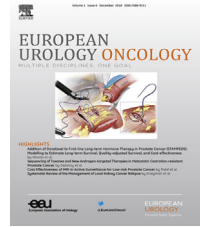


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Phase 2 Multicenter Trial of Heterogeneous-dosing Stereotactic Body Radiotherapy for Low- and Intermediate-risk Prostate Cancer: 5-year Outcomes

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Abstract

Background: Stereotactic body radiation therapy is an emerging treatment for prostate cancer (PC), with potential biological and oncologic advantages. A well-established radiation dosing schedule (38 Gy in 4 fractions) has shown excellent long-term efficacy in high-dose-rate (HDR) brachytherapy.

Objective: To report 5-yr efficacy, toxicity, and quality-of-life (QOL) outcomes of a novel 4-d SBRT regimen.

Design, setting, and participants: This was a single-arm prospective phase 2 trial involving 259 patients with low- or intermediate-risk PC treated at 18 US centers from December 2007 to February 2012. The median follow-up was 5 yr (interquartile range 37–85 mo).

Intervention: SBRT with 38 Gy in four fractions; radiation plans mimicked HDR brachytherapy dosimetry.

Outcome measurements and statistical analysis: We measured freedom from biochemical recurrence (BCR) and assessed toxicities using the Common Terminology Criteria for Adverse Events v3.0 and QOL using the Expanded Prostate Cancer Index Composite.

Results and limitations: The 5-yr BCR-free rates were 100% and 88.5% for patients with low- and intermediate-risk PC, respectively. The cumulative 5-yr grade 2, 3, and 4 toxicity rates were 12.4%, 1.9%, and 0.4% for urinary, and 3.4%, 0%, and 0% for gastrointestinal toxicities, respectively. The median baseline prostate-specific antigen (PSA) level of 5.12 ng/ml decreased to 0.1 ng/ml by ≥ 42 mo. QOL scores decreased at 1 mo but returned to baseline by 6 mo, with a later decline (≥ 24 mo) in the urinary continence domain (pad use was 2% at baseline and 10% at 5 yr), and lower sexual potency over time. Comparative outcomes versus other types of radiotherapy are difficult because the trial was not randomized.

Conclusions: This regimen yields a high rate of BCR-free survival, with a very low median PSA nadir suggesting prostate ablation. For properly selected patients with low- or intermediate-risk PC who choose SBRT, this treatment regimen is effective.

Patient summary: This potent four-treatment stereotactic body radiotherapy regimen appears to be effective for patients with early prostate cancer.

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1. Introduction

Stereotactic body radiotherapy (SBRT) is an evolving option for patients with localized prostate cancer. Traditionally, external beam radiotherapy has involved small doses (1.8–2 Gy) of radiation delivered over 8–9 wk. The recognition of a low α/β ratio [1], suggesting better response to higher doses per fraction, is the basis for hypofractionated radiotherapy for this disease. Several randomized trials have demonstrated the safety and efficacy of moderately hypofractionated radiotherapy [2–5], which shortens the duration to 4–5 wk. The use of SBRT further shortens treatment to 1–2 wk [6,7]. It has been shown that SBRT is less costly than long courses of intensity-modulated radiotherapy (IMRT) [8]. Thus far, SBRT studies have primarily come from large academic centers [6], and the effectiveness of this treatment in the community setting is relatively unknown. Furthermore, published SBRT studies have relatively short follow-up, with undefined long-term efficacy.

A well-established dosing schedule of 38 Gy in four fractions has excellent efficacy in high-dose-rate (HDR) brachytherapy, and has been recognized by the American Brachytherapy Society as a standard option [9]. The current prospective multicenter phase 2 trial was designed to emulate this regimen with SBRT, while eliminating the invasiveness of brachytherapy. We report efficacy, toxicity and quality-of-life (QOL) results at median follow-up of 5 yr.

2. Patients and methods

2.1. Patients and treatment

Eligible patients had low- or intermediate-risk prostate cancer according to the D'Amico classification [10,11]; all pathology was centrally reviewed (Bostwick Laboratories, Glen Allen, VA, USA). Patients were

treated from 2007 through 2012 at 18 institutions; 85% were treated at community centers (Supplementary Table 1). The full inclusion and exclusion criteria are summarized in Supplementary Table 2. The clinical trial was registered with clinicaltrials.gov (NCT00643617); all participating institutions received institutional review board approval.

