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Safety and Efficacy of Virtual Prostatectomy With Single-Dose Radiotherapy in Patients With Intermediate-Risk Prostate Cancer
Results From the PROSINT Phase 2 Randomized Clinical Trial

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IMPORTANCE Ultra-high single-dose radiotherapy (SDRT) represents a potential alternative to curative extreme hypofractionated stereotactic body radiotherapy (SBRT) in organ-confined prostate cancer.

OBJECTIVE To compare toxic effect profiles, prostate-specific antigen (PSA) responses, and quality-of-life end points of SDRT vs extreme hypofractionated SBRT.

DESIGN, SETTING, AND PARTICIPANTS The PROSINT single-institution phase 2 randomized clinical trial accrued, between September 2015 and January 2017, 30 participants with intermediate-risk prostate cancer to receive SDRT or extreme hypofractionated SBRT. Androgen deprivation therapy was not permitted. Data were analyzed from March to May 2020.

INTERVENTIONS Patients were randomized in a 1:1 ratio to receive 5 × 9 Gy SBRT (control arm) or 24 Gy SDRT (test arm).

MAIN OUTCOMES AND MEASURES The primary end point was toxic effects; the secondary end points were PSA response, PSA relapse-free survival, and patient-reported quality of life measured with the International Prostate Symptom Score (IPSS) and Expanded Prostate Cancer Index Composite (EPIC)–26 questionnaires.

RESULTS A total of 30 men were randomized; median (interquartile range) age was 66.3 (61.2-69.9) and 73.6 (64.7-75.9) years for the SBRT and SDRT arms, respectively. Time to appearance and duration of acute and late toxic effects were similar in the 2 trial arms. Cumulative late actuarial urinary toxic effects did not differ for grade 1 (hazard ratio [HR], 0.41; 90% CI, 0.13-1.27) and grade 2 or greater (HR, 1.07; 90% CI, 0.21-5.57). Actuarial grade 1 late gastrointestinal (GI) toxic effects were comparable (HR, 0.37; 90% CI, 0.07-1.94) and there were no grade 2 or greater late GI toxic effects. Declines in PSA level to less than 0.5 ng/mL occurred by 36 months in both study arms. No PSA relapses occurred in favorable intermediate-risk disease, while in the unfavorable category, the actuarial 4-year PSA relapse-free survival values were 75.0% vs 64.0% (HR, 0.76; 90% CI, 0.17-3.31) for SBRT vs SDRT, respectively. The EPIC-26 median summary scores for the genitourinary and GI domains dropped transiently at 1 month and returned to pretreatment scores by 3 months in both arms. The IPSS-derived transient late urinary flare symptoms occurred at 9 to 18 months in 20% (90% CI, 3%-37%) of patients receiving SDRT.

CONCLUSIONS AND RELEVANCE In this randomized clinical trial among patients with intermediate-risk prostate cancer, SDRT was safe and associated with low toxicity, and the tumor control and quality-of-life end points closely match the SBRT arm outcomes. Further studies are encouraged to explore indications for SDRT in the cure of prostate cancer.

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Supplemental content

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Exploration of curative radiotherapy in primary organ-confined prostate cancer has recently expanded as a result of the introduction of advanced computer-driven treatment platforms promoting new standards of high-precision planning and delivery.[1-4] The deployment of image-guided radiotherapy, online real-time target tracking, and differential intensity-modulated dose painting of tumor vs adjacent normal tissues has enabled fine-tuning of tumor-ablative dose delivery to the planning target volume.[5,6] Furthermore, topographic precision in dose delivery has obviated the need for ample safety margins to prevent tumor miss, promoting a sharp decrease in the number of treatment sessions, with higher dose per fraction. This approach, known as hypofractionated stereotactic body radiotherapy (SBRT), has been shown to be safe and effective and is increasingly replacing conventional fractionated radiotherapy.[7-9]

While schedules of 5 fractions of 7.25 to 8 Gy (5 × 7.25-8 Gy) SBRT are effective in low-risk and favorable intermediate-risk prostate cancer,[3,10,11] further dose escalation, required to improve outcomes in higher-risk phenotypes,[12] has been associated with urinary and rectal toxic effects,[13] apparently owing to uncontrolled prostate motion during treatment delivery.[14] The resting anatomical position of the prostate is in the inferior-posterior lesser pelvis, anatomically adhering to the anterior rectal wall via Denonvilliers fascia.[15] The rectum is an inherently mobile organ, which responds to neuronal rectal wall stretch signals produced by passing contents with an anterior-superior translocation,[14,16,17] concomitantly displacing the prostatic gland. Whenever such motion occurs during targeted radiotherapy, part of the prostate moves out of the radiation beam focus, and adjacent normal organs at risk (OARs) may be exposed to potentially toxic high radiation doses.[18]

