ORIGINAL ARTICLE

# Phase 3 Trial of Stereotactic Body Radiotherapy in Localized Prostate Cancer

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## ABSTRACT

### BACKGROUND

Whether stereotactic body radiotherapy (SBRT) is noninferior to conventionally or moderately hypofractionated regimens with respect to biochemical or clinical failure in patients with localized prostate cancer is unclear.

### METHODS

We conducted a phase 3, international, open-label, randomized, controlled trial. Men with stage T1 or T2 prostate cancer, a Gleason score of 3+4 or less, and a prostate-specific antigen (PSA) level of no more than 20 ng per milliliter were randomly assigned (in a 1:1 ratio) to receive SBRT (36.25 Gy in 5 fractions over a period of 1 or 2 weeks) or control radiotherapy (78 Gy in 39 fractions over a period of 7.5 weeks or 62 Gy in 20 fractions over a period of 4 weeks). Androgen-deprivation therapy was not permitted. The primary end point was freedom from biochemical or clinical failure, with a critical hazard ratio for noninferiority of 1.45. The analysis was performed in the intention-to-treat population.

### RESULTS

A total of 874 patients underwent randomization at 38 centers (433 patients in the SBRT group and 441 in the control radiotherapy group) between August 2012 and January 2018. The median age of the patients was 69.8 years, and the median PSA level was 8.0 ng per milliliter; the National Comprehensive Cancer Network risk category was low for 8.4% of the patients and intermediate for 91.6%. At a median follow-up of 74.0 months, the 5-year incidence of freedom from biochemical or clinical failure was 95.8% (95% confidence interval [CI], 93.3 to 97.4) in the SBRT group and 94.6% (95% CI, 91.9 to 96.4) in the control radiotherapy group (unadjusted hazard ratio for biochemical or clinical failure, 0.73; 90% CI, 0.48 to 1.12; P=0.004 for noninferiority), which indicated the noninferiority of SBRT. At 5 years, the cumulative incidence of late Radiation Therapy Oncology Group (RTOG) grade 2 or higher genitourinary toxic effects was 26.9% (95% CI, 22.8 to 31.5) with SBRT and 18.3% (95% CI, 14.8 to 22.5) with control radiotherapy (P<0.001), and the cumulative incidence of late RTOG grade 2 or higher gastrointestinal toxic effects was 10.7% (95% CI, 8.1 to 14.2) and 10.2% (95% CI, 7.7 to 13.5), respectively (P=0.94).

### CONCLUSIONS

Five-fraction SBRT was noninferior to control radiotherapy with respect to biochemical or clinical failure and may be an efficacious treatment option for patients with low-to-intermediate-risk localized prostate cancer as defined in this trial. (Funded by Accuray and others; PACE-B ClinicalTrials.gov number, NCT01584258.)

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Prostate cancer is a considerable global health care challenge, with nearly 1.5 million men receiving a diagnosis annually.[1] In England in 2021, a total of 12% of newly diagnosed prostate cancers were low risk and 29% were intermediate risk.[2] These men have a number of treatment options, including radiotherapy, which is considered to be curative in the majority of patients.

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

PACE (Prostate Advances in Comparative Evidence) is a platform trial evaluating five-fraction SBRT; the trial involves three independently randomized cohorts of men with localized prostate cancer. PACE-A compares SBRT with surgery. PACE-B and PACE-C recruited men who were suitable candidates for radical radiotherapy but who were not suitable candidates for or who were unwilling to undergo radical prostatectomy. PACE-B included men with low- and intermediate-risk disease, not warranting hormone therapy, and has already shown the safety of five-fraction SBRT.[9,10] PACE-C included men with higher-risk disease receiving androgen-deprivation therapy (ADT). Here, we report the primary analysis of PACE-B, which assessed the noninferiority of five-fraction SBRT as compared with conventionally or moderately hypofractionated radiotherapy with respect to biochemical or clinical failure.

## Methods

### Trial Design and Oversight

PACE-B was a phase 3, international, open-label, noninferiority, randomized, controlled trial. Patients were randomly assigned (in a 1:1 ratio) to receive SBRT or control radiotherapy (conventionally or moderately hypofractionated radiotherapy). Randomization was performed centrally by the Institute of Cancer Research Clinical Trials and Statistics Unit (ICR-CTSU) with the use of computer-generated random permuted blocks (size of four and six), stratified according to National Comprehensive Cancer Network (NCCN) risk category (low vs. intermediate) and randomizing center. Treatment was not masked.

This investigator-initiated trial was approved by the London Chelsea Research Ethics Committee in the United Kingdom and the relevant institutional review boards in Canada and Ireland. Since protocol version 5.0 (August 2014), the regulatory sponsor of the trial was the Royal Marsden NHS Foundation Trust, and the trial was coordinated by the ICR-CTSU. Before this, the regulatory sponsor of the trial was Accuray. Accuray had no role in data collection (managed by a third party before February 2014) or statistical analysis (performed by the ICR-CTSU). The trial was conducted in accordance with Good Clinical Practice guidelines. Patients were recruited by their clinical teams and provided written, informed consent before enrollment. The trial management group was overseen by an independent data monitoring committee and an independent trial steering committee.

The first author wrote the first draft. The first author, last author, and three other authors led the manuscript writing; all other authors contributed to and reviewed the manuscript. No one who is not an author contributed to writing the manuscript. The authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol, which was published previously[9] and is available with the full text of this article at NEJM.org.

