)	428(2)	425(5)	422(8)	419(9)	413(12)	406(18)
SBRT: G2+ −	414(0)	414(0)	410(0)	398(2)	384(2)	374(5)	369(6)	362(9)	352(13)
CRT: G2+ −	430(0)	429(1)	426(1)	415(2)	402(5)	392(8)	387(8)	378(11)	367(17)
SBRT: G1+ −	414(0)	414(0)	360(0)	302(2)	254(2)	223(2)	203(2)	190(4)	180(6)
CRT: G1+ −	430(0)	429(1)	378(1)	301(2)	258(4)	224(6)	205(6)	190(6)	174(8)

Figure 8: Incidence of individual CTCAE GI toxicities of grade 2 or higher between 6 and 24 months post-radiotherapy

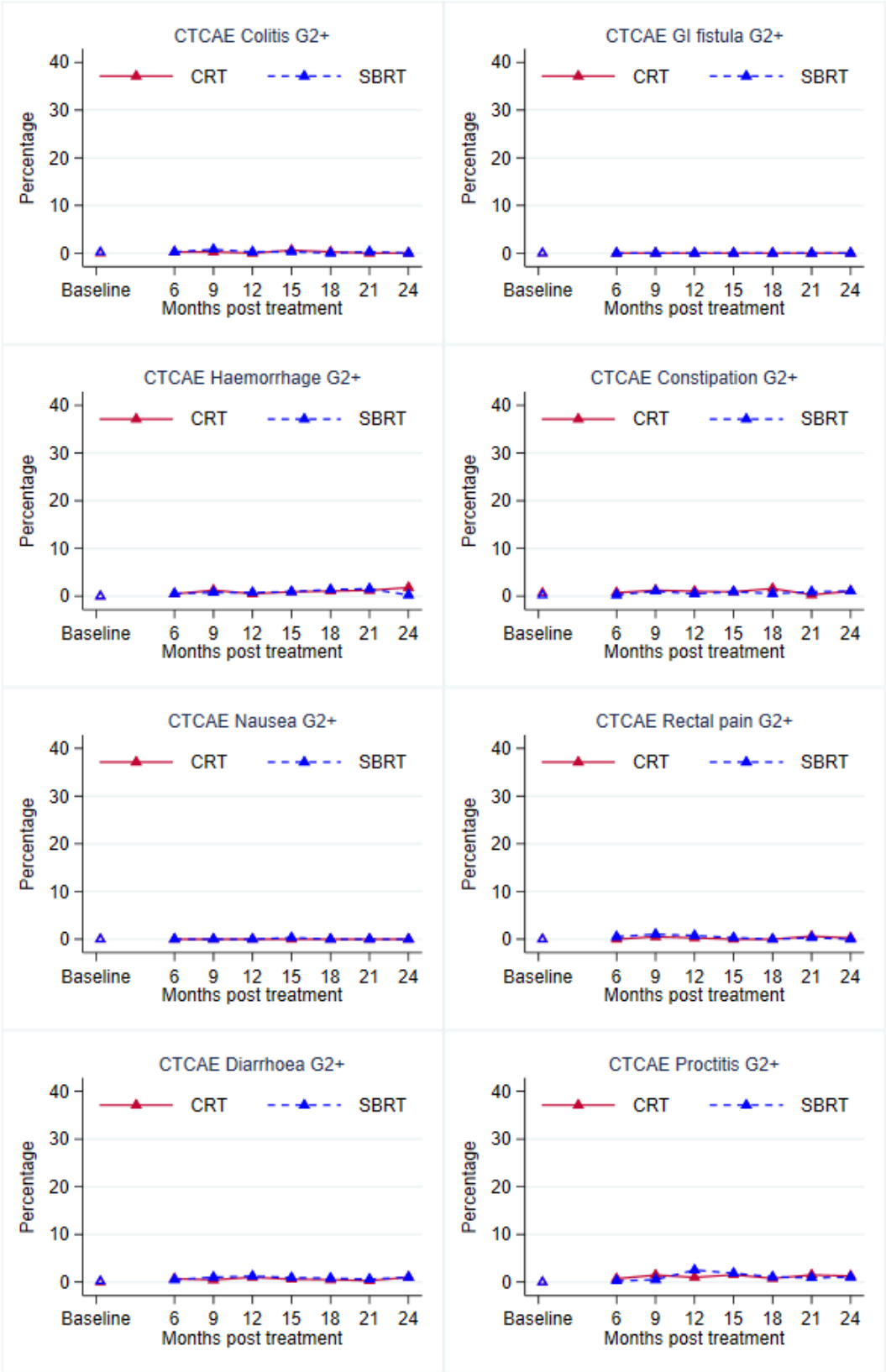


Table 12. Grades for pre-specified CTCAE non GI/GU terms at 24 months

CTCAE Grade At 24 months	Erectile dysfunction				Dermatitis radiation				Hot flashes				Weight loss				Pain				Fatigue				Anorexia				Other			
	CRT		SBRT		CRT		SBRT		CRT		SBRT		CRT		SBRT		CRT		SBRT		CRT		SBRT		CRT		SBRT		CRT		SBRT	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
0	121	35	130	37	355	99	351	100	357	96	369	97	370	98	374	98	342	90	346	93	310	82	299	78	374	98	379	100	369	96	364	95
1	114	33	100	28	3	1	1	0	15	4	9	2	8	2	6	2	29	8	25	7	61	16	80	21	5	1	1	0	7	2	10	3
2	83	24	96	27	0	0	0	0	0	0	2	1	1	0	0	0	7	2	2	1	9	2	2	1	2	1	0	0	4	1	5	1
3	32	9	25	7	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0	0	0	2	1	6	2
4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	1	0	0
missing	80		63		72		62		58		34		51		34		52		40		50		32		49		34		46		29	
Grade 2+																																
Yes	115	33	121	34	0	0	0	0	0	0	2	1	1	0	0	0	7	2	3	1	9	2	3	1	2	1	0	0	8	2	11	3
No	235	67	230	66	358	100	352	100	372	100	378	99	378	100	380	100	371	98	371	99	371	98	379	99	379	99	380	100	376	98	374	97

Figure 9: Incidence of CTCAE erectile dysfunction by grade between 6 and 24 months post-radiotherapy.

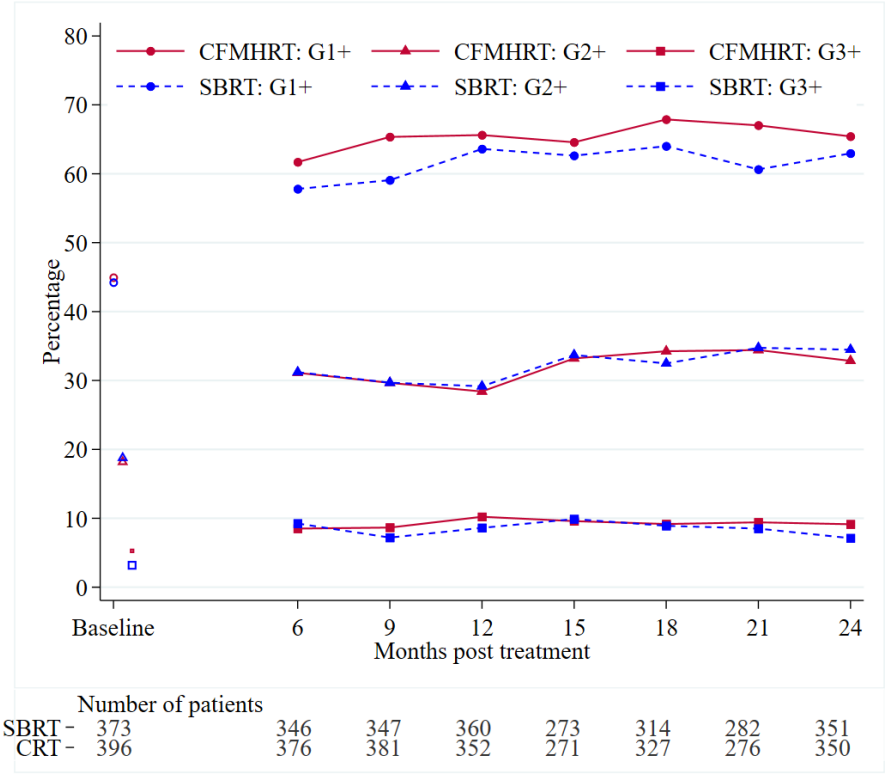


Figure 10: Incidence of individual CTCAE non-GU and non-GI toxicities of grade 2 or higher between 6 and 24 months post-radiotherapy.