We have recently addressed this issue by exploring an approach to mitigate intrafractional prostate motion via using an air-filled (150 cm^3) endorectal balloon during simulation and before treatment delivery.[17] Remarkably, the balloon-induced prostate translocation is not random, but rather reproducibly targets a patient-specific retropubic anatomical niche, daily recapitulating a consistent 3-dimensional anatomical configuration of the prostate and its associated OARs.[17] Furthermore, an intraurethral Foley catheter containing beacon transponders was used for online noninvasive GPS-like prostate motion tracking.[17] This system confirmed that target immobilization is achieved in more than 95% of treatment sessions, requiring corrections when drifts of greater than 2 mm are detected for 5 seconds or longer.[17] The reproducibility of the prostate geometrical setting enabled high-precision dose escalation to 5 × 9 Gy SBRT in a phase 2 trial of 207 homogenously treated patients with prostate cancer, yielding a 5-year actuarial prostate-specific antigen (PSA) relapse-free survival (bRFS) of 91.2%, minimal (<3%) grade 2 late urinary and rectal toxic effects, and excellent patient-reported quality-of-life (QOL) outcomes.[17]

The present proof-of-concept study was designed to test the feasibility and safety of single-dose radiotherapy (SDRT) as a virtual prostatectomy approach, using the same prostate immobilization technique previously developed for 5 × 9 Gy SBRT. Treatment of localized prostate cancer with a single high-dose exposure has been reported using high-dose-rate brachytherapy via temporary invasive transperineal implantation of radioactive sources.[19-21] While tolerance to 19 to 20 Gy appeared acceptable, bRFS rates were disappointing,[22] apparently owing to an insufficient dose to effect tumor ablation.[23] Studies have shown that using 2 consecutive implants of 13.5 Gy each appeared to be more effective.[22] Our early SDRT trials reported that ablation of prostate oligometastases requires 24 Gy to maximize the 5-year local relapse-free survival rates,[24] consistent with the notion that a single dose of 20 Gy or less may be insufficient to ablate primary prostate cancer. While the randomized clinical trial reported here was designed primarily to establish the toxicity and safety of prostate cancer SDRT, it also provides preliminary observations that 24 Gy SDRT renders favorable PSA responses and represents a patient-friendly approach to treat organ-confined prostate cancer.

Key Points

Question Is ultra-high single-dose radiotherapy (SDRT) for treatment of organ-confined prostate cancer as safe and effective as curative hypofractionated stereotactic body radiotherapy (SBRT)?

Findings In this phase 2 randomized clinical trial of 30 men with intermediate-risk prostate cancer, 24 Gy SDRT yielded low toxicity, prostate-specific antigen responses, and patient-reported quality-of-life measures akin to curative 5 × 9 Gy SBRT.

Meaning The safety of 24 Gy SDRT encourages further studies to establish SDRT as a cost-effective and patient-friendly treatment in prostate cancer.

Methods

Trial Design and Participants

The PROSINT proof-of-concept trial (protocol in Supplement 1) is a single-institution, parallel-group feasibility study of patients randomized 1:1 to receive either extreme hypofractionated SBRT in 5 fractions of 9 Gy over 5 consecutive days (arm A) or 24 Gy SDRT (arm B) (eFigure 1 in Supplement 2). The study was approved by the Champalimaud Foundation institutional review board. Randomization was provided by the data management office, using a permutated block method in sequentially numbered sealed containers. An institutional review board–approved informed consent was signed by each participant. Eligible patients had centrally reviewed biopsy-proven prostate adenocarcinoma of International Society of Urological Pathology grade 2 or 3, magnetic resonance (MR) stage T2a to T2c, a PSA level less than 20 ng/mL (to convert to µg/L, multiply by 1.0), and no nodal involvement as assessed by prostate-specific membrane antigen positron emission tomography/

computed tomography in unfavorable intermediate-risk (UIR) disease (eMethods in Supplement 2). Androgen deprivation therapy was not allowed. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Treatment Planning and Radiation Delivery

The treatment planning protocol has been described previously.[17] Briefly, following a rectal enema and bladder voiding, an endorectal balloon (Rectal Pro, QLRAD Inc) was inserted and inflated with 150 cm^3 of air. A 12-French gauge Foley catheter with 3 embedded beacon transponders was used for intrafractional tracking (Calypso, Varian Medical Systems). Fused computed tomography and T2-weighted 3-dimensional MR image sets were used to delineate the gross tumor volume (prostate and proximal two-thirds of the seminal vesicles) and the OARs (ie, rectal wall, bladder trigone, urogenital diaphragm, urethral wall, and neurovascular bundles). The planning target volume consisted of the target volume with a 2-mm margin, reduced to 0 mm at the OAR interface, providing effective OAR conformal avoidance and sparing, obviating the need of a perirectal spacer to protect the rectal mucosa.[17] A 10-MV flattening filter-free beam energy and 4 volumetric-modulated arc therapy arcs were used in all patients. Treatment was delivered on a linear accelerator with a 2.5-mm leaf width (EDGE, Varian Medical Systems). Cone beam computed tomography matching ensured final target alignment,[17] and online tracking-detected motion of greater than 2 mm was realigned by cone beam computed tomography. All patients received dexamethasone (4 mg) after each treatment session, oral ciprofloxacin (250 mg/d) for 3 days, and oral tamsulosin (0.4 mg/d) for 30 days after treatment.