### Patients

Eligible patients were 18 years of age or older and had histologically confirmed prostate ade-

nocarcinoma, a World Health Organization performance-status score of 0 to 2 (on a scale of 0 to 5, with higher scores indicating greater disability), and a life expectancy of more than 5 years. All the patients had clinical or magnetic resonance imaging (MRI)–defined T1 or T2 disease categorized according to NCCN criteria as low risk (Gleason score of 3+3 and a prostate-specific antigen [PSA] level of ≤10 ng per milliliter) or intermediate risk (Gleason score of 3+4, PSA level of 10.1 to 20.0 ng per milliliter, or both). Among the exclusion criteria were primary Gleason grade 4 or higher disease, any NCCN high-risk factors, previous pelvic radiotherapy, previous treatment for prostate cancer, or prostheses in both hips.

### TREATMENT AND ASSESSMENTS

For SBRT, insertion of three or more prostatic fiducial markers was recommended. Moderate bladder filling and bowel preparation (enemas) were advised for treatment planning. Computed tomography (CT) was completed, with MRI recommended for radiotherapy planning purposes. CT and MRI scans were fused by fiducial matching. The clinical target volume was defined as prostate only in low-risk patients or prostate plus proximal 1 cm of seminal vesicles in intermediate-risk patients. A planning target volume margin of 4 to 5 mm isotropic was applied, except for 3 to 5 mm posteriorly. A total dose of 36.25 Gy in 5 fractions over a period of 1 or 2 weeks (daily or on alternate days) was delivered to 95% of the planning target volume, and a secondary target dose of 40 Gy was delivered to 95% of the clinical target volume only. SBRT was permitted on noncoplanar robotic linear accelerators and (since protocol version 5.0, August 2014) conventional linear accelerator platforms. Further details are provided in Section S14 in the Supplementary Appendix, which is available at NEJM.org. For control radiotherapy, the protocol initially mandated 78 Gy in 39 fractions over a period of 7.5 weeks but after a protocol amendment (version 7.1 [March 24, 2016]), 62 Gy in 20 fractions over a period of 4 weeks was also permitted. Centers were required to choose a schedule to be used for all their trial patients. ADT was not permitted.

The PSA level was recorded at 12 weeks and at 6, 9, and 12 months after treatment and annually thereafter. Safety was assessed with the use of the Common Terminology Criteria for Adverse Events (CTCAE), version 4.03,[5] and the Radiation Therapy Oncology Group (RTOG) assessment tool before treatment, every 3 months until 24 months, every 6 months in years 2 through 5, and then annually to a maximum of 10 years.

Patient-reported outcomes were assessed at baseline; at months 6, 9, and 12; and then annually to year 5 with the use of the 26-question Expanded Prostate Cancer Index Composite (EPIC-26) instrument,[11] the International Prostate Symptom Score scale (regarding urinary incontinence), the Vaizey fecal-incontinence scale, and the five-item International Index of Erectile Function (IIEF-5) Questionaire (omitted at month 9). Scores for each subdomain of the EPIC-26 instrument range from 0 to 100, with higher scores indicating better quality of life. Patient-reported outcomes were collected by means of paper questionnaires distributed in the clinic or mailed by centers. A history of substantial amendments to the protocol is provided in Section S13 in the Supplementary Appendix.

### END POINTS

The primary end point was freedom from biochemical or clinical failure. Biochemical failure was based on increases in the PSA levels (according to Phoenix criteria, with three consecutive increases required for failure before 24 months to rule out postradiotherapy PSA "bounce"), commencement of ADT, or date of orchidectomy, and clinical failure was defined as local recurrence, nodal recurrence, distant metastases, or death from prostate cancer. The prespecified time point of primary interest was 5 years. Data from patients without an event were censored on the date of the last PSA assessment. Secondary end points included commencement of ADT, diagnosis of metastatic disease, disease-free survival, overall survival, and clinician- and patient-assessed side effects.

### STATISTICAL ANALYSIS

The PACE-B trial was designed to assess the noninferiority of SBRT as compared with control radiotherapy with respect to biochemical or clinical

**Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.***

| Characteristic | Stereotactic Body Radiotherapy (N=433) | Control Radiotherapy (N=441) | Total (N=874) |
|---|---|---|---|
| Age at randomization — yr | | | |
| Median (IQR) | 69.8 (65.4–74.1) | 69.7 (65.5–73.9) | 69.8 (65.4–74.0) |
| Range | 45.8–84.5 | 48.1–86.7 | 45.8–86.7 |
| Race or ethnic group — no. (%)† | | | |
| Black | 35 (8.1) | 26 (5.9) | 61 (7.0) |
| East Asian | 4 (0.9) | 3 (0.7) | 7 (0.8) |
| Mixed heritage | 2 (0.5) | 2 (0.5) | 4 (0.5) |
| Southern Asian | 20 (4.6) | 10 (2.3) | 30 (3.4) |
| White | 367 (84.8) | 393 (89.1) | 760 (87.0) |
| Other | 5 (1.2) | 7 (1.6) | 12 (1.4) |
| Family history of prostate cancer — no. (%) | | | |
| No | 312 (72.1) | 326 (73.9) | 638 (73.0) |
| Yes | 89 (20.6) | 88 (20.0) | 177 (20.3) |
| Unknown | 32 (7.4) | 27 (6.1) | 59 (6.8) |
| WHO performance-status score — no. (%)‡ | | | |
| 0 | 389 (89.8) | 391 (88.7) | 780 (89.2) |
| 1 | 44 (10.2) | 48 (10.9) | 92 (10.5) |
| 2 | 0 | 2 (0.5) | 2 (0.2) |
| T stage — no. (%)§ | | | |
| T1c | 82 (18.9) | 81 (18.4) | 163 (18.6) |
| T2a | 105 (24.2) | 133 (30.2) | 238 (27.2) |
| T2b | 81 (18.7) | 59 (13.4) | 140 (16.0) |
| T2c | 162 (37.4) | 168 (38.1) | 330 (37.8) |
| Unknown | 3 (0.7) | 0 | 3 (0.3) |
| Method of staging — no. (%) | | | |
| ≥1 Staging method performed | 430 (99.3) | 441 (100) | 871 (99.7) |
| Digital rectal examination | 156 (36.0) | 166 (37.6) | 322 (36.8) |
| Transrectal ultrasonography | 280 (64.7) | 264 (59.9) | 544 (62.2) |
| MRI of the pelvis | 339 (78.3) | 359 (81.4) | 698 (79.9) |
| Gleason score — no. (%)¶ | | | |
| 3+3 | 63 (14.5) | 90 (20.4) | 153 (17.5) |
| 3+4 | 370 (85.5) | 351 (79.6) | 721 (82.5) |
| Prostate-specific antigen level | | | |
| Median (IQR) — ng/ml | 7.9 (5.5–10.9) | 8.1 (6.3–11.0) | 8.0 (5.9–11.0) |
| Range — ng/ml | 0.5–20.0 | 0.8–20.0 | 0.5–20.0 |
| Distribution — no. (%) | | | |
| <10 ng/ml | 297 (68.6) | 303 (68.7) | 600 (68.6) |
| 10–20 ng/ml | 136 (31.4) | 138 (31.3) | 274 (31.4) |
| Percentage of positive biopsy cores — no. (%) | | | |
| <50% | 287 (66.3) | 304 (68.9) | 591 (67.6) |
| ≥50% | 146 (33.7) | 137 (31.1) | 283 (32.4) |

**Table 1. (Continued.)**

| Characteristic | Stereotactic Body Radiotherapy (N=433) | Control Radiotherapy (N=441) | Total (N=874) |
|---|---|---|---|
| NCCN risk category — no. (%) | | | |
| Low | 32 (7.4) | 41 (9.3) | 73 (8.4) |
| Intermediate | 401 (92.6) | 400 (90.7) | 801 (91.6) |
| Favorable | 86 (21.4) | 106 (26.5) | 192 (24.0) |
| Unfavorable | 315 (78.6) | 294 (73.5) | 609 (76.0) |
| Prostate volume — no. (%) | | | |
| <40 ml | 192 (44.3) | 163 (37.0) | 355 (40.6) |
| 40 to <80 ml | 198 (45.7) | 223 (50.6) | 421 (48.2) |
| ≥80 ml | 23 (5.3) | 28 (6.3) | 51 (5.8) |
| Unknown | 20 (4.6) | 27 (6.1) | 47 (5.4) |
| Testosterone level | | | |
| No. of patients evaluated | 403 | 407 | 810 |
| Median (IQR) — μmol/liter | 11.5 (9.0–15.0) | 11.3 (8.7–15.0) | 11.3 (8.9–15.0) |
| Range — μmol/liter | 0.4–30.5 | 0.4–30.6 | 0.4–30.6 |
| International Prostate Symptom Score grade — no. (%)‖ | | | |
| No symptoms: score of 0 | 16 (3.7) | 21 (4.8) | 37 (4.2) |
| Mild symptoms: score of 1–7 | 202 (46.7) | 197 (44.7) | 399 (45.7) |
| Moderate symptoms: score of 8–19 | 136 (31.4) | 141 (32.0) | 277 (31.7) |
| Severe symptoms: score of 20–35 | 20 (4.6) | 23 (5.2) | 43 (4.9) |
| Unknown | 59 (13.6) | 59 (13.4) | 118 (13.5) |
| Time from diagnosis to randomization — wk** | | | |
| Median (IQR) | 9.9 (6.6–16.1) | 11.0 (6.9–17.0) | 10.1 (6.7–16.6) |
| Range | 0.1–225.0 | 0.9–335.0 | 0.1–335.0 |

* Percentages may not total 100 because of rounding. IQR denotes interquartile range, and NCCN National Comprehensive Cancer Network.
† Race or ethnic group was reported by the patients. Included in "other" are four patients who did not disclose their race or ethnic group and eight who belonged to another race or ethnic group.
‡ World Health Organization (WHO) performance-status scores range from 0 to 5, with higher scores indicating greater disability.
§ When different staging techniques resulted in different tumor (T) stages, the highest T stage was used.
¶ A Gleason score of 3+3 indicates low-grade prostate cancer, and a score of 3+4 indicates intermediate-grade prostate cancer.
‖ The International Prostate Symptom Score scale is used to measure symptoms of urinary incontinence due to benign prostatic hyperplasia. Scores range from 0 to 35, with higher scores indicating more severe symptoms.
** According to the protocol, histologic confirmation of prostate adenocarcinoma was to be performed within the previous 18 months unless the patient was undergoing active surveillance and histologic confirmation was not clinically indicated.