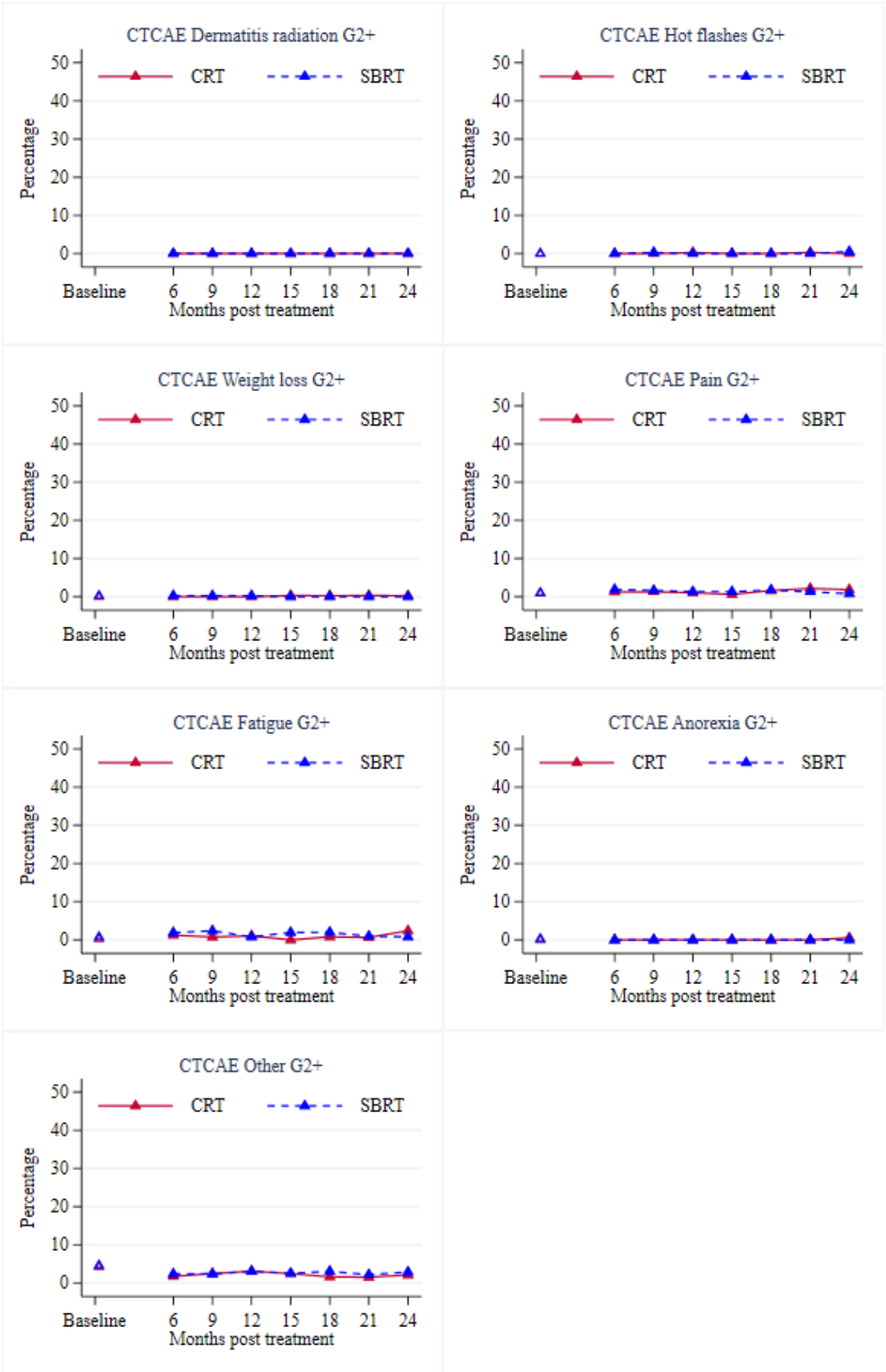


Table 13: Comparison of median scores for EPIC-26 composite scores
The EPIC-26 form is a short form version of the full Expanded Prostate cancer Index Composite (EPIC) form and contains 26 items and has 5 domains: urinary incontinence, urinary irritative/obstructive, bowel, sexual, and hormonal. EPIC was developed to measure health related quality of life among men with prostate cancer. Response options for each EPIC item form a Likert scale, and multi-item scale scores are transformed linearly to a 0-100 scale, with higher scores representing better health related quality of life.

EPIC-26 domain	Treatment received						Mann-Whitney test
	CRT			SBRT			
	n	Median	IQR	n	Median	IQR	p-value
Urinary incontinence							
Baseline	367	100	85.5-100	343	100	85.5-100	0.95
24 months post treatment	312	100	79.3-100	309	93.8	79.3-100	0.069
Urinary irritative/obstructive							
Baseline	361	87.5	81.3-100	331	93.8	81.3-100	0.60
24 months post treatment	301	93.8	87.5-100	294	93.8	81.3-100	0.018
Bowel							
Baseline	367	100	95.8-100	347	100	91.7-100	0.021
24 months post treatment	305	95.8	87.5-100	309	100	87.5-100	0.10
Sexual							
Baseline	349	52.8	26.3-75	340	48.7	22.2-75	0.23
24 months post treatment	300	36.2	16.7-66.7	300	34.7	16.7-65.3	0.28
Hormonal							
Baseline	370	97.5	90-100	347	95	90-100	0.82
24 months post treatment	302	97.5	90-100	312	95	85-100	0.11

Table 14. EPIC-26 score reductions at 24 months post radiotherapy exceeding minimal clinically important differences

A clinically important point reduction in EPIC-26 subdomain score defined separately by domain: urinary incontinence (8 point) urinary obstructive (6 point), bowel (5 point), sexual (11 point), hormonal (5 point). Here we show EPIC-26 score reductions at 24 months post radiotherapy exceeding minimal clinically important differences. A reduction in EPIC-26 score corresponds to a lower health related quality of life.

EPIC-26 MCID reduction at 24 Months	Treatment received				Chi-square test
	CRT		SBRT		
	n	%	n	%	p-value
Urinary incontinence					
No	213	76%	178	68%	0.011
Yes	62	23%	85	32%	
Missing Data	155		151		
Urinary irritative/obstructive					
No	195	74%	162	67%	0.12
Yes	70	26%	79	33%	
Missing Data	165		173		
Bowel					
No	177	66%	203	76%	0.0076
Yes	93	34%	64	24%	
Missing Data	160		147		
Sexual					
No	131	51%	148	57%	0.19
Yes	126	49%	113	43%	
Missing Data	173		153		
Hormonal					
No	193	72%	185	68%	0.38
Yes	77	29%	87	32%	
Missing Data	160		142		

Figure 11. Proportion patients with a benefit or reduction that exceeds the MCID for EPIC-26 urinary incontinence

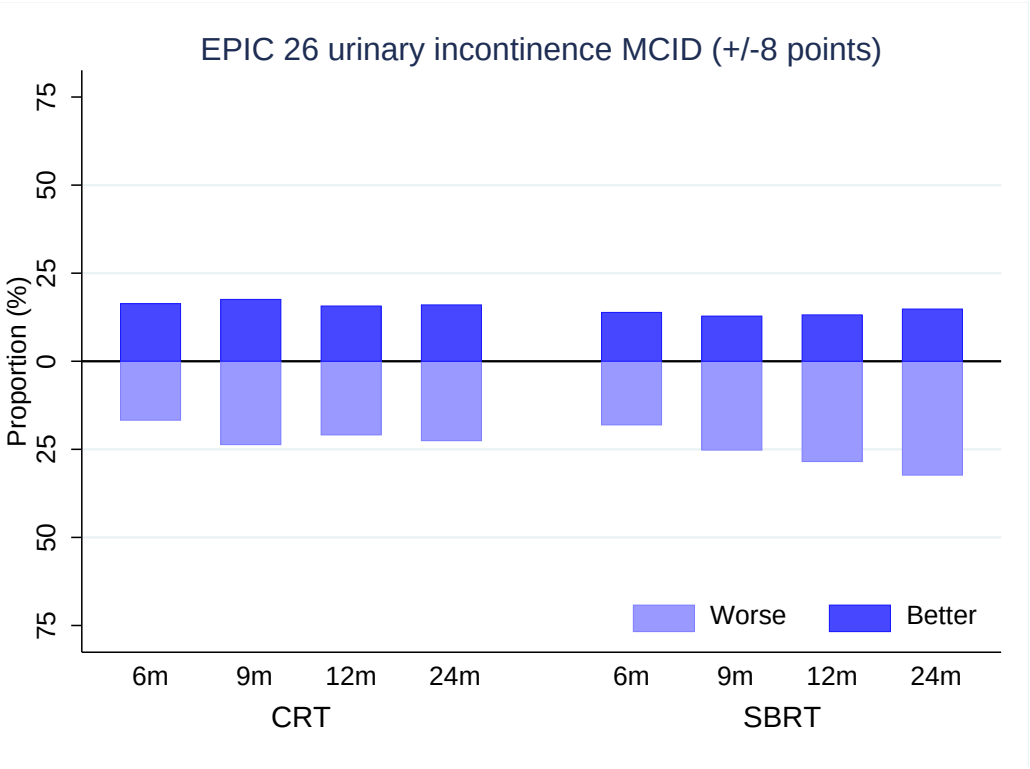


Figure 12. Proportion of patients with a benefit or reduction that exceeds the MCID for EPIC-26 urinary irritative/obstructive