End Points, Adverse Events, and QOL Assessment

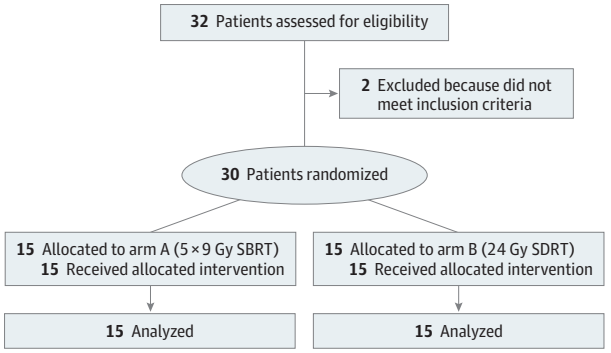
Primary end points were acute and late genitourinary (GU) and gastrointestinal (GI) physician-reported toxic effects and adverse events (National Cancer Institute Common Terminology Criteria for Adverse Events, version 4). Secondary end points were PSA response and bRFS (RTOG Phoenix definition)[25]; patient-reported QOL metrics for the urinary, bowel, and sexual domains; multiparametric MR imaging tumor response; and repeated prostate biopsy at 24 months. The International Prostate Symptom Score (IPSS), Expanded Prostate Cancer Index Composite (EPIC)-26, and International Index Erectile Function-15 forms were used for QOL assessment and collected at baseline, posttreatment at 1, 3, 6, 9, and 12 months (±4 weeks), and at every 6 months thereafter. Diagnostic multiparametric MR scans were performed at baseline and at 3, 6, 12, and 24 months posttreatment.

To ensure patient safety, the protocol included the stopping rule if any grade 3 or greater adverse event occurred in the first 3 patients or in 2 patients in either arm at any time point during the study.

Statistical Analysis

The sample size was calculated using the precision analysis. With the proposed study sample size (ie, 30 patients), the half-width of the 90% CI for the difference of toxic effect rates between the 2 arms is approximately 20%. This calculation assumes that the true difference of the toxic effect rate between the study arms is less than 8% and that the maximum toxic effect rate for a study arm is less than 20%. Actuarial bRFS and toxic effect incidence were analyzed using the Kaplan-Meier method. Alive, relapse-free patients were censored at the time of last follow-up. For each EPIC-26 domain, the significance of the mean score changes was assessed by the mixed-effects model.[26] The clinically meaningful decline in QOL (minimally important difference [MID])[27] was defined as 0.5 of the SD from baseline for each domain. Univariate analysis was performed using the Cox proportional hazards regression method. Statistical computations were performed using the Prism 7.0 software (GraphPad Inc).

Figure 1. CONSORT Diagram



SBRT indicates stereotactic body radiotherapy; SDRT, single-dose radiotherapy.

Results

Patient Demographics

Between September 2015 and January 2017, 30 participants were randomized to either 5 fractions of 9 Gy SBRT, a fraction each day for 5 consecutive days, or a single dose of 24 Gy SDRT (**Figure 1**). Baseline demographic characteristics were well balanced between the 2 protocol arms (**Table**), except for the median (interquartile range [IQR]) age (66.3 [61.2-69.9] and 73.6 [64.7-75.9] years for SBRT and SDRT, respectively). All protocol dose/volume constraints were met (eTable 1 in Supplement 2), except for a minor violation (≤5%) in a bladder constraint for SDRT (dose to 1 cm^3). Workflow patterns of the 2 regimens (eTable 2 in Supplement 2) indicated the mean (SD) treatment time was 19.1 (12.5) minutes for each SBRT session and 25.9 (17.7) minutes for SDRT.