Patients received 38 Gy in four daily fractions of 9.5 Gy per fraction using a fiducial-guided robotic SBRT technique (CyberKnife; Accuray, Sunnyvale, CA, USA). Androgen deprivation therapy was not allowed. All centers had three treatment plans centrally approved before their participation was allowed. Computed tomography (CT)-based simulation was performed using a Foley catheter for urethra delineation (the catheter was not used during treatment); prostate magnetic resonance imaging with CT co-registration was encouraged (not required). The clinical target volume (CTV) included the prostate for all patients; for patients with intermediate-risk disease, 1 cm of the proximal seminal vesicles was included. The planning target volume (PTV) margin was a 2-mm expansion in all directions, except posteriorly where the prostate abutted the rectum, which had a 0-mm margin. For Gleason 7 cancer, the dorsolateral side(s) of the involved prostate had a 5-mm PTV expansion to cover potential extracapsular extension. Regardless of the margin expansion, dosimetry requirements remained constant. Treatment coverage and normal tissue constraints are detailed in Supplementary Table 3. Bladder, urethra, and rectal wall constraints were fully achieved in 82.2%, 92.9%, and 64.1% of cases, respectively, with minor deviations in the majority of the remainder and major deviations in 1.5%. The trial required $\geq 1\%$ of the PTV to receive at least 150% of the prescription dose (achieved in 100% of cases) to emulate HDR brachytherapy dosimetry (Fig. 1). There was no prostate volume limitation.

2.2. Outcomes assessed

Patients were evaluated at 3, 6, 12, 18, and 24 mo and every 6–12 mo thereafter. Biochemical recurrence was according to the Phoenix definition (nadir plus 2 ng/ml) [12].

Toxicity was assessed using the Common Terminology Criteria for Adverse Events version 3.0. Patient-reported QOL was assessed using the validated Expanded Prostate cancer Index Composite-26 (EPIC-26) [13] for four domains: urinary incontinence; urinary irritation or obstruction;

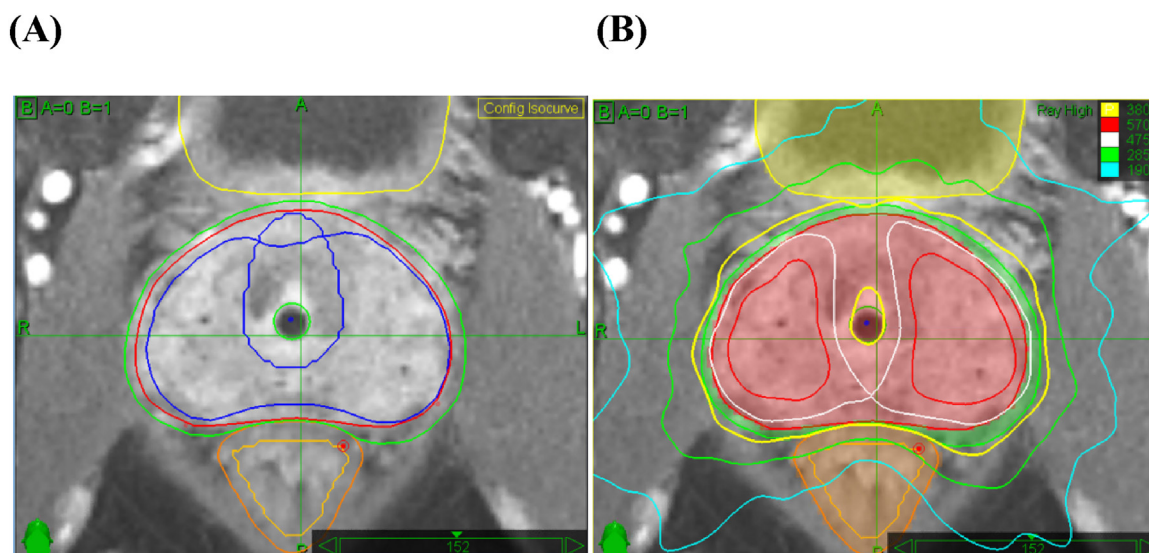


Fig. 1 – Mid axial section of (A) a typical SBRT contour and (B) treatment plan for a patient with intermediate-risk prostate cancer (Gleason score 7 with left-sided involvement, with corresponding larger GTV to PTV expansion on that side). In (A) the GTV is outlined in red, PTV in green, and peripheral-zone tuning structure in blue. In (B) the 38-Gy prescription isodose line is in yellow, and the 125%, 150% and 75% isodose lines in white, red, and green, respectively. The isodose morphology is intended to substantially recapitulate that of high-dose-rate brachytherapy. For the entire cohort, the median prostate volume receiving $>150\%$ of the prescribed dose was 11.7% (range 0.1–32.2%). GTV = gross tumor volume; PTV = planning target volume.

bowel score, and sexual score, with scores ranging from 0 (worst) to 100 (best).