failure. The sample size was calculated under the assumption that 85% of the patients in the control radiotherapy group would be free from biochemical or clinical failure at 5 years. A noninferiority margin of 6 percentage points at 5 years (critical hazard ratio, 1.45; selected on the basis of expert clinical opinion), 80% power, 5% one-sided significance, and allowance for 10% loss to follow-up yielded a sample size of 858. After a recommendation by the independent data monitoring committee, the trial management group and the trial steering committee independently

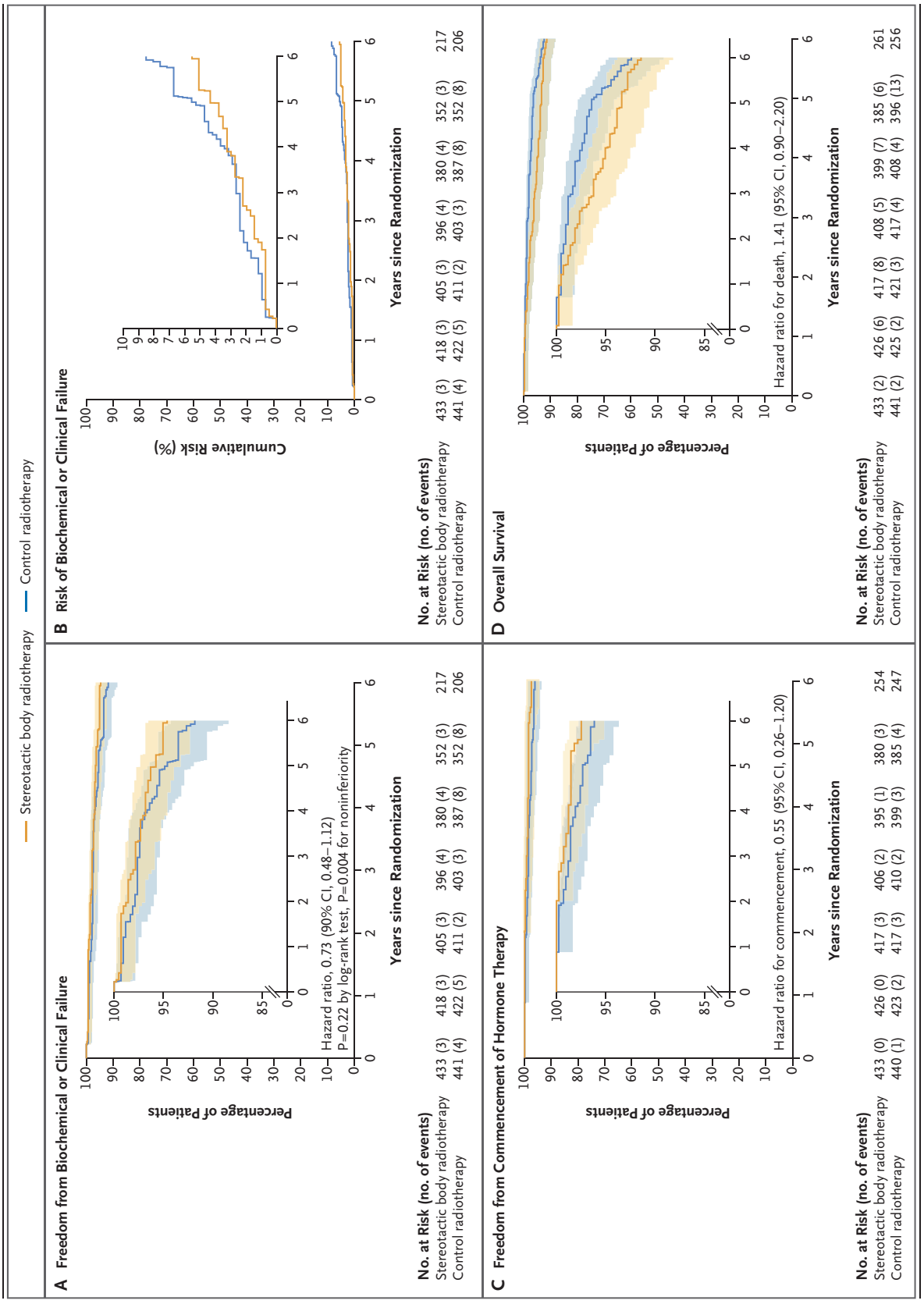

**Figure 1 (facing page). Efficacy Outcomes.**
Panel A shows Kaplan–Meier curves for freedom from biochemical or clinical failure, Panel B Nelson–Aalen curves for the cumulative risk of biochemical or clinical failure, Panel C Kaplan–Meier curves for freedom from commencement of hormone therapy, and Panel D Kaplan–Meier curves for overall survival. The shaded areas indicate 95% confidence intervals. Insets show the same data on an expanded y axis.

agreed (before any data release) to fix the critical hazard ratio at 1.45, if the observed estimate of freedom from biochemical or clinical failure in the control group differed from that assumed. The protocol specified that the principal analysis would take place once the required number of events had been observed (194) or after a minimum of 5 years of follow-up in all the patients, whichever occurred first.