Toxic Effects

Acute grade 1 GU symptoms peaked at 1 week in both treatment arms, largely consisting of frequency and dysuria (27% [90% CI, 6%-47%] vs 40% [90% CI, 17%-63%] after SBRT and SDRT, respectively). Symptoms mostly resolved within 4 weeks in both arms. The 3-month incidence of

Table. Patient and Tumor Characteristics

Characteristic	No. (%)		
	All patients	Arm A (5 × 9 Gy SBRT)	Arm B (24 Gy SDRT)
Age, y			
Mean (SD)	69.0 (6.7)	66.5 (6.5)	71.5 (6.6)
Median (IQR)	69.5 (64.3-74.7)	66.3 (61.2-69.9)	73.6 (64.7-75.9)
Gland size, cm^3			
Mean (SD)	54.9 (27.4)	53.3 (23.9)	55.7 (30.8)
Median (IQR)	47.2 (38.9-65.2)	46.9 (40.4-75.5)	45.6 (37.7-75.2)
Pretreatment PSA level, ng/mL			
Mean (SD)	7.6 (2.9)	8.3 (2.8)	7.0 (2.9)
Median (IQR)	6.7 (5.9-8.7)	7.5 (6.2-9.5)	6.0 (5.6-7.6)
ISUP grade			
Group 2	23 (76.6)	11 (73.3)	12 (80.0)
Group 3	7 (23.3)	4 (23.7)	3 (20.0)
T stage			
T2a	15 (50.0)	9 (60.0)	6 (40.0)
T2b	6 (20.0)	1 (6.7)	5 (33.3)
T2c	9 (30.0)	5 (33.3)	4 (26.7)
Risk category			
FIR	10 (33.3)	6 (40.0)	5 (33.3)
UIR	20 (66.7)	9 (60.0)	10 (66.7)

Abbreviations: FIR, favorable intermediate risk; IQR, interquartile range; ISUP, International Society of Urological Pathology; PSA, prostate-specific antigen; SBRT, stereotactic body radiotherapy; SDRT, single-dose radiotherapy; UIR, unfavorable intermediate risk.

SI conversion factor: To convert PSA to µg/L, multiply by 1.0.

grade 1 toxic effects was 7% (90% CI, 0%-18%) and 27% (90% CI, 6%-47%) after SBRT and SDRT, respectively. Acute GI toxic effects were minimal with no instances of isolated rectal toxic effects. Time to appearance and duration of late toxic effects were similar between the 2 arms, although there was a trend toward a higher incidence of GU toxic effects after SDRT at all time points. **Figure 2**A shows cumulative actuarial probabilities of grade 1 GI toxic effects (HR, 0.37; 90% CI, 0.07-1.94). There were no grade 2 or greater GI toxic effects in either arm. The SBRT and SDRT cumulative late actuarial GU toxic effects did not differ for grade 1 (Figure 2B; HR, 0.41; 90% CI, 0.13-1.27) and grade 2 or greater (Figure 2C; HR, 1.07; 90% CI, 0.21-5.57), with only 1 patient developing a grade 3 late toxic effect (ureteric stenosis at 30 months; SDRT arm). There were no grade 4 treatment-related acute or late GU or GI toxic effects. Analysis of potential predictors of grade 2 or greater toxic effects following 24 Gy SDRT (eTable 1 in Supplement 2) revealed that bladder trigone D5% 19 Gy or greater and D50% 9 Gy or greater appeared to be associated with an increased risk (2 of 3 cases with D50% ≥ 9 Gy vs 0 of 12 cases with D50% < 9 Gy). All patients who experienced GU toxic effects of grade 2 or greater had a gland volume of 50 cm^3 or greater. Incidence was equally distributed between the 2 arms.