2.3. Statistical methods

The Kaplan-Meier method was used to estimate freedom from biochemical recurrence (FFBR) and a log-rank test was applied for comparison of risk groups.

As QOL scores are difficult to interpret [14], we indicate if QOL score changes are clinically meaningful using the published minimally clinically important difference (MCID) for each EPIC-26 domain [15,16] and report the prevalence of each symptom assessed following established methodology [17].

All statistical analysis was performed using SAS v.9.4 (SAS Institute, Cary, NC, USA), and two-sided *p* values of < 0.05 were considered statistically significant.

3. Results

Overall, 259 patients were enrolled and the median age was 68.7 yr (Table 1). Of these, 43% had low-risk and 57% had intermediate-risk (114/147 favorable; 33/147 unfavorable) prostate cancer.

3.1. PSA response and FFBR

The median follow-up was 5 yr (interquartile range [IQR] 37–85 mo). The median prostate-specific antigen (PSA) continued to decrease to 0.1 ng/ml by 42 mo (IQR 0.1–0.3), remaining at or below that level through last follow-up (Fig. 2). Eighty-nine patients (34.4%) experienced continuously decreasing PSA throughout their entire follow-up; the remaining 170 patients (65.6%) had at least one increased PSA, although only 13 patients developed biochemical recurrence, yielding a benign PSA bounce rate of 61% (median rise 0.2 ng/ml, median time 18 mo). PSA rises of ≥ 2 ng/ml had a benign etiology in 4/17 cases (ie, lower subsequent nadir with no added treatment) and are not counted as relapses, while 13/17 had a continued rise and confirmed relapse. PSA rises associated with relapse had a higher nadir (2.2 vs 1.2 ng/ml) and a shorter interval to occurrence (16 vs 23 mo post-SBRT).

The 5-yr FFBR was 100% for low-risk and 88.5% for intermediate-risk cases (Fig. 3). Subdivision of intermediate-risk cases into favorable and unfavorable intermediate-risk (National Comprehensive Cancer Network criteria) yielded 5-yr FFBR rates of 90.7% and 81.0%, respectively (*p* = 0.158), with a recurrence hazard ratio of 2.3 for unfavorable-risk disease (95% confidence interval 0.7–7.4). Seven patients had distant metastases, three experienced biopsy-proven local failure (1 with concurrent distant metastases), and 11 received additional anticancer treatment (androgen deprivation therapy [ADT]). There was a single prostate cancer-specific death and 19 deaths from unrelated causes.

3.2. Toxicity

Acute genitourinary (GU) toxicity rates (≤ 90 d) were 35.1% for grade 2 and 1.1% for grade 3, including one patient (0.4%) with urinary retention requiring catheterization and two

Table 1 – Patient characteristics (n = 259)

Parameter	Result
Age at diagnosis, n (%)	
40–49 yr	1 (0)
50–59 yr	36 (14)
60–64 yr	46 (18)
65–69 yr	69 (27)
70–74 yr	67 (26)
75–79 yr	35 (14)
≥ 80 yr	5 (2)
Race, n (%)	
White	232 (90)
Black or African American	8 (3)
Hispanic or Latino	13 (5)
Asian	2 (1)
Other	4 (2)
Risk group, n (%)	
Low	112 (43)
Intermediate	147 (57)
Favorable intermediate	114 (44)
Unfavorable intermediate	33 (13)
Median PSA at baseline, ng/ml (range)	5.1 (0.1–19.3)
Baseline PSA, n (%)	
≤ 4 ng/ml	76 (29)
4.01–10 ng/ml	170 (66)
> 10 ng/ml	13 (5)
Gleason score, n (%)	
3 + 3	128 (49)
3 + 4	109 (42)
4 + 3	22 (9)
Clinical T stage, n (%)	
T1c	183 (71)
T2a	73 (28)
T2b	3 (1)
Median IPSS at baseline (range)	5 (0–29)
Patients with TURP at baseline	
Yes	9 (4)
No	250 (96)
Median prostate volume, cm ³ (range)	38 (14–145.1)
PSA = prostate-specific antigen; IPSS = International Prostate Symptom Score; TURP = transurethral resection of the prostate.	