Efficacy analyses were conducted in the intention-to-treat population, which included all randomly assigned patients regardless of ineligibility for trial treatment or deviation from assigned treatment. A sensitivity analysis of the primary end point was conducted in the per-protocol population, which included all randomly assigned patients who were eligible for and received at least one fraction of their assigned treatment. Kaplan–Meier methods were used to estimate the incidence of events. Estimates of treatment effect were made with the use of unadjusted and adjusted (for NCCN risk category) Cox regression models. For the primary end point, the hazard ratio is reported with the 90% confidence interval, in accordance with the one-sided noninferiority design. A hazard ratio of less than 1 would favor SBRT. The absolute treatment difference in the incidence of freedom from biochemical or clinical failure at 5 years is presented by application of the hazard ratio to the estimated incidence in the control group and 90% confidence interval.[12] The log-rank test was used to compare groups. Hazard ratios with 95% confidence intervals are presented for all other efficacy outcomes (widths of confidence intervals have not been adjusted for multiplicity and should not be used in place of hypothesis testing). The proportional-hazards assumption was assessed with the use of Schoenfeld residuals and held for all time-to-event end points. A competing-risks analysis was conducted for the primary end point with deaths not from prostate cancer as the competing event and differences between SBRT and control radiotherapy assessed with the use of Gray's test. Prespecified subgroup analyses of the primary end point according to NCCN risk category, age, and Gleason score were conducted.

For clinician-assessed toxic effects (genitourinary effects, gastrointestinal effects, and erectile dysfunction), the percentage of patients with grade 2 or higher toxic effects at 5 years was compared with chi-square or Fisher's exact tests. The cumulative incidence of late toxic effects (defined as adverse events that occurred ≥6 months after treatment) was estimated, and the time to the first late adverse event was compared with the use of Kaplan–Meier methods. For patient-reported outcomes, responses to the EPIC-26 instrument were analyzed as composite scores (bowel, urinary, sexual, and hormonal), and single-item EPIC questions about overall bowel, urinary, and sexual function were presented at each time point assessed. All analyses are based on data as of September 11, 2023, and were conducted with the use of Stata software, version 17.0.

## RESULTS

### RANDOMIZATION AND PATIENT CHARACTERISTICS

Between August 2012 and January 2018, a total of 874 men underwent randomization (433 in the SBRT group and 441 in the control radiotherapy group) at 38 centers across the United Kingdom, Ireland, and Canada (Section S2). A total of 414 of 433 men in the SBRT group and 424 of 441 men in the control radiotherapy group received their assigned treatment; 25 received neither trial treatment (Section S3). Eleven patients (3 in the SBRT group and 8 in the control radiotherapy group) were deemed to be ineligible but were included in analyses. Reasons for ineligibility were fewer than 10 core biopsy samples being obtained (in 5 patients), prostate volume not being measured within 6 months after randomization (in 3), clinically significant urinary symptoms not being identified until the planning scan (in 1), no MRI being performed (in 1), and biopsy not being performed within 18 months after randomization (in 1).

The characteristics of the patients at baseline were well balanced between the randomized groups (Table 1). The median age of the patients was 69.8 years (interquartile range, 65.4 to 74.0),