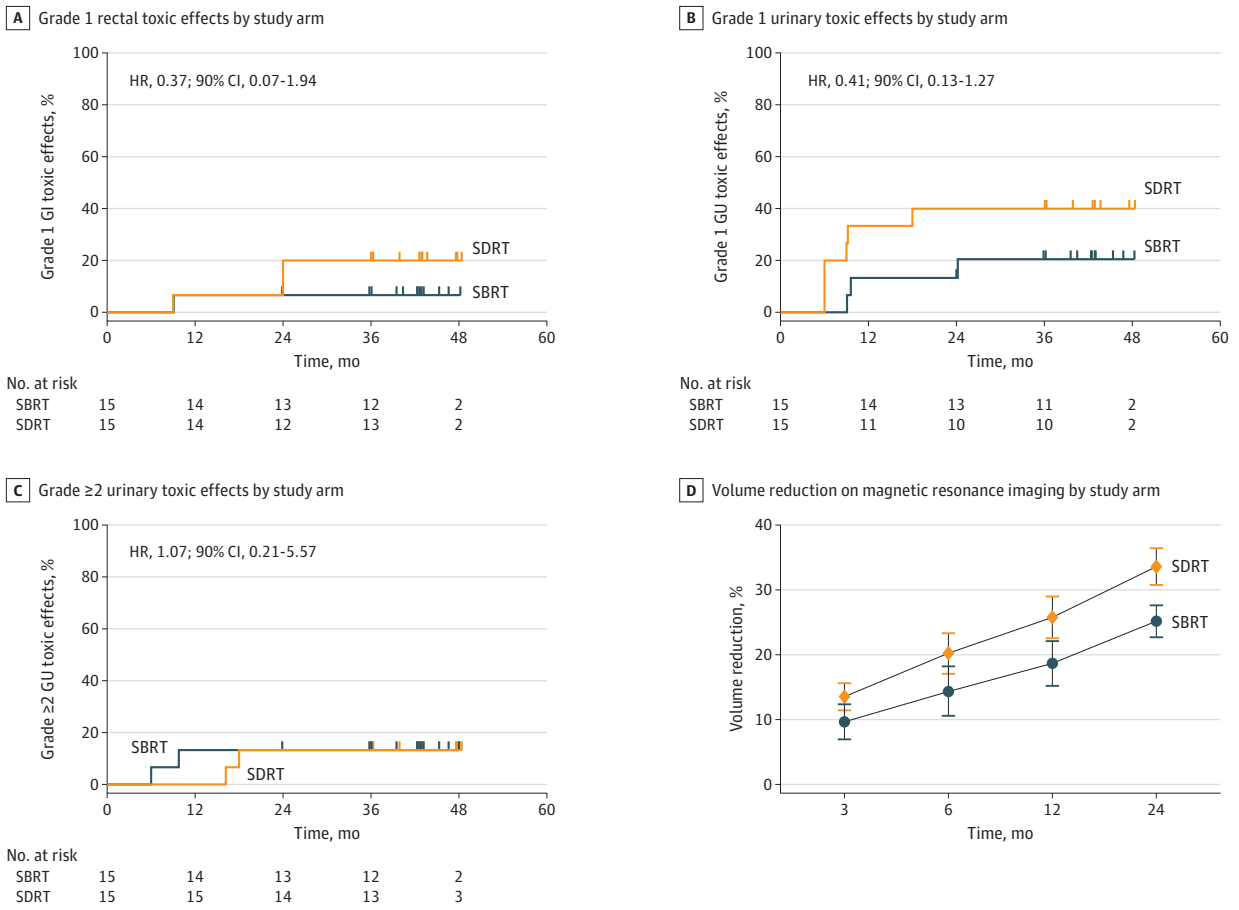
MR Findings

All patients had a detectable PI-RADS (Prostate Imaging Reporting and Data System) 4 or 5 dominant lesion (median [IQR] linear diameter, 15 [11-19] mm), exhibiting a similar progressive reduction in lesion mean maximum diameter (eTable 3 in Supplement 2) in the 2 arms. There was an increasing proportion of complete MR responses over time (eTable 4 in Supplement 2) in both study arms at 12 months (71% [90% CI, 49%-94%] for SBRT and 53% [90% CI, 30%-77%]) and 24 months (85% [90% CI, 66%-100%] and 62% [90% CI, 37%-87%]. Follow-up MR imaging showed progressive glandular atrophy with prostate volume reduction with both regimens (Figure 2D). Mean volume reductions at 12 and 24 months were 19% (90% CI, 12%-24%) and 26% (90% CI, 20%-32%) vs 25% (90% CI, 21%-32%) and 34% (90% CI, 29%-39%) for SBRT and SDRT, respectively.

PSA Outcomes

Median follow-up duration was 48 months. No patient was lost to follow-up, although 2 patients in the SBRT arm died of a second primary malignant neoplasm at median time of 48.5 months, mandating the 48-month time point for data analysis. **Figure 3**A shows similar PSA declines for the 2 arms. Median (IQR) PSA level at 3 years was 0.30 (0.10-0.59) ng/mL and 0.40 (0.30-0.48) ng/mL for the SBRT and SDRT arms, respectively. Relapses in PSA occurred in 2 patients in the SBRT arm and 3 patients in the SDRT arm at a median of 26.6 and 27.3 months, respectively, rendering 48-month actuarial bRFS of 85.7% vs 77.1% (Figure 3B; HR, 0.69; 90% CI, 0.16-3.03). A detailed account of patterns of failures and their management is provided in the eResults in Supplement 2. None of the patients with favorable intermediate-risk (FIR) disease experienced biochemical failure in either regimen (Figure 3C). In the UIR group, bRFS was 75.0% vs 64.0% (HR, 0.76; 90% CI, 0.17-3.31) for the

Figure 2. Clinical Outcomes of Stereotactic Body Radiotherapy (SBRT) vs Single-Dose Radiotherapy (SDRT) Stratified by Treatment Arm



A, Cumulative incidence of bowel grade 1 gastrointestinal (GI) toxic effects. B, Cumulative incidence of genitourinary (GU) grade 1 toxic effects. C, Cumulative incidence of urinary grade ≥2 toxic effects. D, Percentage volume reductions compared to baseline measured by magnetic resonance imaging. Error bars indicate SE; HR, hazard ratio.