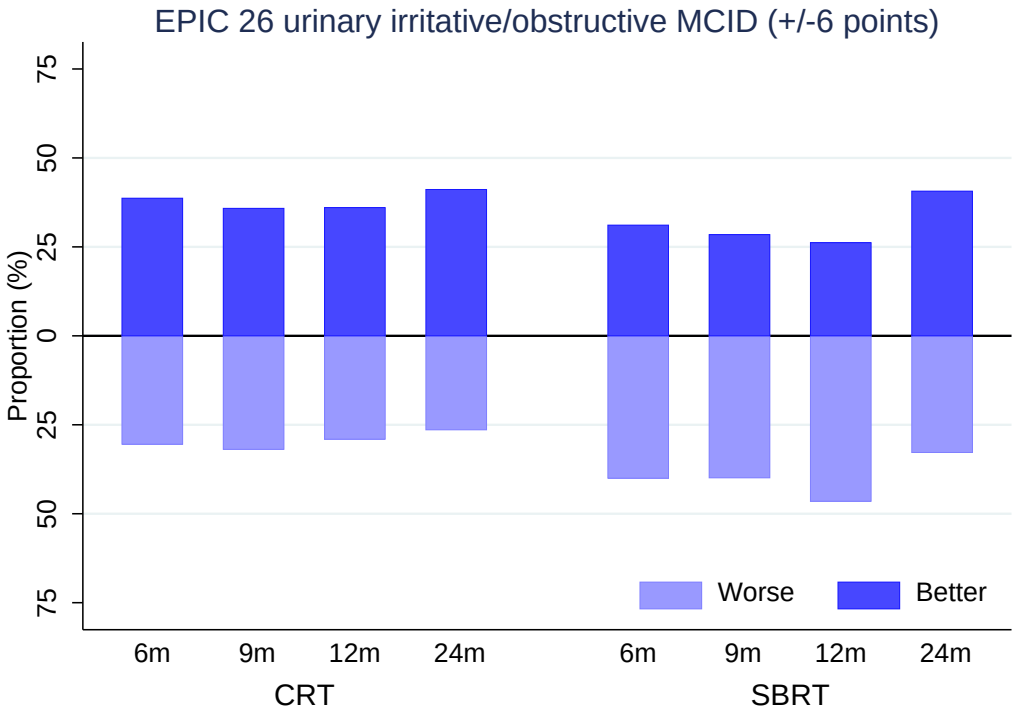


Figure 13: Proportion of patients with a benefit or reduction that exceeds the MCID for EPIC-26 Bowel

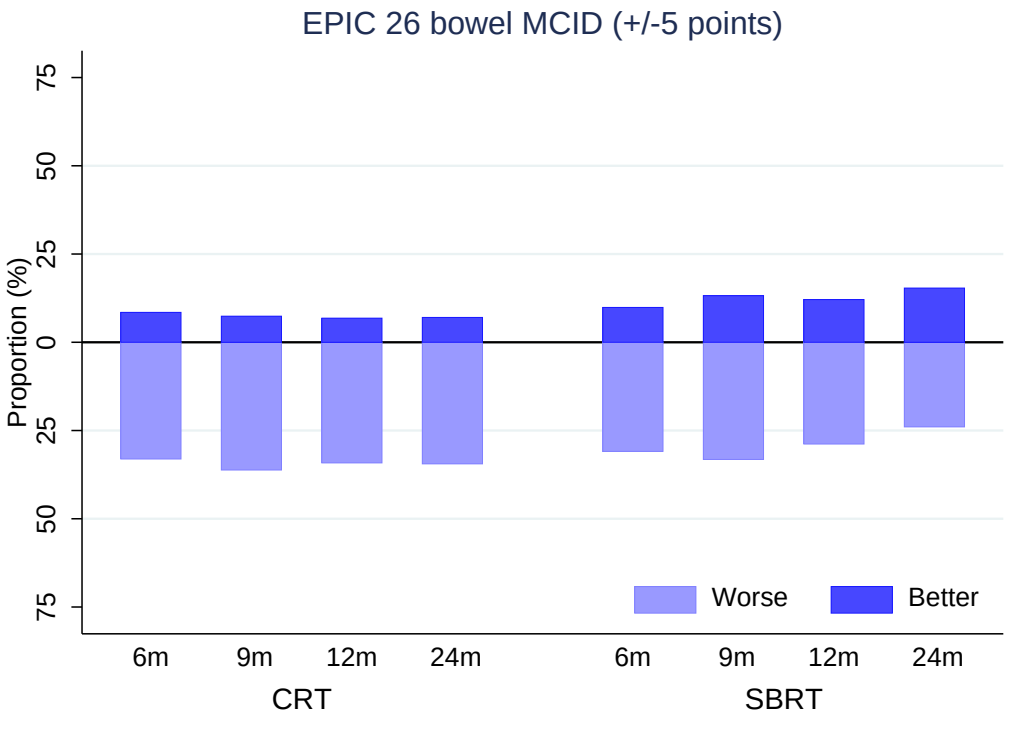


Table 15: Comparison of EPIC-26 overall urinary bother at baseline and 24 months post treatment

	CRT		SBRT		
	n	**%**	**n**	**%**	**Chi-square test (p-value)**
Overall urinary function at baseline					
No problem/very small problem/small problem	355	(93)	337	(92)	0.66
Moderate problem/big problem	27	(7)	29	(8)	
Overall urinary function at 24 months post treatment					
No problem/very small problem/small problem	308	(95)	294	(90)	0.014
Moderate problem/big problem	17	(5)	34	(10)	

Table 16: Comparison of EPIC-26 overall bowel bother at baseline and 24 months post treatment

	CRT		SBRT		
	n	**%**	**n**	**%**	**Chi-square test (p-value)**
Overall bowel bother at baseline					
No problem/very small problem/small problem	376	(98)	362	(98)	0.95
Moderate problem/big problem	6	(2)	6	(2)	
Overall bowel bother at 24 months post treatment					
No problem/very small problem/small problem	312	(96)	311	(95)	0.57
Moderate problem/big problem	12	(4)	15	(5)	

Table 17: IPSS total score and QoL score at baseline and 24 months post treatment
The International prostate symptom score (IPSS) questionnaire contains 7 questions relating to different GU symptoms the patient might be experiencing and one question relating to the patient's overall quality of life. The 7 GU questions include cover incomplete bladder emptying, frequency of urination, intermittency, urgency, weak stream, straining, and nocturia. Once the patient has scored each question, the values are added together to give an indication of the severity of their symptoms. A score of 1-7 is categorised as mildly symptomatic, 8-19 is categorised as moderately symptomatic, and 20-35 is categorised as severely symptomatic

IPSS parameter	Treatment received						Mann-Whitney
	CRT			SBRT			
	n	Median	IQR	n	Median	IQR	p-value
IPSS total score							
Baseline	359	6	3 – 11	340	6	3-11	0.55
24 months post treatment	301	6	2-10	293	7	3 – 11	0.0075
IPSS QoL score							
Baseline	394	2	1 – 3	379	1	1 – 3	0.62
24 months post treatment	304	1	0 – 2	302	1	1-3	0.0022

Figure 14: Total IPSS scores at baseline and 24 months by treatment received
A higher score indicates worse function

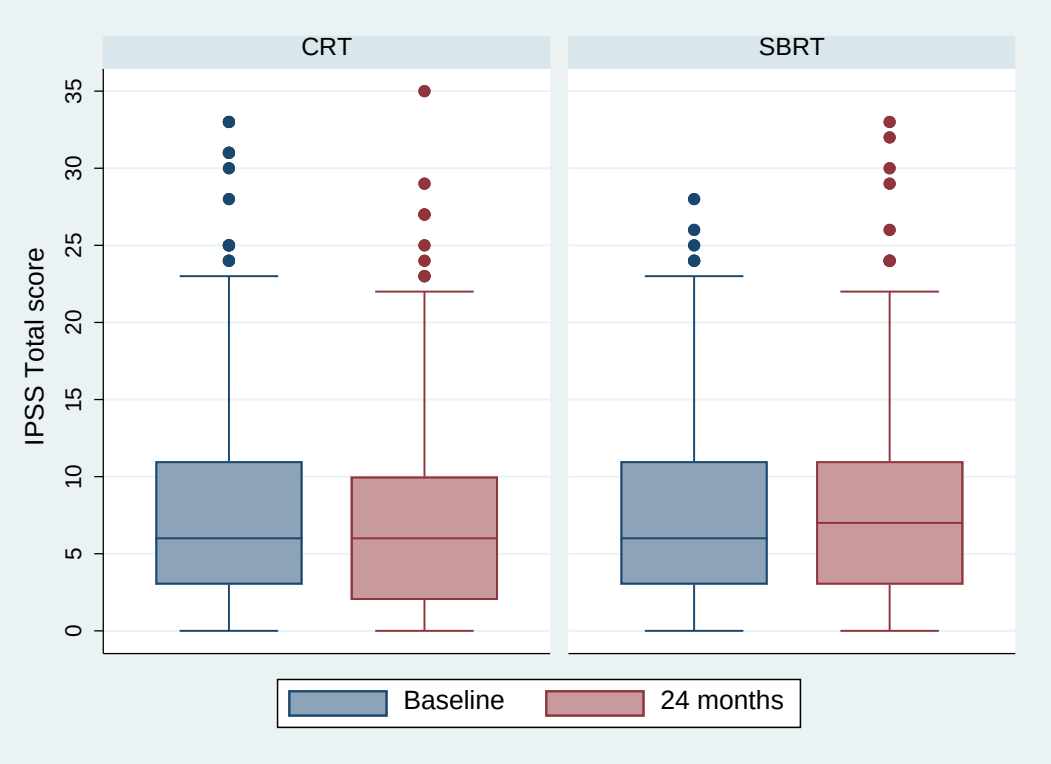
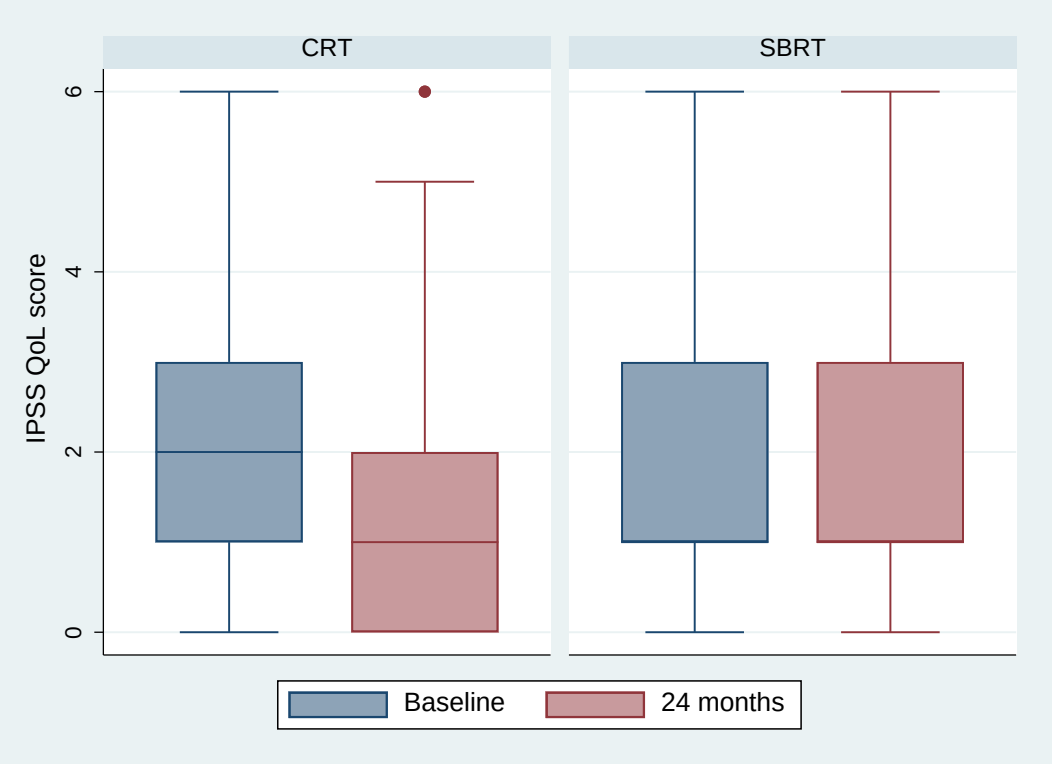