with frequency/dysuria. Acute gastrointestinal (GI) toxicity rates were 6.9% for grade 2 and 0% for grade ≥ 3 . After 90 d, the 5-yr cumulative incidence of late GU toxicity was 12.7% for grade 2, 1.9% for grade 3, and 0.4% for grade 4 (1 patient had total cystoprostatectomy for cystourethritis). The 5-yr cumulative incidence of grade 2 GI toxicity was 3.4% (including 0.8% due to rectal bleeding). No grade ≥ 3 long-term GI toxicity was observed. There was no increase in grade ≥ 3 GU or GI toxicity beyond 5 yr and no toxicity differences between risk groups.

3.3. Quality of life

Patients reported urinary obstructive and irritative symptoms by 1 mo after treatment, which resolved to near baseline levels by 6 mo (Fig. 4A). The proportion of patients reporting dysuria, a weak stream, and urinary frequency increased from baseline to 1 mo (Table 2), but long-term results at 60 mo were similar to baseline, with no patient reporting late hematuria. Incontinence increased from 2% of patients reporting pad use at baseline to 10% at 60 mo, typically 1 pad/d (Fig. 4B and Table 2). No specific prostate, bladder, or

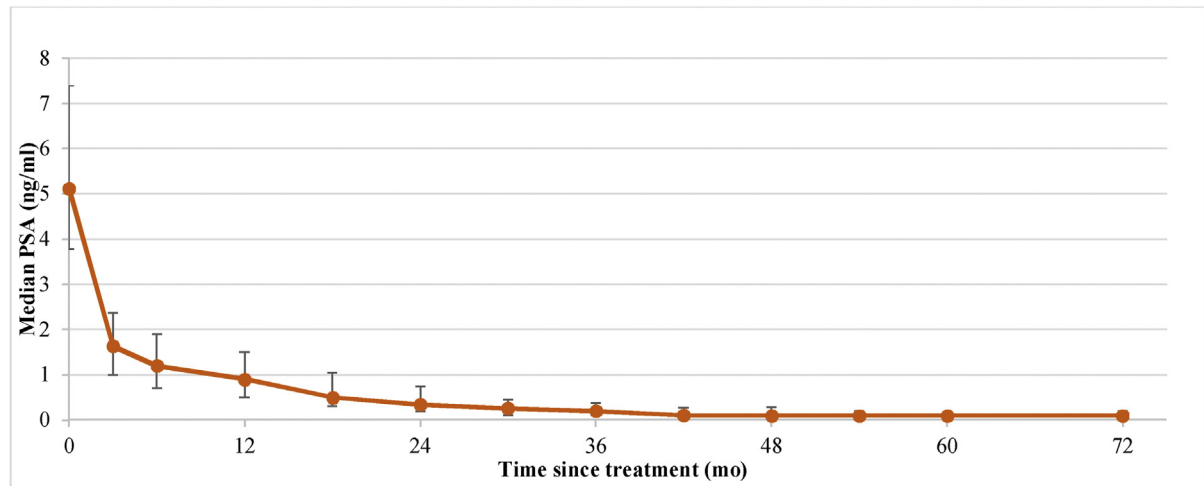


Fig. 2 – Median prostate-specific antigen (PSA) over time for the overall trial population. The median and interquartile range are plotted.

urethra dosimetry factor was associated with long-term pad use; however, the risk of pad use was 1.72 times higher for patients with baseline transurethral resection of the prostate (TURP) than for patients without TURP.

Short-term increases in bowel urgency and frequency and rectal pain (Table 2) improved between 1 and 6 mo. Bowel scores were similar to baseline at ≥ 36 mo (Fig. 4C). By 60 mo, the proportion of patients reporting bloody stools was $<1\%$.

Sexual function scores declined gradually (Fig. 4D). Overall, 42% of patients reported poor erections at baseline, which increased to 67% by 60 mo (Table 2). Of patients who were fully potent at baseline, 47% remained so at 5 yr. There was no difference in any GU, GI, or sexual QOL outcome between risk groups.