SBRT and SDRT arms, respectively (Figure 3D). Consistent with this observation, initial biopsy International Society of Urological Pathology grade, presence of perineural invasion, pretreatment PSA level, and MR stage were all associated with PSA relapse probability (eTable 5 in Supplement 2). None of the PSA kinetic parameters differed between the 2 regimens (eTable 6 in Supplement 2). Benign PSA bounces were similar in rates of occurrence, time to bounce, and magnitude or duration between the 2 regimens.

Repeated Biopsy

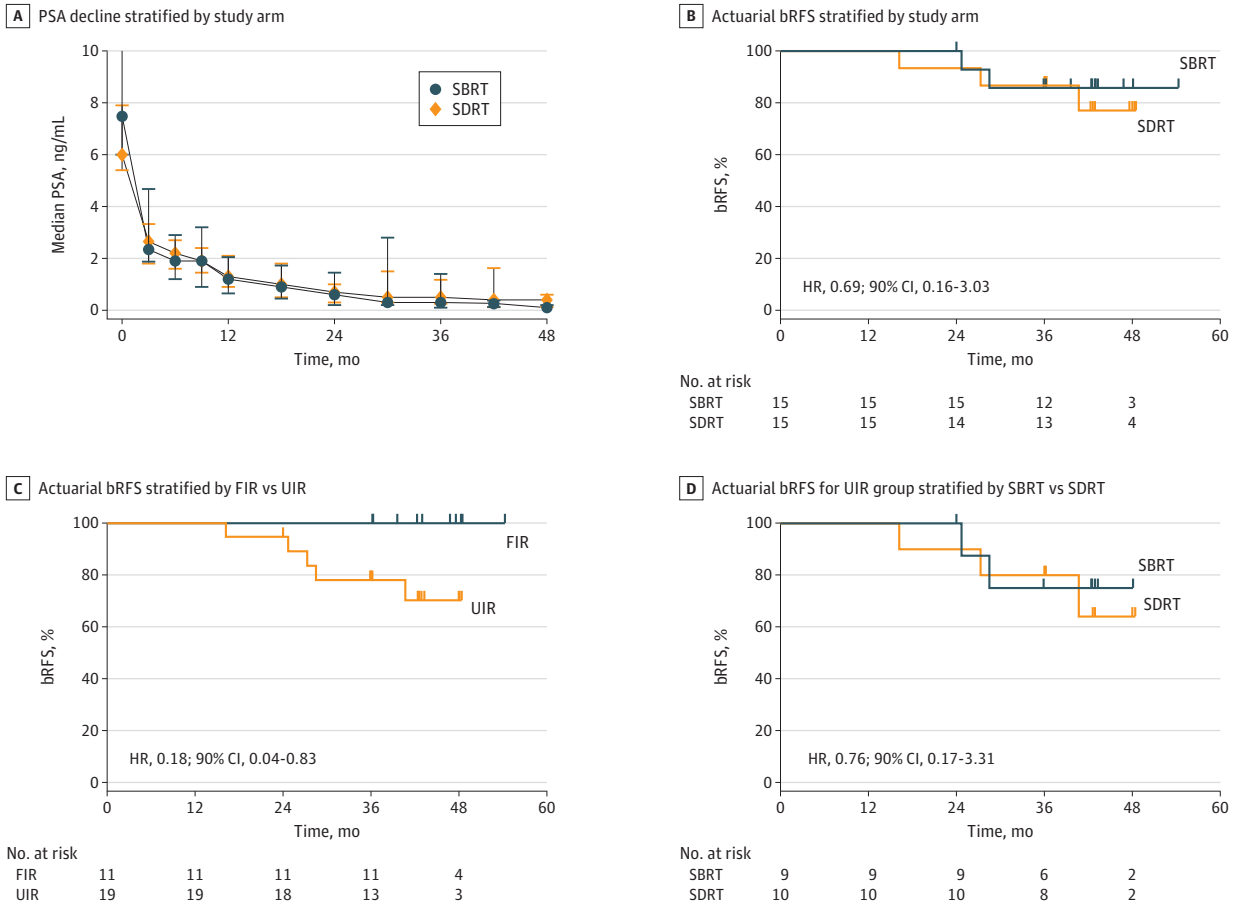
As part of the study, all patients were offered a planned 24-month posttreatment biopsy. However, more than 90% of the patients refused this biopsy, rendering analysis of this response metric unfeasible.

Patient-Reported Outcomes

Overall questionnaire adherence was 92%. **Figure 4** and eFigure 4 in Supplement 2 show median EPIC-26 summary scores and above-MID proportions for the GU, GI, and sexual domains. The 2 trial arms had similar mean scores at the study time points for the GU and GI domains. The above-MID proportions at 18 months were 25% (90% CI, 1.6%-48%) vs 47% (90% CI, 23%-70%) for SBRT vs SDRT, respectively.