Figure 15: IPSS quality of life score at baseline and 24 months by treatment received
A higher score indicates worse function



Median represented by horizontal line in box; where no line visible the median and 25th percentile are the same

Table 18: IPSS total score categories at baseline and 24 months post treatment

IPSS Total Score Categories	Treatment received			
	CRT		SBRT	
	n	%	n	%
Baseline				
None	20	6	16	5
Mild (1-7)	183	51	186	55
Moderate (8-19)	134	37	121	36
Severe (20-35)	22	6	17	5
24 months post treatment				
None	20	7	9	3
Mild (1-7)	173	58	148	51
Moderate (8-19)	93	31	118	40
Severe (20-35)	15	5	18	6
Chi square test for trend (p-value)	0.0056			

Table 19: IIEF-5 total scores at baseline and 24 months post treatment

The International Index of Erectile Function -5 Questionnaire (IIEF-5) contains 5 items, and each IIEF-5 item is scored on a five-point ordinal scale where lower values represent poorer sexual function. A response of 0 for a question was considered the least functional, whereas a response of 5 was considered the most functional. The possible scores for the IIEF-5 range from 1 to 25 (one question has scores of 1–5). According to this scale, ED is classified into four categories based on IIEF-5 scores: severe (1–7), moderate (8–11), mild to moderate (12–16), mild (17–21), and no ED (22–25).

IIEF – 5 Scores	Treatment received						Mann-Whitney
	CRT			SBRT			
	n	Median	IQR	n	Median	IQR	p-value
Baseline	308	16	8-21	293	14	7-20	0.14
24 months post treatment	242	12	5-18	233	10	5-18	0.29

Figure 16: Total IIEF-5 score at baseline and 24 months post treatment by treatment received

A higher score represents better function

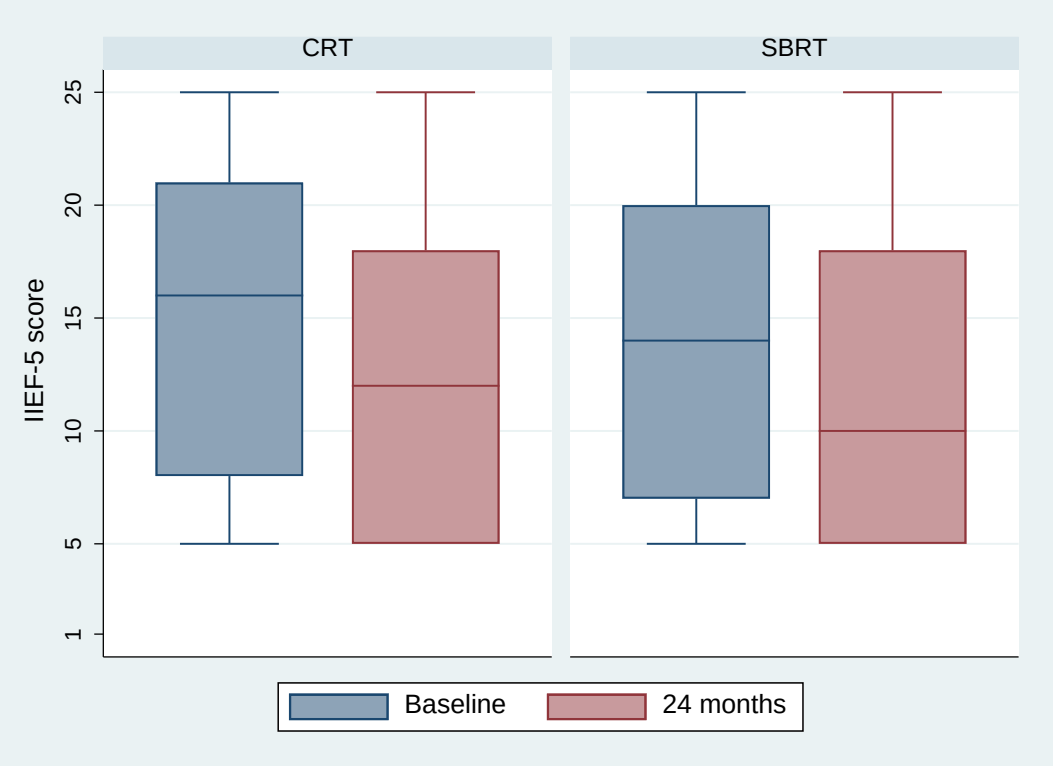


Table 20: Median Vaizey scores at baseline and 24 months by treatment recevied

A higher score indicates worse function

	Treatment Received						Mann-Whitney test
	CRT			SBRT			
	n	Median	IQR	n	Median	IQR	p-value
Total Vaizey Score							
Baseline	355	1	0-4	341	1	0-4	0.80
24 months post treatment	306	2	0-5	298	2	0-5	0.75

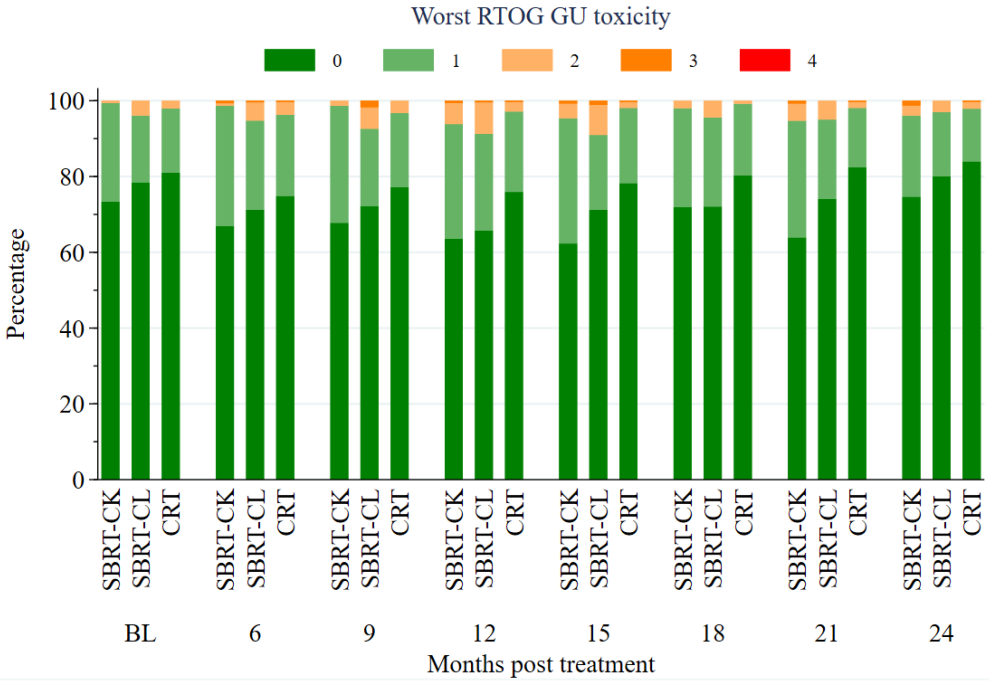
Table 21: Baseline characteristics for patients receving SBRT, by treatment platform;

SBRT-CK = SBRT delivered by CyberKnife; SBRT-CL = SBRT delivered on conventional linac