4. Discussion

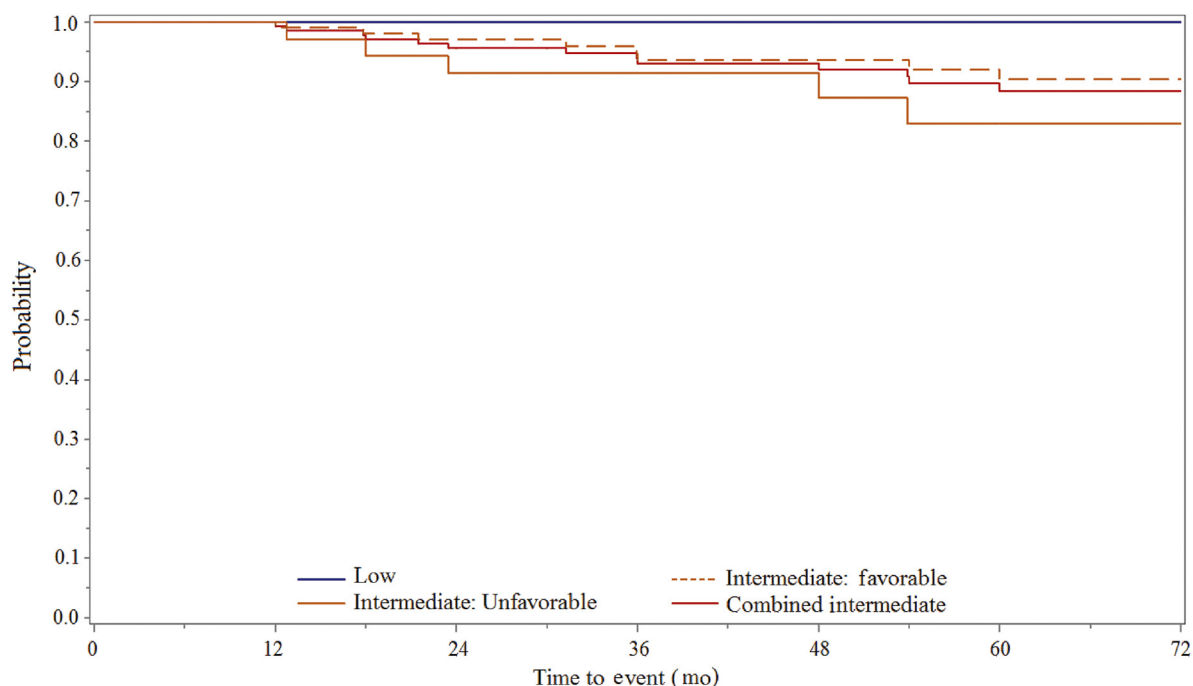
Prostate cancer radiotherapy is getting shorter, from conventional fractionation to moderate hypofractionation (4–5 wk), to increasing use of SBRT (1–2 wk) [18]. The current prospective SBRT trial is the first to report results at median follow-up of 5 yr, with a comprehensive assessment of efficacy, physician-assessed toxicity, and patient-reported QOL. To the best of our knowledge, ours is the first large, prospective, multi-institutional trial to use this novel four-fraction dosing regimen for SBRT. Within this context, several features and findings of the trial warrant discussion.

First, we used a dosing regimen (38 Gy in 4 fractions) that has well-established efficacy in HDR brachytherapy, although the safety and efficacy have not been well studied for external beam radiotherapy. The most commonly published SBRT regimen uses 35–36.25 Gy in five fractions over 1–2 wk [6,19]. The use of HDR-like planning and a higher total dose (38 Gy) represents a more intensive

treatment than the common SBRT regimen. Assuming the α/β ratio for prostate cancer to be 2.0, this regimen delivered an equivalent dose at 2 Gy per fraction (EQD2) of 110 Gy to the margin of the PTV, with a substantially higher dose in the peripheral zone, compared to an EQD2 of 82 Gy for the common five-fraction regimen.

The higher biologically effective dose delivered with SBRT might result in greater toxicity. A prior study using Surveillance, Epidemiology and End Results-Medicare claims data [8] and a phase 1 dose-escalation trial [20] suggested high toxicity rates after SBRT, increasing this concern. The current study adds to the literature by providing comprehensive data on treatment-related toxicity via both physician-assessed grading and patient-reported QOL through 60 mo of follow-up. Overall, these results seem comparable in the context of published data for conventionally fractionated radiotherapy, with an acceptably low incidence of late grade ≥ 3 GU or GI toxicity (2.3% and 0%, respectively). However, we did observe a patient-reported rate of incontinence requiring pad use at 5 yr of 10%. This observation requires additional investigation as to whether better patient selection, such as caution in using this regimen for patients with prior TURP, might reduce this risk. This incontinence rate might not apply to less potent SBRT regimens. It is also possible that the catheter for simulation might distort the urethra position, and other methods to identify the urethra for treatment planning could be explored.