The overall GU bother[28] (eFigure 2A in Supplement 2) mirrored the tendency of increased urinary symptoms in the SDRT arm. None of the trial patients reported experiencing a major GU bother at any poststudy time point, although the IPSS-derived[29] patterns late urinary symptom flare suggests a trend of higher prevalence after SDRT between months 9 and 18 (20% [90% CI, 3%-37%] vs none after SBRT). The Radiation Therapy Oncology Group (RTOG) GU and GI meaningful end points for the tolerability and safety for prostate SBRT (RTOG 0938)[30] were met in both regimens (eFigure 3 in Supplement 2). The sexual domain had large time-dependent variations in both arms (eTable 7 and eFigure 4C in Supplement 2), with proportions of above-MID patients peaking at 12 months (46% [90% CI, 21%-72%] and 62% [90% CI, 37%-87%] for SBRT and SDRT, respectively).

Figure 3. Prostate-Specific Antigen (PSA) Response With Stereotactic Body Radiotherapy (SBRT) vs Single-Dose Radiotherapy (SDRT)



A, Median PSA over time stratified by treatment arm; error bars indicate interquartile range. B, Actuarial PSA relapse-free survival (bRFS) stratified by treatment arm. C, Actuarial bRFS stratified by favorable intermediate-risk (FIR) vs unfavorable intermediate-risk (UIR) categories. D, UIR actuarial bRFS stratified by treatment arm. HR indicates hazard ratio.

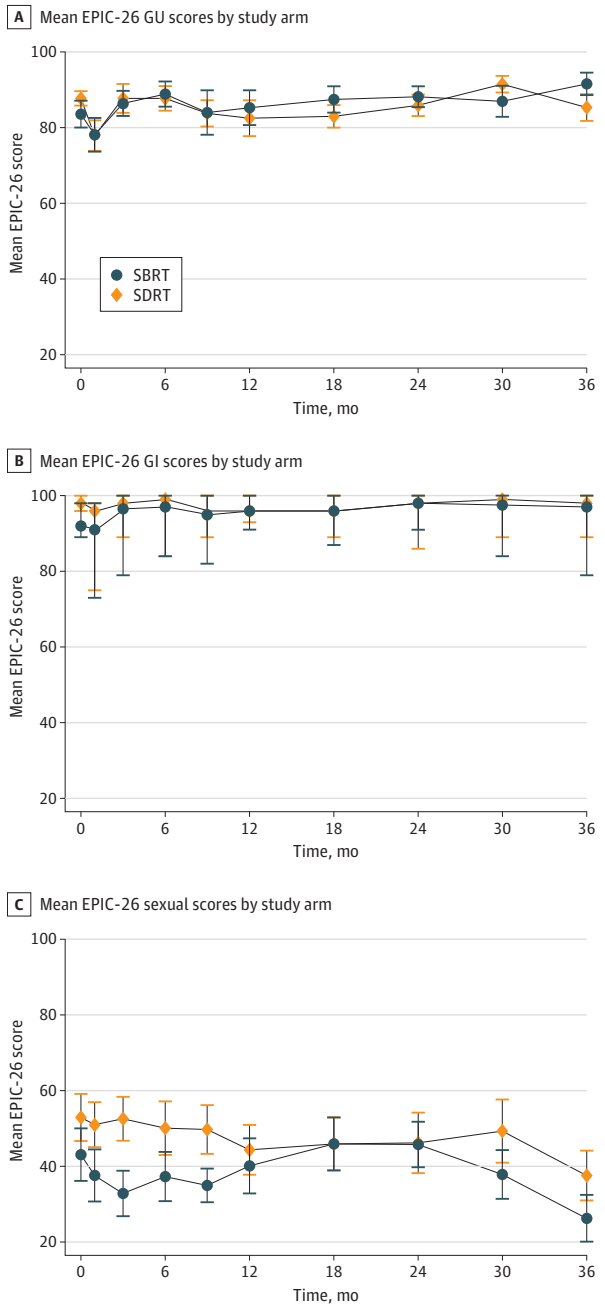
Discussion

This proof-of-concept parallel-group randomized clinical trial confirms that 24 Gy SDRT is feasible and safe in the treatment of organ-confined prostate cancer. The 5 × 9 Gy SBRT prostate immobilization and high-precision technique had been previously proven feasible and safe.[17] The present study shows that 24 Gy SDRT and 5 × 9 Gy SBRT match in each and every tumor toxic effect and PSA end points. Unlike the randomized approach adopted here, other phase 1/2 nonrandomized trials (ClinicalTrials.gov identifiers: NCT03294889 and NCT04004312) are currently under way to examine the safety and efficacy of SDRT in localized prostate cancer.[31,32]

The present trial data suggest that prostate cancer SDRT is not a mere tumor-directed ablative modality, but that it has collateral normal prostate tissue effects, as progressive radiation-induced glandular atrophy was markedly pronounced with SDRT, leading to a median gland volume reduction of 35% at 24 months with a concomitant PSA decline to 0.5 ng/mL or lower at 3 years.[33] The glandular ablative effect defines SDRT akin to a virtual prostatectomy, with the entire therapeutic dose delivered in a single, short, noninvasive procedure. Current artificial intelligence–based deep learning and machine learning developments might yield algorithms enabling same-day online target/OAR registration, fast artificial intelligence–derived treatment planning,[34] and SDRT delivery as a continuous multifunctional procedure, completed within a reasonably short time frame.