Baseline characteristics	SBRT-CK (N=170)		SBRT-CL (N=244)		Test for differences between groups (N=414)
	n	%	n	%	
T-Stage[1]					
T1c	19	(11)	58	(24)	0.00097 (T1 vs T2)
T2a	47	(28)	56	(23)	
T2b	40	(24)	40	(16)	
T2c	64	(38)	87	(36)	
Risk group[1]					
Low	21	(12)	14	(6)	0.017
Intermediate	149	(88)	230	(94)	
Gleason score[1]					
3+3	36	(21)	25	(10)	0.0020
3+4	134	(79)	219	(90)	
Prostate volume[2]					
<40 mL	69	(41)	96	(39)	0.59
40 - <80 mL	76	(45)	98	(40)	
80+ mL	10	(6)	11	(5)	
Unknown	15	(9)	39	(16)	
Alpha blockers at randomisation[1]					
Yes	18	(11)	52	(21)	0.0046
No	150	(88)	191	(78)	
Unknown	2	(1)	1	(<1)	
Aspirin at randomisation[1]					
Yes	15	(9)	54	(22)	0.00050
No	151	(89)	190	(78)	
Unknown	4	(2)	0	(0)	
Statin at randomisation[1]					
Yes	37	(22)	95	(39)	0.00046
No	128	(75)	149	(61)	
Unknown	5	(3)	0	(0)	
Anticholinergic for bladder symptoms at randomisation[1]					
Yes	2	(13)	8	(3)	0.21
No	164	(97)	236	(97)	
Unknown	4	(2)	0	(0)	
Age at randomisation (years)[3]					
Median (IQR)	68.8	(65.3, 73.3)	70.2	(65.5, 74.6)	0.098
N (Range)	170	(49.2, 82.7)	244	(45.8, 84.5)	
PSA (ng/mL)[3]					
Median (IQR)	7.7	(5.3, 10.9)	8.3	(5.8, 11.0)	0.56
N (Range)	170	(1.3, 20.0)	244	(0.5, 18.9)	
Time from biopsy to randomisation (weeks)[3]					
Median (IQR)	9.7	(6.7, 17.1)	9.9	(6.6, 16.1)	0.48
N (Range)	170	(0.1, 107.1)	244	(2.0, 225.0)	

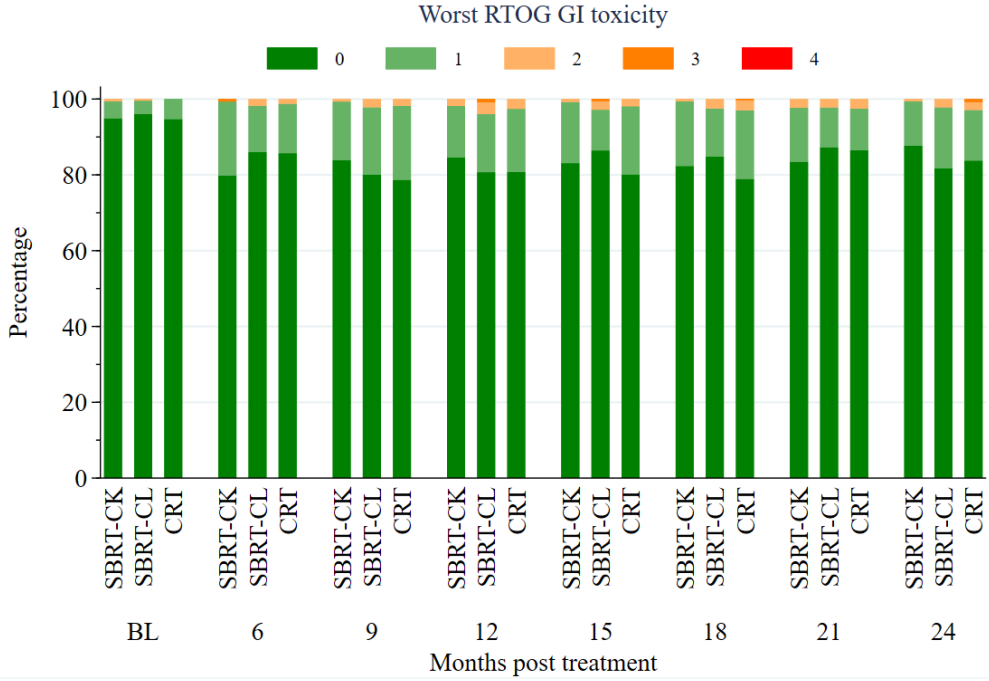
Test used were: 1. Chi-square trend test for ordinal, 2. Chi-square test for binary variables 3. t-test for continuous data

Figure 17: RTOG GU toxicity by treatment platform for SBRT delivery
SBRT-CK = SBRT delivered by CyberKnife; SBRT-CL = SBRT delivered on conventional linac; CRT = conventional radiotherapy



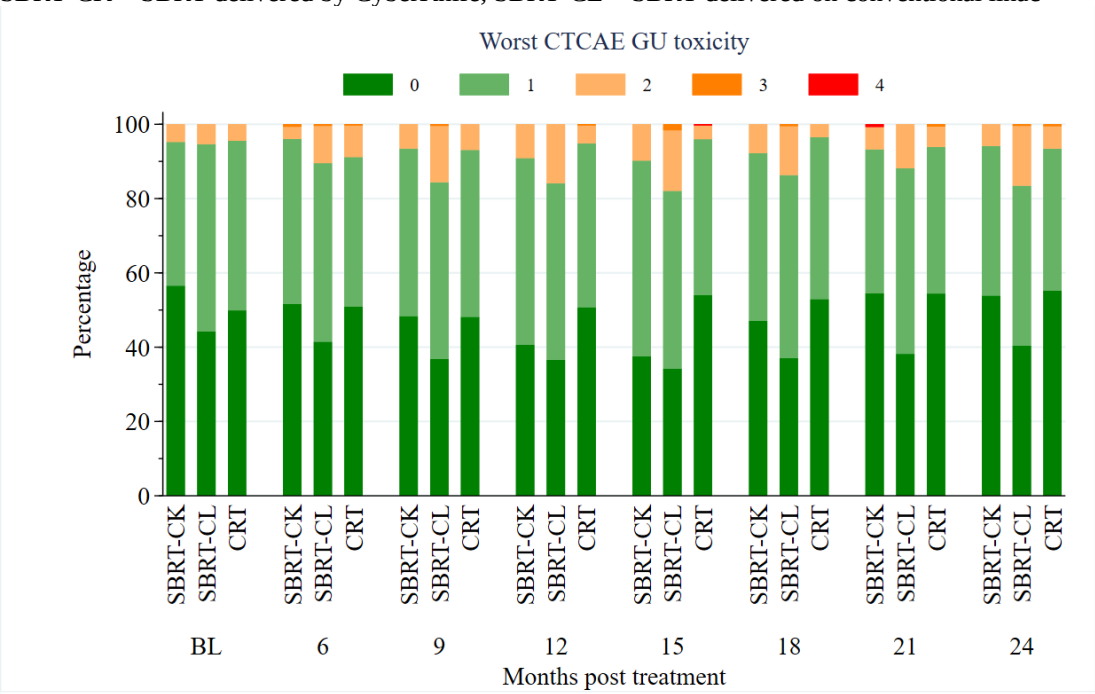
Number of patients								
CRT	399	406	399	386	317	375	318	381
SBRT-CL	232	229	230	228	177	204	181	230
SBRT-CK	158	148	149	162	130	153	133	154

Figure 18: RTOG GI toxicity by treatment platform for SBRT delivery
SBRT-CK = SBRT delivered by CyberKnife; SBRT-CL = SBRT delivered on conventional linac: CRT = conventional radiotherapy



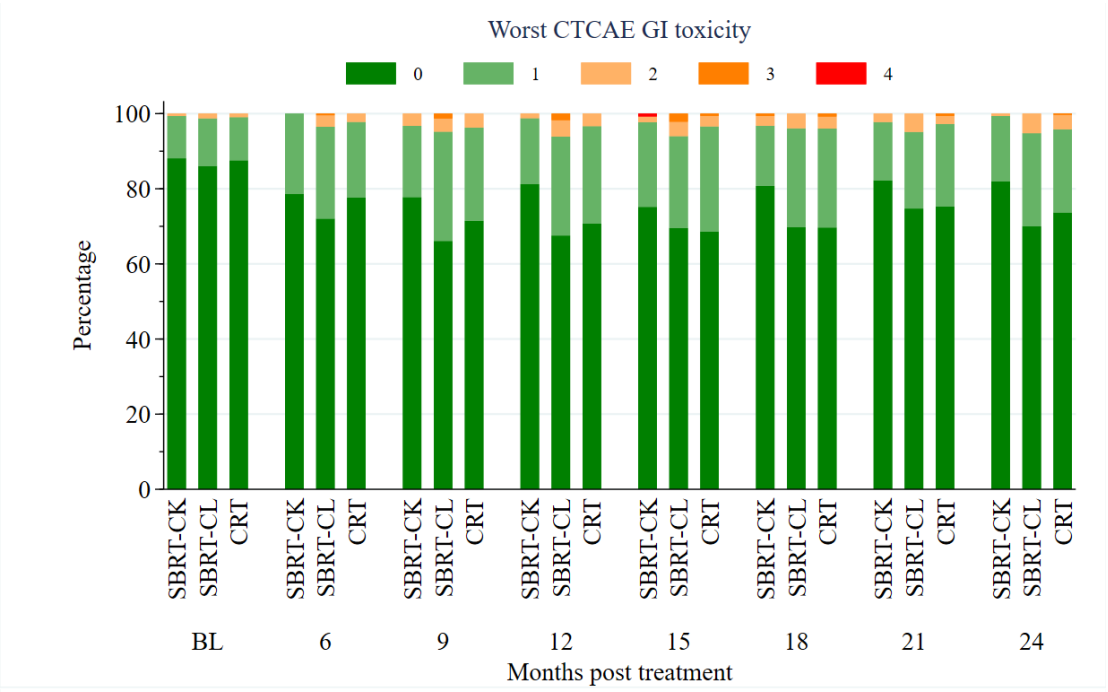
Number of patients								
CRT	399	406	399	386	317	375	319	382
SBRT-CL	232	229	230	228	177	204	181	230
SBRT-CK	158	149	149	162	130	153	133	154