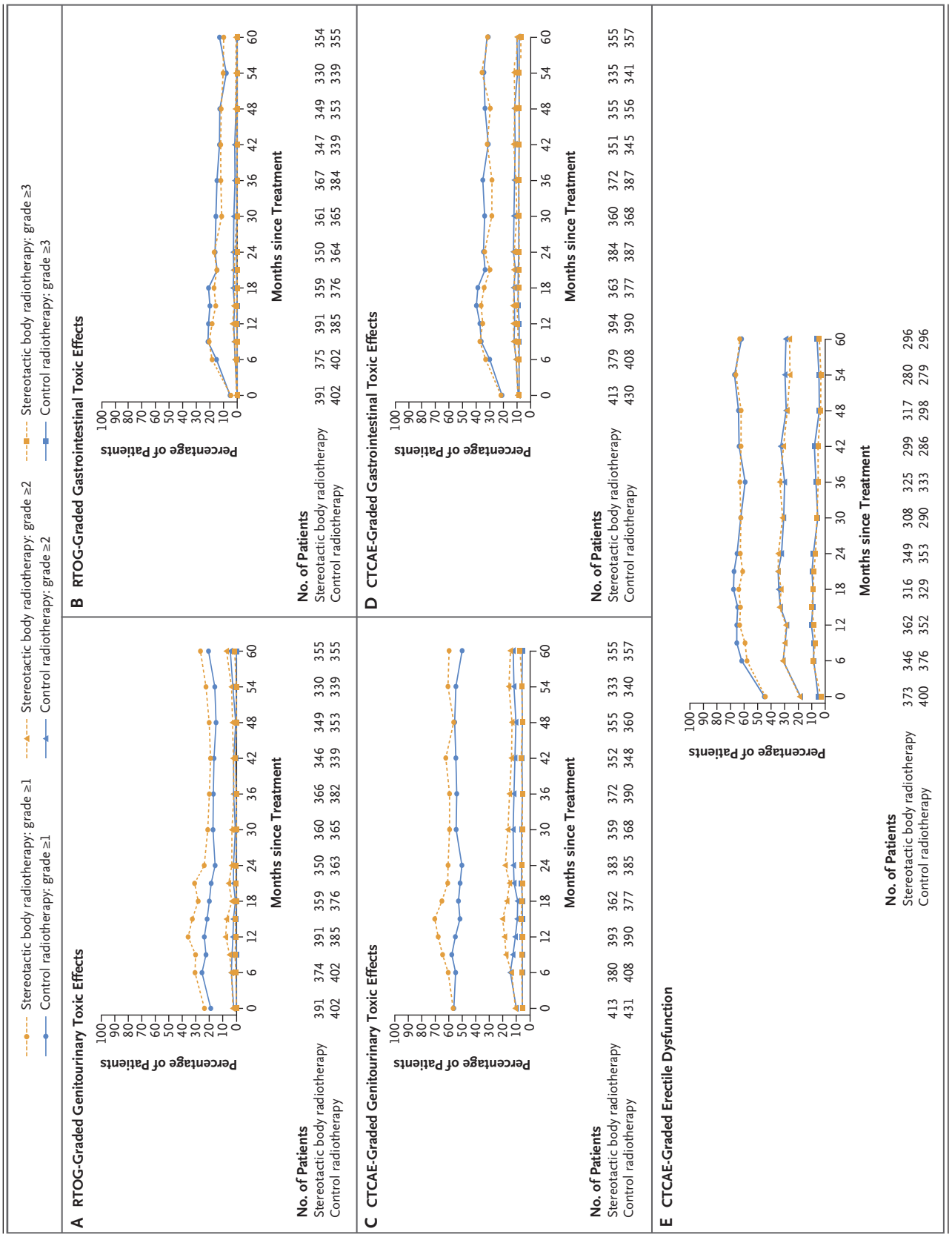

**Figure 2 (facing page). Genitourinary and Gastrointestinal Toxic Effects and Erectile Dysfunction.**

Shown are Radiation Therapy Oncology Group (RTOG)–graded or Common Terminology Criteria for Adverse Events (CTCAE)–graded events at each time point assessed according to treatment received.

and the median PSA level was 8.0 ng per milliliter (interquartile range, 5.9 to 11.0); the NCCN risk category was low for 73 of 874 patients (8.4%) and intermediate for 801 of 874 (91.6%).

SBRT was delivered over a period of 2 weeks in 74.9% of the patients and with the CyberKnife device (Accuray) in 40.7% of the patients. The use of fiducial markers was more common with SBRT than with control radiotherapy (in 73.0% vs. 56.6% of the patients) (Section S5).

### EFFICACY END POINTS

At a median follow-up of 74.0 months (interquartile range, 64.8 to 86.3), biochemical or clinical failure had occurred in 26 patients in the SBRT group and in 36 patients in the control radiotherapy group. The 5-year incidence of freedom from biochemical or clinical failure was 95.8% (95% confidence interval [CI], 93.3 to 97.4) with SBRT and 94.6% (95% CI, 91.9 to 96.4) with control radiotherapy. SBRT was noninferior to control radiotherapy, with an unadjusted hazard ratio for biochemical or clinical failure of 0.73 (90% CI, 0.48 to 1.12; P=0.004 for noninferiority) (Fig. 1A and Section S6). A post hoc test for superiority was not significant (hazard ratio, 0.73; 95% CI, 0.44 to 1.21; P=0.22). The estimated absolute difference in the percentage of patients who were event-free in the SBRT group as compared with the control radiotherapy group at 5 years was 1.4 percentage points (90% CI, −0.6 to 2.8). An adjusted Cox model (hazard ratio, 0.72; 90% CI, 0.47 to 1.10) and an analysis in the per-protocol population (hazard ratio, 0.65; 90% CI, 0.42 to 1.01) supported noninferiority. Competing-risks analysis showed no significant difference in the incidence of biochemical or clinical failure between the treatment groups (P=0.18). Prespecified subgroup analysis showed no meaningful interactions with treatment group (Section S7).

A total of 29 patients commenced hormone therapy (10 in the SBRT group and 19 in the control radiotherapy group), with a hazard ratio of 0.55 (95% CI, 0.26 to 1.20) (Fig. 1C). A total of 79 patients died (46 in the SBRT group and 33 in the control radiotherapy group), with 4 deaths due to prostate cancer (2 in each group) and 28 due to other primary cancers (Section S8); the hazard ratio for death was 1.41 (95% CI, 0.90 to 2.20) (Fig. 1D).

### TOXIC EFFECTS

At 5 years, RTOG grade 2 or higher genitourinary toxic effects were seen in 26 of 355 patients (7.3%) who received SBRT and in 16 of 355 (4.5%) who received control radiotherapy (P=0.11). CTCAE grade 2 or higher genitourinary toxic effects were reported in 31 of 355 patients (8.7%) in the SBRT group and in 24 of 357 (6.7%) in the control radiotherapy group at 5 years (P=0.32) (Fig. 2A and 2C and Sections S9 and S11). The cumulative incidence differed between the two groups for both RTOG and CTCAE grade 2 or higher genitourinary toxic effects (Section S10). For RTOG genitourinary toxic effects, the cumulative incidence of late grade 2 or higher events up to 5 years was 26.9% (95% CI, 22.8 to 31.5) in the SBRT group and 18.3% (95% CI, 14.8 to 22.5) in the control radiotherapy group (hazard ratio, 1.59; 95% CI, 1.18 to 2.12; P<0.001).