Whereas 24 Gy SDRT exceeds the radiosensitivity thresholds of prostate-associated OARs, the use of an appropriate high-precision targeting technology and a target immobilization throughout treatment delivery are absolutely critical in providing effective conformal avoidance of normal tissues by means of intensity-modulated inverse dose painting.[35] In addition, MR-based treatment planning was an integral component in achieving favorable OAR outcomes, as MR imaging permits identification and sparing of critical tissues, including the urogenital diaphragm and neurovascular bundles. This trial did not make use of hydrogel spacers, a procedure that has been consistently shown to reduce rectal toxicity.[36] Rather, rectal sparing was achieved

Figure 4. EPIC-26 Patient-Reported Outcomes of Stereotactic Body Radiotherapy (SBRT) vs Single-Dose Radiotherapy (SDRT) Over Time Stratified by Treatment Arm



Mean summary scores for the genitourinary (GU) domain (A), gastrointestinal (GI) domain (B), and sexual domain (C). Error bars indicate SEM. EPIC indicates Expanded Prostate Cancer Index Composite.

through a noninvasive air-filled endorectal balloon approach to immobilize the prostate during treatment delivery.[17]

Patient-reported outcomes[37-39] were an integral part of this study and mostly showed similar results between the 2 regimens. Urethra sparing with the same dose reductions was also used in both study arms. Nonetheless, there was a trend toward higher patient-reported mild GU discomfort with SDRT, and, consistently, the incidence of a transient late urinary flare syndrome[40-44] was higher following SDRT. The cause of this self-limiting phenomenon probably resides in the dose to the bladder trigone,[45] rather than in the urethra, and the implementation of stricter SDRT dose/volume constraints in this area is therefore warranted, as it may abrogate this late adverse effect.[46] The excellent profiles of the GI self-reported outcomes with both dose regimens confirm the reliability of the rectal sparing effect provided by the target immobilization technique. Analysis of patient-reported sexual domain outcomes and their interpretation is highly complex given the multifaceted nature of sexuality. Preliminary assessment, however, indicates that comprehensive conformal avoidance of vascular structures, including the MR-detectable neurovascular bundles, may lead to preservation of erectile function in sexually active patients, showing no obvious difference between the 2 ultra-high-dose regimens.

Lastly, SDRT provides advantages in patient convenience as a result of the reduced number of visits. This could potentially lead to same-day planning and treatment, as well as provide significant cost savings, an issue already addressed relative to SBRT schemes,[47,48] a major consideration in today's increasingly cost-conscious environment.

Limitations

This trial has several limitations. Of note are the single institution, small sample size, and median follow-up of only 48 months.

Conclusions

This study offers encouraging perspectives on the feasibility and safety of 24 Gy SDRT in organ-confined prostate cancer. Despite the limitation of a small sample size, the SDRT PSA end points recapitulate the outcomes of curative extreme hypofractionated 5 × 9 Gy SBRT reported here and in the recent literature.[17] These observations encourage further exploration of the SDRT virtual-prostatectomy approach. A phase 2 single-arm study designed to accrue 200 patients is currently under way (ClinicalTrials.gov identifier: NCT04035642) to further establish the efficacy, safety, and indications for SDRT for treatment of organ-confined primary prostate cancer.

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Concept and design: Greco, Mateus, Fuks.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Greco, Mateus, Fuks.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Greco, Marques, Fuks.
Obtained funding: Greco.
Administrative, technical, or material support: Greco, Pares, Vieira, Stroom, Mateus, Soares, Freitas, Coelho, Seixas, Fuks.
Supervision: Greco, Fuks.

Conflict of Interest Disclosures: Drs Greco and Fuks are founders of Ceramedix Inc and also reported patent application number PTC/PT2020/050027 related to this work. Dr Fuks also reported patents unrelated to this work (US10413533B2, US20170333413A1, US20180015183A1). No other disclosures were reported.

Meeting Presentation: This study was presented at the American Society for Radiation Oncology 2020 Annual Meeting (Poster No. 3994: Single-Dose vs 5-Fraction SBRT for Intermediate-Risk Prostate Cancer: 4-Year Results From a Randomized Trial); October 28, 2020.

Data Sharing Statement: See Supplement 3.

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