Figure 19: CTCAE GU toxicity by treatment platform for SBRT delivery
SBRT-CK = SBRT delivered by CyberKnife; SBRT-CL = SBRT delivered on conventional linac



Number of patients								
CRT	427	408	405	390	324	376	327	382
SBRT-CL	244	229	231	227	184	205	186	230
SBRT-CK	168	151	153	165	133	155	134	154

Figure 20: CTCAE GI toxicity by treatment platform for SBRT delivery;
SBRT-CK = SBRT delivered by CyberKnife; SBRT-CL = SBRT delivered on conventional linac



Number of patients								
CRT	426	408	403	390	325	376	328	384
SBRT-CL	244	229	230	228	184	205	186	230
SBRT-CK	168	150	153	165	133	156	135	155

Table 22: Worst grade toxicity recorded at 24 months by SBRT platform in use at centre and treatment received

Of the 430 patients treated with CRT, 6 were treated at centres not delivering any SBRT, so are excluded from these comparison. Of the 414 patients that received SBRT, 188 had their treatment at a cyberknife centre. 18 of these patients received SBRT on a conventional linac and so are excluded from these comparison.

CRT=conventional radiotherapy; SBRT-CK = SBRT delivered by CyberKnife; SBRT-CL = SBRT delivered on conventional linac. Fishers exact test used when numbers in cells <=5.

Table 18a: Worst RTOG GU toxicity at 24 months

Worst RTOG GU toxicity	CyberKnife centres				Conventional linac centres			
	SBRT-CK (N=170)		CRT (N=186)		SBRT-CL (N=226)		CRT (N=238)	
	n	%	n	%	n	%	n	%
Worst grade								
0	115	75	137	81.1	174	82	180	87
1	33	21	29	17	31	15	22	11
2	4	3	3	2	7	3	4	2
3	2	1	0	0	0	0	1	1
4	0	0	0	0	0	0	0	0
Unobtainable/missing	16		17		14		31	16
Grade 2+								
Yes	6	4	3	2	7	3	5	2
No	148	96	166	98	205	97	202	98
Comparisons (G2+)								
Fishers exact (p)	SBRT v CRT in CK centres		0.32					
Fishers exact (p)					SBRT-CL v CRT in CL centres		0.77	
Chi-squared (p)	SBRT-CK v SBRT-CL				0.77			
Fishers exact (p)			CRT in CK centres v CRT in CL centres				0.74	

Table 18b: Worst RTOG GI toxicity at 24 months

Worst RTOG GI toxicity	CyberKnife centres				Conventional linac centres			
	SBRT-CK (N=170)		CRT (N=186)		SBRT-CL (N=226)		CRT (N=238)	
	n	%	n	%	n	%	n	%
Worst grade								
0	135	88	138	81	172	81	177	86
1	18	12	26	15	36	17	25	12
2	1	1	4	2	4	2	4	2
3	0	0	2	1	0	0	1	1
4	0	0	0	0	0	0	0	0
Unobtainable/missing	16		16		14		31	
Grade 2+								
Yes	1	1	6	4	4	2	5	2
No	153	99	164	97	208	98	202	98
Comparisons (G2+)								
Fisher's exact(p)	SBRT v CRT in CK centres		0.12					
Fisher's exact(p)					SBRT-CL v CRT in CL centres		0.75	
Fisher's exact(p)	SBRT-CK v SBRT_CL				0.40			
Fisher's exact(p)			CRT in CK centres v CRT in CL centres				0.56	

Table 18c: Worst CTCAE GU toxicity at 24 months

Worst CTCAE GU toxicity	Cyberknife centres				Conventional Linac centres			
	SBRT-CK (N=170)		CRT (N=186)		SBRT-CL (N=226)		CRT (N=238)	
	n	%	n	%	n	%	n	%
Worst grade								
0	84	54	107	62	90	43	103	50
1	62	40	58	34	87	41	85	41
2	9	6	7	4	34	16	16	8
3	0	0	0	0	1	1	2	1
4	0	0	0	0	0	0	0	0
Unobtainable/missing	16		14		14		33	
Grade 2+								
Yes	9	6	7	4	35	17	18	8
No	145	94	165	96	177	84	187	91
Comparisons (G2+)								
Chi-squared (p)	SBRT v CRT in CK centres		0.46					
Chi-squared (p)					SBRT-CL v CRT in CL centres		0.019	
Chi-squared (p)	SBRT-CK v SBRT-CL				0.0020			
Chi-squared (p)			CRT in CK centres v CRT in CL centres				0.095	

Table 18d. Worst CTCAE GI toxicity at 24 months

Worst CTCAE GI toxicity	Cyberknife centres				Conventional linac centres			
	SBRT-CK (N=170)		CRT (N=186)		SBRT-CL (N=226)		CRT (N=238)	
	n	%	n	%	n	%	n	%
Worst grade								
0	127	(82)	135	(77)	147	(70)	145	(70)
1	27	(17)	33	(19)	54	(25)	52	(25)
2	1	(1)	7	(4)	11	(5)	8	(4)
3	0	(0)	0	(0)	0	(0)	1	(1)
4	0	(0)	0	(0)	0	(0)	0	(0)
Unobtainable/missing	15		13		14		32	
Grade 2+								
Yes	1	1	7	4	11	5	9	4
No	154	99	166	96	201	95	197	96
Comparisons (G2+)								
Fisher's Exact(p)	SBRT v CRT in CK centres		0.070					
Chi-squared (p)					SBRT-CL v CRT in CL centres		0.82	
Fisher's Exact(p)	SBRT-CK v SBRT-CL				0.016			
Chi-squared (p)			CRT in CK centres v CRT in CL centres				1.0	

Unobtainable/missing includes those no longer in follow up at 24 months

Figure 21: Incidence of individual CTCAE toxicities of grade 2 or higher between 6 and 24 months post-radiotherapy by SBRT platform