In one of the most commonly cited studies, Sanda et al. [17] described prevalence data for urinary, bowel, and sexual domain symptoms (2 yr) similar to the current study (5 yr) using the same EPIC-26 instrument among 292 IMRT patients. The CHHiP randomized trial reported approximately 30% acute grade 2 GU and GI toxicity after a regimen



Year	1	2	3	4	5	6
Low risk						
Number at risk	104	99	80	64	50	27
Cumulative failures	0	0	0	0	0	0
Kaplan-Meier estimate (%)	100.00	100.00	100.00	100.00	100.00	100.00
95% confidence interval (%)	NA	NA	NA	NA	NA	NA
Intermediate risk: favorable						
Number at risk	110	99	86	71	57	29
Cumulative failures	1	3	6	6	8	8
Kaplan-Meier estimate (%)	99.10	97.20	93.90	93.90	90.70	90.70
95% confidence interval (%)	93.7–99.9	91.5–99.1	86.8–97.2	86.8–97.2	82.0–95.3	82.0–95.3
Intermediate risk: unfavorable						
Number at risk	31	28	26	20	13	9
Cumulative failures	0	3	3	4	5	5
Kaplan-Meier estimate (%)	100	90.30	90.30	85.80	81.00	81.00
95% confidence interval (%)	NA	72.9–96.8	72.9–96.8	66.0–94.5	59.6–91.8	59.6–91.8
Intermediate risk: all						
Number at risk	141	127	112	91	70	38
Cumulative failures	1	6	9	10	13	13
Kaplan-Meier estimate (%)	99.30	95.60	93.10	92.10	88.50	88.50
95% confidence interval (%)	95.1–99.9	90.5–98.0	87.1–96.3	85.7–95.7	80.7–93.2	80.7–93.2

Fig. 3 – Freedom from biochemical recurrence for the overall trial population and stratified by risk group.

of 60 Gy in 20 fractions [3]. These results are comparable to or somewhat worse than the toxicity reported in the present study.

The toxicity profile in our trial also compares favorably with brachytherapy. Post-brachytherapy acute urinary retention has been reported following both permanent source and HDR prostate brachytherapy, with an incidence of up to 12% [21–23]. In our trial the incidence of acute retention was <1%. Similarly, our QOL results for short-term urinary obstruction and irritation symptoms seem better than those reported by the brachytherapy patients in the study by Sanda et al. [17]. Avoidance of needle trauma, a

possible contributor to acute post-brachytherapy urinary retention, might explain our result.

The second novel finding for this SBRT regimen is long-term PSA nadirs approaching those observed after radical prostatectomy, suggesting eventual total prostate glandular ablation. Prior SBRT and conventionally fractionated radiotherapy series without concurrent ADT had higher PSA nadir values (0.23–0.70 ng/ml after SBRT, 0.37–1.0 ng/ml after conventionally fractionated radiation) [24,25]. In our trial, median PSA reached 0.1 ng/ml by 42 mo and remained there at all time points beyond. Furthermore, 61% of patients experienced a benign PSA bounce, higher than