At 5 years, RTOG grade 2 or higher gastrointestinal toxic effects were seen in 3 of 354 patients (0.8%) who received SBRT and in 1 of 355 (0.3%) who received control radiotherapy (P=0.37) (Fig. 2B). No significant between-group difference was observed at 5 years in CTCAE grade 2 or higher gastrointestinal toxic effects: 9 of 355 patients (2.5%) in the SBRT group and 6 of 357 (1.7%) in the control radiotherapy group (P=0.43) (Fig. 2D); no significant difference was observed in the cumulative incidence of RTOG or CTCAE grade 2 or higher gastrointestinal toxic effects. For RTOG gastrointestinal toxic effects, the cumulative incidence of late grade 2 or higher events up to 5 years was 10.7% (95% CI, 8.1 to 14.2) in the SBRT group and 10.2% (95% CI, 7.7 to 13.5) in the control radiotherapy group (hazard ratio, 1.03; 95% CI, 0.68 to 1.56; P=0.94) (Section S10).

At 5 years, 78 of 296 patients (26.4%) in the SBRT group and 86 of 296 (29.1%) in the control radiotherapy group reported CTCAE grade 2 or higher erectile dysfunction (P=0.46). The incidence of clinician-reported grade 2 or higher erectile symptoms was similar in the two treatment groups at baseline and was stable from 2

**Figure 3 (facing page). EPIC-26 Subdomain Scores.**
Shown are patient-reported mean scores at each time point assessed according to treatment received. Scores for each subdomain of the 26-question Expanded Prostate Cancer Index Composite (EPIC-26) instrument range from 0 to 100, with higher scores indicating better quality of life. Scores at week 0 are the baseline scores obtained before the start of radiotherapy. I bars indicate 95% confidence intervals.

to 5 years after treatment (Fig. 2E). Treatment-related serious adverse events were reported in 12 patients (6 in each group).

### EPIC-26 SUBDOMAIN SCORES

Patients reported stable urinary and bowel symptoms from 2 to 5 years, with little difference between treatment groups (Fig. 3 and Section S12). At 5 years, the median urinary-incontinence score was 96.9 (interquartile range, 73.0 to 100) in the SBRT group and 100 (interquartile range, 79.3 to 100) in the control radiotherapy group (P=0.45). No difference in the score for urinary irritation or obstruction was noted at 5 years, with a median score of 93.8 (interquartile range, 81.3 to 100) in each group. Similar bowel subdomain scores were reported at 5 years, with a median score of 100 (interquartile range, 87.5 to 100) in the SBRT group and 95.8 (interquartile range, 87.5 to 100) in the control radiotherapy group (P=0.10). Sexual subdomain scores declined from 2 to 5 years, with no evidence of a significant difference between treatment groups at 5 years (P=0.87).

## DISCUSSION

The PACE-B trial showed the noninferiority of 5-fraction SBRT as compared with moderately fractionated image-guided radiotherapy, given that the 5-year incidence of freedom from biochemical or clinical failure was similar in the two groups. The previous U.K. fractionation trial, CHHiP, included a slightly higher risk group and showed a 5-year incidence of freedom from biochemical or clinical failure of 90.6% with moderately fractionated 60 Gy in 20 fractions.[6] In our trial, the incidence of freedom from biochemical or clinical failure of 96% with SBRT and 95% with control radiotherapy was achieved without ADT and exceeded the expectations of the trial design.

These outcomes may reflect advancements in radiotherapy delivery, including improved image guidance with fiducial markers and cone-beam CT, and enhanced treatment delivery with volumetric arc therapy, which leads to greater accuracy and improved dose distributions. The trial protocol included comprehensive guidelines on treatment, delineation of clinical target volume and planning target volume, treatment planning, margins, image guidance, and treatment delivery. These guidelines could be used for the adoption of five-fraction SBRT with appropriate quality assurance.

Our randomized, controlled trial showed the noninferiority of SBRT in this context. Our results align with those of the HYPO-RT-PC phase 3 noninferiority trial, which randomly assigned 1200 men to receive 42.7 Gy in 7 fractions over a period of 2.5 weeks or 78 Gy in 39 fractions over a period of 8 weeks. That trial showed a 5-year failure-free survival of 84% (95% CI, 80 to 87) in each group, with an adjusted hazard ratio for biochemical or clinical failure of 1.00 (95% CI, 0.76 to 1.33; P=0.99 by log-rank test).[13] The differing outcomes between the two trials may be attributed to the inclusion of deaths not from prostate cancer as events in the HYPO-RT-PC trial.

The strengths of the PACE-B trial include its large sample size and multicenter recruitment across three countries, with quality-assured radiotherapy delivered in both the experimental and control groups to a well-defined and homogeneous trial population. The absence of hormonal therapy in both groups ensures that the outcomes were not confounded by variable use of such therapy. At the time of the trial design, the current NCCN classifications for favorable and unfavorable intermediate-risk disease did not exist. However, the majority of patients in the trial would now be classified as having unfavorable intermediate-risk cancer (Table 1). A limitation is that recommendations for 5-fraction SBRT are restricted to men with risk features similar to those in the trial. What proportion of the patients in this trial would now receive active surveillance remains unclear, given the lack of data showing that treatment influences overall survival among some patients with localized disease.[14] Overtreatment is best avoided. The efficacy results of the PACE-C trial, which is evaluating the noninferiority of 5-fraction SBRT as compared with 60 Gy in 20 fractions in men

with higher-risk disease warranting ADT, are being analyzed.