Figure 21a: G2+ CTCAE GU toxicities

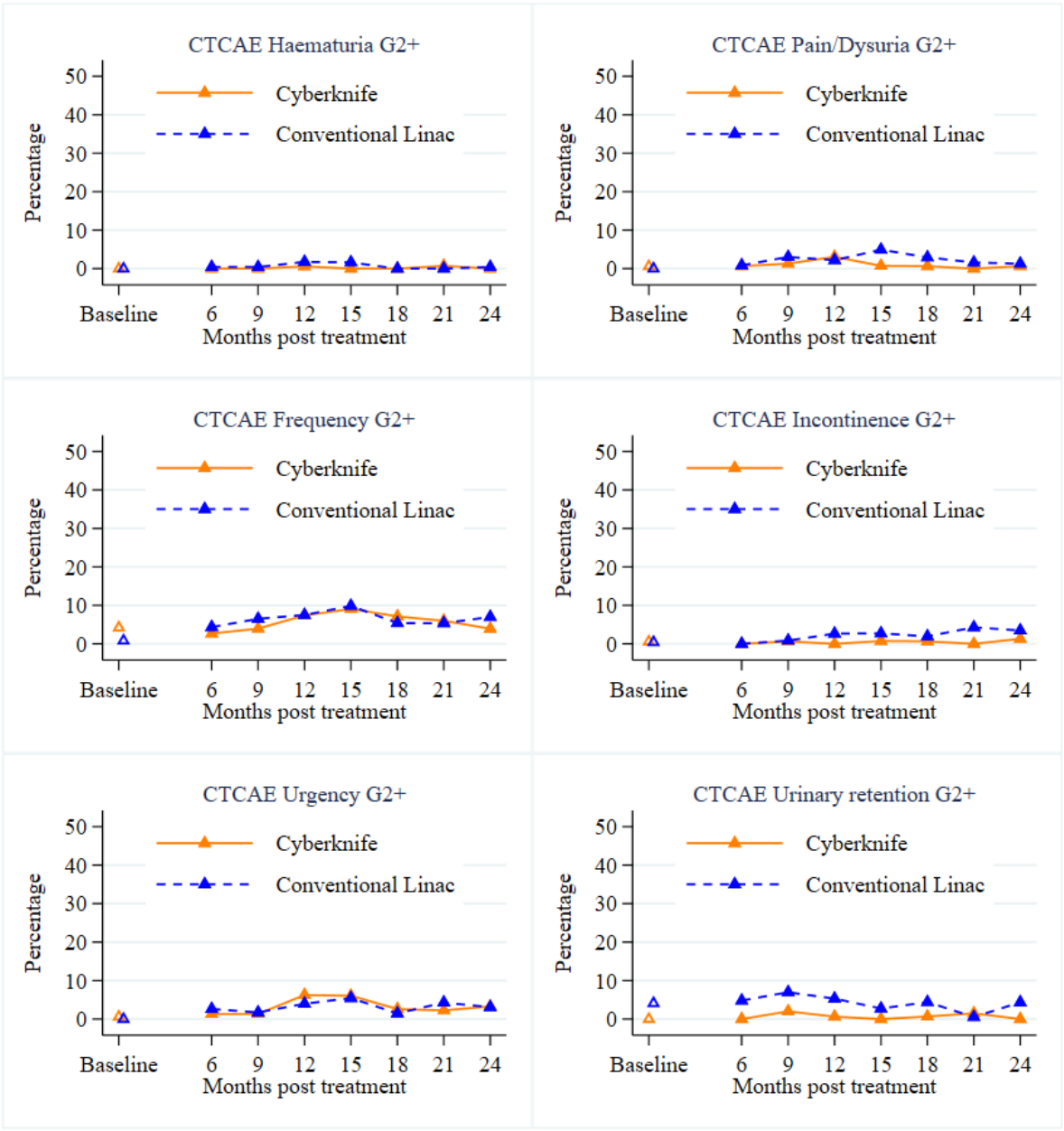


Figure 21b: Grade 2+ CTCAE GI toxicities

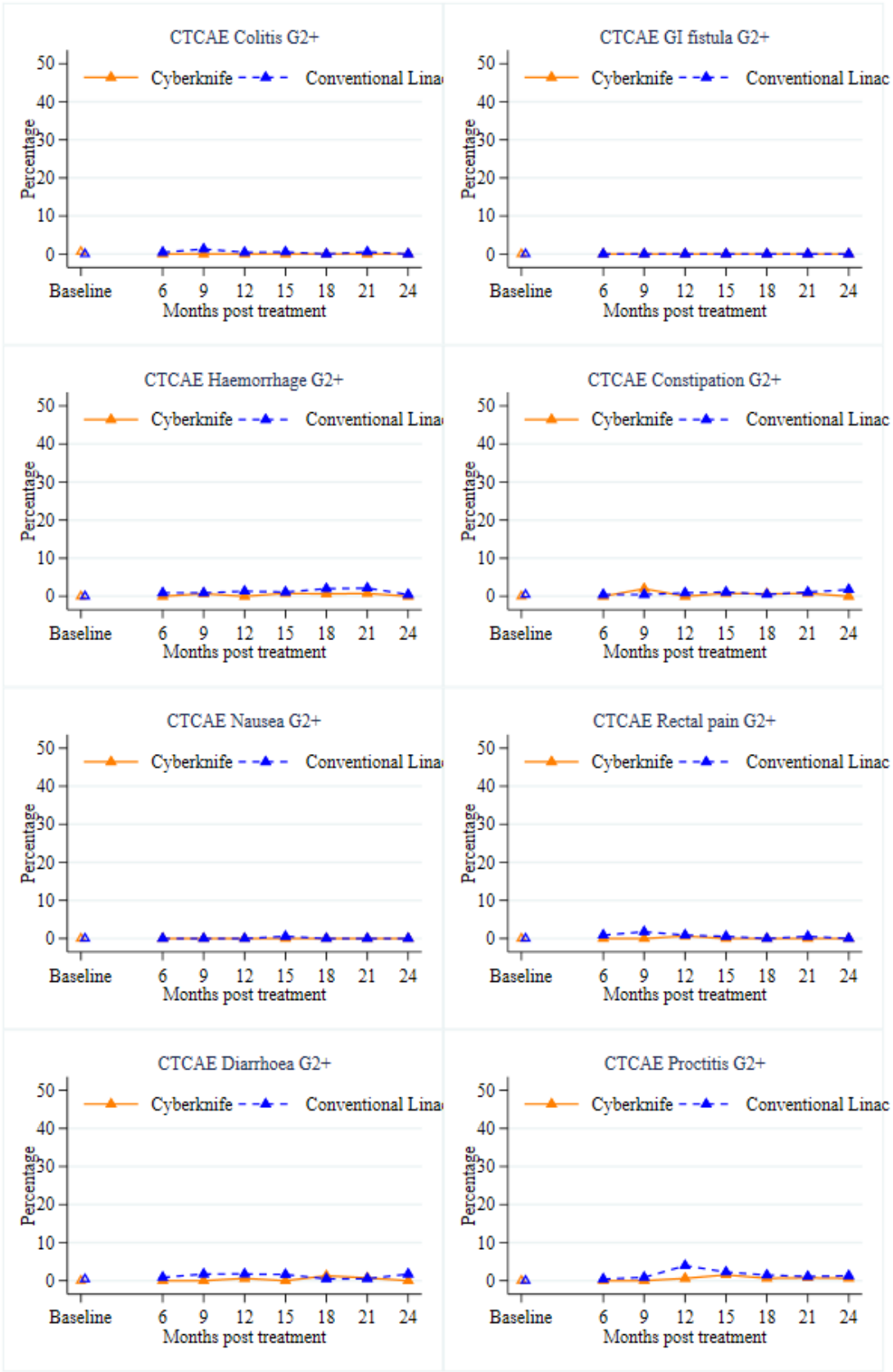


Figure 21c: G2+ CTCAE non-GI and non-GU toxicities

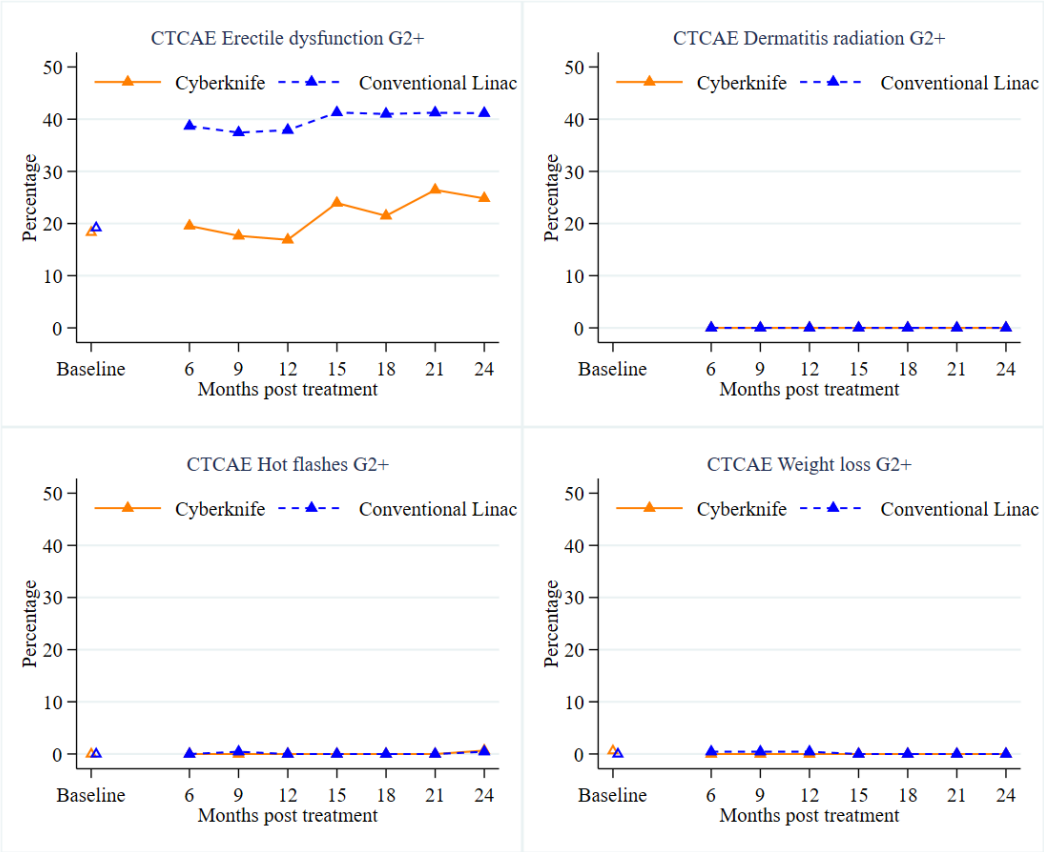


Table 23: Incidence of grade 2+ CTCAE GU events at 24 months post treatment by treatment received and by fiducials used

CRT= conventional radiotherapy, SBRT-CK = SBRT delivered by CyberKnife, SBRT-CL = SBRT delivered on conventional linac

Fiducials used	Treatment received	Worst CTCAE GU grade 2+					
		No		Yes		Total	
		n	%	n	%	n.	%
Yes	CRT	211	95	10	5	221	100
	SBRT-CK	145	94	9	6	154	100
	SBRT-CL	95	76	30	24	125	100
	Total	451	90	49	10	500	100
No	CRT	146	91	15	9	161	100
	SBRT-CK (not applicable)	-	-	-	-	-	-
	SBRT-CL	97	92	8	8	105	100
	Total	243	91	23	9	266	100
Total	CRT	357	93	25	7	382	100
	SBRT-CK	145	94	9	6	154	100
	SBRT-CL	192	83	38	17	230	100
	Total	694	91	72	9	766	100

Figure 22 Incidence of CTCAE erectile dysfunction by grade and SBRT platform between 6 and 24 months post-radiotherapy