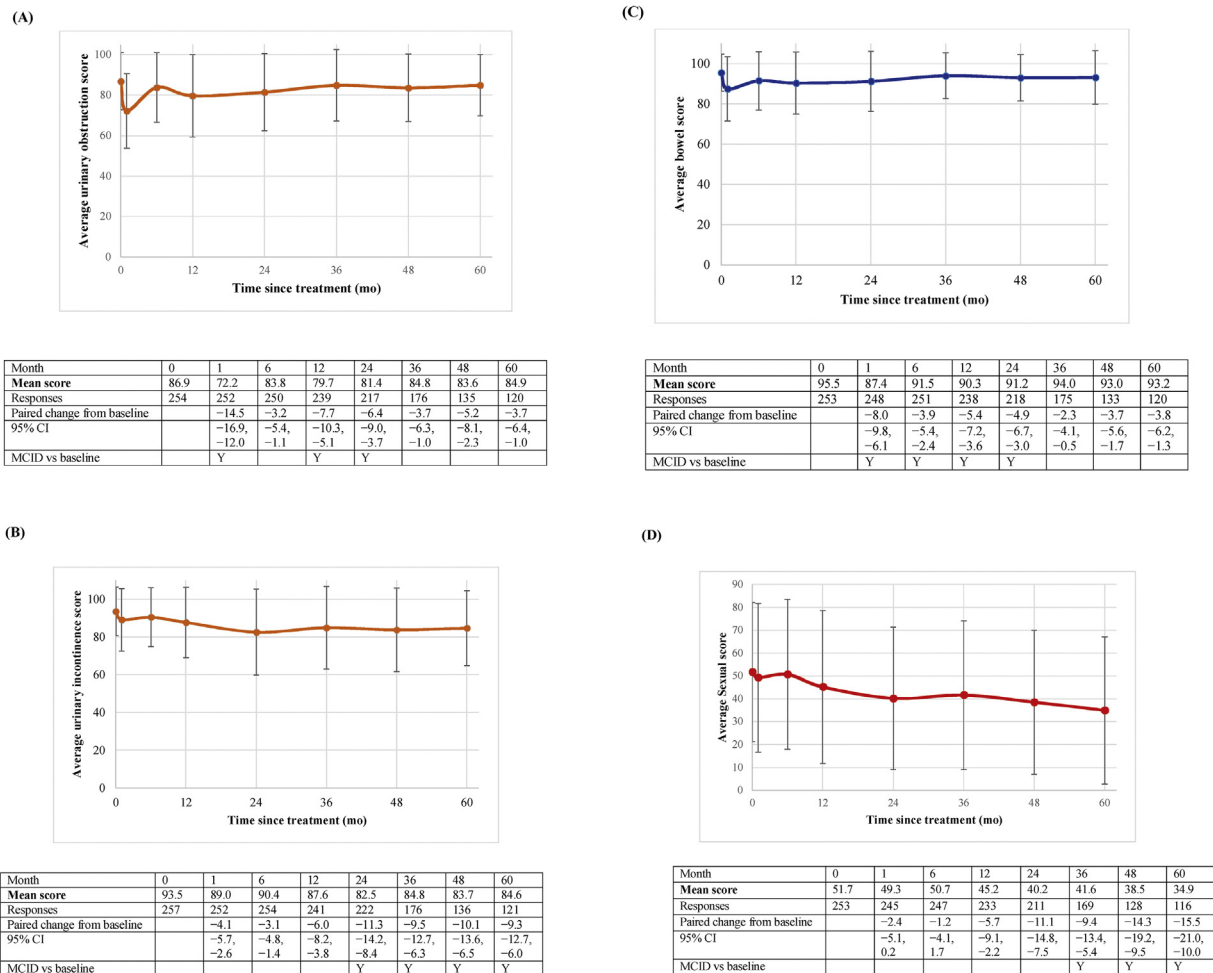


Fig. 4 – Patient-reported quality of life. The mean and standard deviation are plotted. The minimally clinically important difference (MCID) for the EPIC-26 questionnaire has been defined as 10–12 points in the sexual domain, 6 points for urinary incontinence, 5 points for urinary irritation and obstruction, and 4 points for the bowel domain [16]. (A) Urinary irritation or obstruction score. (B) Urinary incontinence score. (C) Bowel score. (D) Sexual score. CI = confidence interval.

the rates reported for other types of radiation treatment [26]. The low PSA nadir suggests biologically unique effects of this SBRT regimen compared with conventional fractionation, as previously reported by others [25].

Third, our results demonstrate efficacy, with 5-yr FFBR of 100% and 88.5% for low- and intermediate-risk disease, respectively, without ADT, comparing favorably to published series that used conventionally fractionated radiation [10,27,28]. The biochemical relapses that have occurred were limited to the intermediate-risk group, with a higher rate for unfavorable intermediate-risk (not significant) and most commonly observed within the first 3 yr after treatment, suggesting that occult disease beyond the prostate may have been present in many cases before treatment, with durable control in the remaining majority. The small number of patients with unfavorable intermediate-risk disease in the study limits the statistical power for ruling out significantly lower efficacy for them.

Owing to concerns about potential toxicity because of the high EQD2, the trial was designed with small CTV to PTV margins, especially posteriorly, with no margin to spare the

rectum. We have not observed marginal failures in this trial to date. The result of this specific approach may not be generalizable to all SBRT methods; in general there is a lack of data on the efficacy and safety of prostate SBRT using non-CyberKnife treatment machines.