We previously found a significant difference in the incidence grade 2 or higher genitourinary toxic effects at 2 years after treatment (12% with SBRT vs. 7% with control radiotherapy). The updated 5-year toxicity analysis indicates a decrease in the incidence of these symptoms, with no significant differences between the two groups at 5 years, and low overall levels of side effects. Patients should be informed of the higher medium-term risk of genitourinary toxic effects, especially patients with clinically significant lower urinary tract symptoms at baseline, who may have better outcomes with respect to symptoms with 20-fraction intensity-modulated radiotherapy than with SBRT. Patients with lower urinary tract symptoms at baseline or clinically significant acute toxic effects are more likely to have long-term toxic effects, facts that should allow for better patient selection for SBRT and that support careful counseling and monitoring of those with acute toxic symptoms.[15]

Radiotherapy for prostate cancer represents a substantial portion of the workload in radiotherapy departments worldwide. In England, more than 16,000 patients received prostate radiotherapy in 2022, with an estimated 4800 meeting PACE-B eligibility criteria.[2] Transitioning these patients to a 5-fraction regimen could reduce the number of fractions administered by approximately 72,000 across the United Kingdom. This regimen also minimizes the socioeconomic and psychological burdens of treatment. In addition, patients with NCCN-defined low-risk disease and some patients with favorable intermediate-risk disease could be considered for active surveillance.

The findings from the PACE-B trial show that five-fraction SBRT is a robust and viable alternative to moderately fractionated radiotherapy for prostate cancer, offering equivalent efficacy with enhanced convenience for patients. The high 5-year incidence of biochemical control and the acceptable side-effect profile, coupled with the considerable advancements in radiotherapy delivery, underscore the potential of the use of SBRT in prostate cancer treatment. The reduction in treatment fractions would alleviate the burden on health care systems while yielding favorable cancer-control outcomes without the addition of hormonal treatment.

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## APPENDIX

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## REFERENCES


1. American Cancer Society. Key statistics for prostate cancer (https://www.cancer.net/cancer-types/prostate-cancer/statistics).
2. National Prostate Cancer Audit. NPCA state of the nation report. London: the Royal College of Surgeons of England, 2024.
3. Michalski JM, Moughan J, Purdy JA, et al. Long-term outcomes of NRG/RTOG 0126, a randomized trial of high dose (79.2 Gy) vs. standard dose (70.2 Gy) radiation therapy (RT) for men with localized prostate cancer. In: Proceedings of the American Society for Radiation Oncology, ASTRO 2023 65th annual meeting, San Diego, CA, October 1–4, 2023. Int J Radiat Oncol Biol Phys 2023;117(2): Suppl:S4-S5.
4. Hennequin C, Sargos P, Roca L, et al. Long-term results of dose escalation (80 vs 70 Gy) combined with long-term androgen deprivation in high-risk prostate cancers: GETUG-AFU 18 randomized trial. J Clin Oncol 2024;42(4):Suppl:LBA259 (https://ascopubs.org/doi/10.1200/JCO.2024.42.4_suppl.LBA259).
5. Michalski JM, Moughan J, Purdy J, et al. Effect of standard vs dose-escalated radiation therapy for patients with intermediate-risk prostate cancer: the NRG Oncology RTOG 0126 randomized clinical trial. JAMA Oncol 2018;4(6):e180039.
6. Dearnaley D, Syndikus I, Mossop H, et al. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. Lancet Oncol 2016; 17:1047-60.
7. Lee WR, Dignam JJ, Amin MB, et al. Randomized phase III noninferiority study comparing two radiotherapy fractionation schedules in patients with low-risk prostate cancer. J Clin Oncol 2016;34:2325-32.
8. Catton CN, Lukka H, Gu C-S, et al. Randomized trial of a hypofractionated radiation regimen for the treatment of localized prostate cancer. J Clin Oncol 2017; 35:1884-90.
9. Brand DH, Tree AC, Ostler P, et al. Intensity-modulated fractionated radiotherapy versus stereotactic body radiotherapy for prostate cancer (PACE-B): acute toxicity findings from an international, randomised, open-label, phase 3, non-inferiority trial. Lancet Oncol 2019; 20:1531-43.
10. Tree AC, Ostler P, van der Voet H, et al. Intensity-modulated radiotherapy versus stereotactic body radiotherapy for prostate cancer (PACE-B): 2-year toxicity results from an open-label, randomised, phase 3, non-inferiority trial. Lancet Oncol 2022;23:1308-20.
11. Szymanski KM, Wei JT, Dunn RL, Sanda MG. Development and validation of an abbreviated version of the expanded prostate cancer index composite instrument for measuring health-related quality of life among prostate cancer survivors. Urology 2010;76:1245-50.
12. Altman DG, Andersen PK. Calculating the number needed to treat for trials where the outcome is time to an event. BMJ 1999;319:1492-5.
13. Widmark A, Gunnlaugsson A, Beckman L, et al.. Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer: 5-year outcomes of the HYPO-RT-PC randomised, non-inferiority, phase 3 trial. Lancet 2019;394: 385-95.
14. Hamdy FC, Donovan JL, Lane JA, et al. Fifteen-year outcomes after monitoring, surgery, or radiotherapy for prostate cancer. N Engl J Med 2023;388:1547-58.
15. Ratnakumaran R, Hinder V, Brand D, et al. The association between acute and late genitourinary and gastrointestinal toxicities: an analysis of the PACE B study. Cancers (Basel) 2023;15:1288.