Note toxicity is Grade 1+, 2+ and 3+ hence percentages add up to more than 100

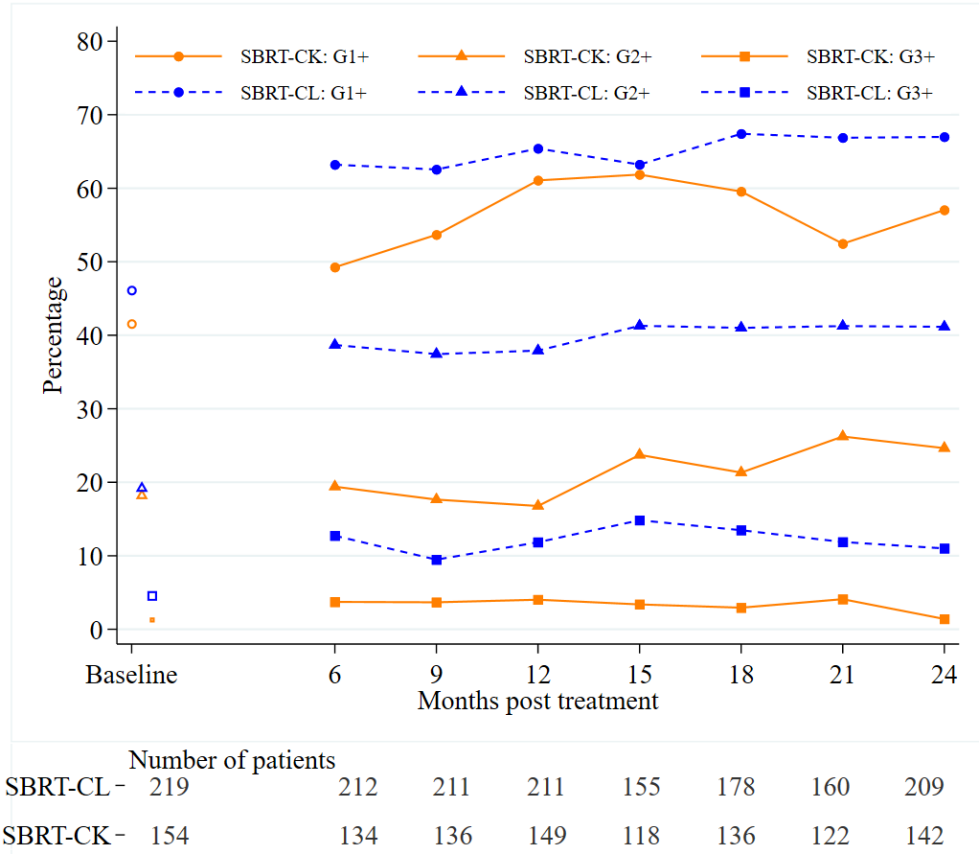


Table 24: Proportion of patients with a drop in quality of life exceeding the exceeding minimal clinically important difference threshold at 24 months post-treatment by SBRT platform

SBRT-CK = SBRT delivered by CyberKnife, SBRT-CL = SBRT delivered on conventional linac

EPIC-26 MCID reduction at 24 months	Treatment received				Chi-square test
	SBRT-CK		SBRT-CL		
	n	%	n	%	p-value
Urinary incontinence					
No	74	76	104	63	0.036
Yes	24	25	61	37	
Missing Data	72		79		
Urinary obstructive					
No	66	70	96	65	0.43
Yes	28	30	51	35	
Missing Data	76		97		
Bowel					
No	75	74	128	77	0.60
Yes	26	26	38	23	
Missing Data	69		78		
Sexual					
No	56	54	92	59	0.45
Yes	48	46	65	429	
Missing Data	66		87		
Hormonal					
No	76	72	109	66	0.30
Yes	30	28	57	34	
Missing Data	64		78		

Table 25: IIEF-5 scores by SBRT platform at baseline and at 24 months post-treatment

SBRT-CK = SBRT delivered by CyberKnife, SBRT-CL = SBRT delivered on conventional linac

IIEF – 5 Scores	Treatment received						Mann-Whitney
	SBRT-CK			SBRT-CL			
	n	Median	IQR	n	Median	IQR	p-value
Baseline	121	14	8-20	172	14	6-20	0.43
24 months post treatment	96	11	5-18.5	137	9	5-18	0.22

Figure 23a-d): Proportion of patients with a benefit or worsening of domain-specific quality of life composite score that exceeds the MCID for EPIC-26, by SBRT platform a) Urinary incontinence b) Urinary irritative/obstructive c) Bowel d) Sexual

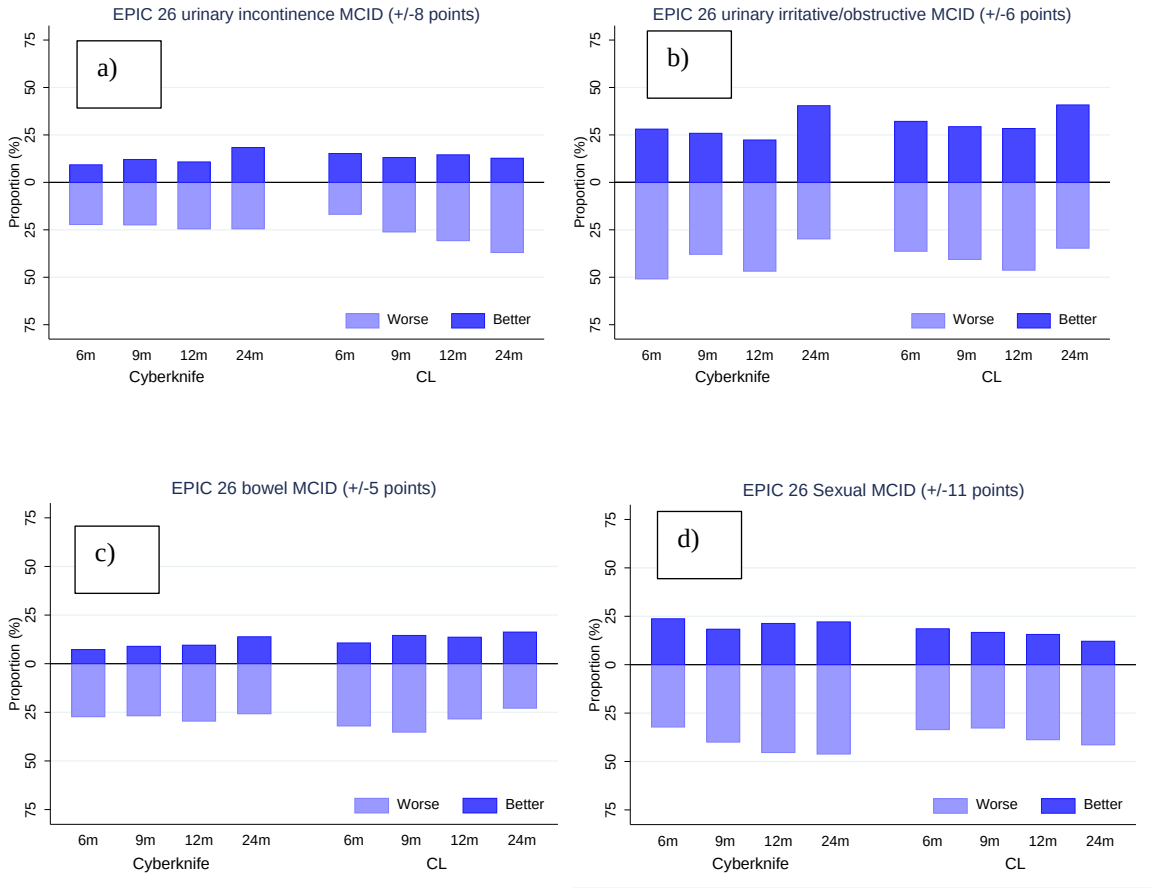


Table 26: Standardized scores for EPIC-26 overall urinary function at 24 months post treatment by SBRT platform

SBRT-CK = SBRT delivered by CyberKnife, SBRT-CL = SBRT delivered on conventional linac

	Treatment received			
	SBRT-CK		**SBRT-CL**	
Standardized score at 24 months post treatment	**n**	**%**	**n**	**%**
0 [big problem]	5	(4)	8	(4)
25 [moderate problem]	11	(8)	10	(5)
50 [small problem]	13	(10)	26	(13)
75 [very small problem]	35	(27)	55	(28)
100 [no problem]	67	(51)	98	(50)

*The question is "Overall, how big a problem has your urinary function been for you **during the last 4 weeks**?", and responses range from "No problem" (a score of 1) to "Big problem" (a score of 5). The scores of 1-5 are standardized to 0-100 with higher scores representing better health related quality of life.

Table 27: IPSS total score and QoL score at baseline and 24 months post treatment by SBRT platform

SBRT-CK = SBRT delivered by CyberKnife, SBRT-CL = SBRT delivered on conventional linac

IPSS parameter	Treatment received						Mann-Whitney
	SBRT-CK			SBRT-CL			
	n	Median	IQR	n	Median	IQR	p-value
IPSS total score							
Baseline	129	5	3 – 11	211	6	3-12	0.35
24 months post treatment	111	8	3-12	182	7	4-11	0.80
IPSS QoL score							
Baseline	144	1	1-3	219	1	0-3	0.37
24 months post treatment	113	1	1 – 3	189	2	1-2	0.88

Table 28: IPSS score categories by SBRT platform at baseline and at 24 months post-treatment

SBRT-CK = SBRT delivered by CyberKnife, SBRT-CL = SBRT delivered on conventional

IPSS total score categories at time point	Treatment received			
	SBRT-CK		SBRT-CL	
	n	%	n	%
Baseline				
None	8	6	8	4
Mild (1-7)	75	58	111	53
Moderate (8-19)	41	32	80	38
Severe (20-35)	5	4	12	6
24 months post treatment				
None	8	7	1	1
Mild (1-7)	46	41	102	56
Moderate (8-19)	48	43	70	39
Severe (20-35)	9	8	9	5
Chi square test for trend (p value)	0.58			