Recently, large randomized trials have compared conventionally fractionated radiotherapy to moderately hypofractionated radiotherapy [3,4,29]. These trials demonstrated the safety and efficacy of hypofractionated treatment. While many patients with early prostate cancer are eligible for active surveillance, for those who choose treatment, hypofractionated radiotherapy appears to be similarly effective to and potentially more efficient than conventional fractionation methods. For patients with low- or intermediate-risk prostate cancer, we report favorable 5-yr cancer control, toxicity, and QOL outcomes after a regimen of even shorter duration, with nadir PSA results beyond 3 yr that are lower than in other IMRT and SBRT studies [24,25].

The strengths of this study include a comprehensive assessment of efficacy, toxicity, and QOL over median

Table 2 – Percentage of patients reporting each symptom^a

	Baseline	1 mo	6 mo	12 mo	24 mo	36 mo	48 mo	60 mo
Patients (n)	257	252	255	241	222	176	135	115
Urinary function (%)								
Irritation or obstruction								
Dysuria	1	16	4	10	6	2	<1	2
Hematuria	<1	0	2	<1	1	1	2	0
Weak stream	9	17	9	17	11	11	13	13
Frequency	12	24	14	22	16	15	14	17
Incontinence								
Leaking ≥ 1 times/d	3	5	4	5	10	11	11	6
Frequent dribbling	2	4	3	4	9	8	10	6
Any pad use	2	5	4	4	9	8	10	10
Leaking problem	2	4	4	7	11	6	9	8
Overall urinary problem	6	17	8	16	13	12	10	10
Bowel function								
Urgency	3	10	7	11	8	5	4	6
Frequency	1	9	5	6	4	2	3	4
Fecal incontinence	2	2	2	4	2	1	2	2
Bloody stools	0	<1	<1	1	2	<1	0	<1
Rectal pain	<1	6	5	3	3	0	0	2
Overall bowel problem	2	10	6	6	6	2	4	7
Sexual function								
Poor erections	42	44	47	52	58	58	60	67
Difficulty with orgasm	34	45	40	48	50	55	52	65
Erections not firm	48	59	59	62	71	68	70	75
Erections not reliable	50	55	56	61	68	64	69	71
Poor sexual function	41	49	48	54	60	60	64	69
Overall sexuality problem	28	33	29	36	40	36	37	44
Vitality or hormonal function								
Hot flashes	1	0	<1	2	1	1	2	2
Breast problems	<1	<1	0	<1	0	<1	0	<1
Depression	4	7	5	5	5	3	4	2
Lack of energy	10	15	13	14	11	7	10	13
Weight change	3	3	5	6	5	4	4	<1

^a Reported as in Sanda et al. [17], where a symptom was scored if a patient reported a “moderate or big problem”.

follow-up of 5 yr. Furthermore, the low PSA-nadir results we observed provide insight into the biological potency of this treatment regimen. It is also noteworthy that these outcomes were obtained across 18 mostly nonacademic centers. We recognize that the excellent disease-free outcomes in low-risk disease are expected, as these patients are eligible for active surveillance. However, some patients with low-risk disease do choose treatment, and the results from this trial provide data on a treatment course that is significantly shorter than conventional fractionation. A five-treatment SBRT regimen used in a majority of other SBRT studies also appears to be highly effective for low-risk cases, although data beyond 5 yr to assess late recurrence and toxicity remain limited [6,7].

The main limitation of this study is that this is not a randomized trial, which would require a very large sample size and many years to complete. Further longer-term follow-up is needed to assess whether there are later toxicities and recurrences beyond 5 yr.

5. Conclusions

In summary, this multi-institutional trial of a novel four-fraction heterogeneous SBRT regimen demonstrated favorable disease control, toxicity, and QOL outcomes at median

follow-up of 5 yr. The median PSA nadir was lower than previously reported in the radiotherapy literature. This study contributes to the accumulating data on long-term outcomes after different SBRT regimens for low- and intermediate-risk prostate cancer.

Author contributions: Donald B. Fuller had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Fuller.

Acquisition of data: All authors.

Analysis and interpretation of data: Fuller, Chen.

Drafting of the manuscript: Fuller, Chen, Falchook.

Critical revision of the manuscript for important intellectual content: Fuller, Chen.

Statistical analysis: Crabtree.

Obtaining funding: Fuller.

Administrative, technical, or material support: None.

Supervision: Fuller, Chen.

Other: None.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.euo.2018.06.013](https://doi.org/10.1016/j.euo.2018.06.013).

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