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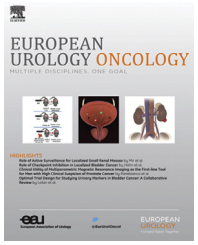

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Early Tolerance and Tumor Control Outcomes with High-dose Ultrahypofractionated Radiation Therapy for Prostate Cancer

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Abstract

Background: Studies using stereotactic body radiotherapy (SBRT) dose escalation in in low- and intermediate-risk prostate cancer patients have indicated favorable outcomes.

Objective: To evaluate tolerance and tumor control outcomes in low- and intermediate-risk prostate cancer patients treated with high-dose SBRT following our phase 1 trial.

Design, setting, and participants: A total of 551 patients with low- or intermediate-risk prostate cancer were treated with SBRT.

Intervention: Treatment with 37.5–40 Gy SBRT in five fractions directed to the prostate and seminal vesicles.

Outcome measurements and statistical analysis: Outcome measurements included acute toxicities (<3 mo after radiotherapy [RT]) and late toxicities (>3 mo after RT) and tumor control evaluation (prostate-specific antigen [PSA] levels at 3–6-mo intervals and post-treatment prostate biopsy at 2 yr).

Results and limitations: Acute grade 2 gastrointestinal (GI) toxicities occurred in 1.8% of patients, and late grade 2 and 3 GI toxicities were observed in 3.4% and 0.4% of patients, respectively. Acute grade 2 genitourinary (GU) toxicities occurred in 10% of patients, and grade 3 acute GU toxicities were observed in 0.7% of patients. Late grade 2 and 3 GU toxicities were observed in 21.1% and 2.5% of patients, respectively. The use of a hydrogel rectal spacer was significantly associated with reduced late GI toxicity and lower odds of developing late GU toxicity. The median follow-up was 17 mo, and 53% of those with at least 2 yr of follow-up (103/193) had a biopsy performed. The 5-yr cumulative incidence of PSA failure was 2.1%, and the incidence of a positive 2-yr treatment biopsy was 12%. Limitations to this report include its retrospective nature and short follow-up time.

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Conclusions: Favorable short-term outcomes were achieved with high-dose SBRT for low- and intermediate-risk disease. Severe late toxicities were observed and favorable tumor control was found.

Patient summary: We utilized stereotactic body radiotherapy, a form of external beam radiotherapy that delivers highly targeted high-dose treatment to the prostate, to treat over 500 localized prostate cancer patients in five sessions over 1.5 wk. Treatments were well tolerated without significant urinary or rectal side effects. Nearly 90% of those who underwent biopsies after treatment did not demonstrate residual active disease.

1. Introduction

Ultrahypofractionated stereotactic body radiotherapy (SBRT) regimens have increasingly been used to treat clinically localized prostate cancer [1–7]. We conducted a phase 1 dose escalation study in low- and intermediate-risk prostate cancer patients and demonstrated improved tumor control outcomes in patients who received 40 Gy prescription doses based on 2-yr post-treatment biopsies [8]. Favorable tolerance profiles may be attributed to the use of image guidance to track inter- and intrafraction motion and tight planning target volume (PTV) margins with magnetic resonance imaging (MRI)-computed tomography (CT) fusion for target delineation and normal tissue contouring.

Several single-institution reports have demonstrated favorable tolerance and 5-yr prostate-specific antigen (PSA) relapse-free survival outcomes for low- and intermediate-risk disease using dose levels in the range of 35–36.25 Gy. Follow-up at 5 yr showed that SBRT is well tolerated, with outcomes comparable with patients treated with conventionally fractionated intensity modulated radiation therapy (IMRT) [1–6]. Based on the available clinical evidence in the literature for low- and intermediate-risk patients, SBRT has recently become incorporated as part of treatment guidelines within the management of localized prostate cancer [9,10].

Pathologic assessments of local tumor control based on post-treatment biopsies have not been performed routinely when evaluating PSA relapse–free survival outcomes. Additionally, there are limited data on toxicity outcomes when higher SBRT dose levels are used. This report summarizes our experience using high-dose SBRT for low- and intermediate-risk prostate cancer following our phase 1 trial. In this trial, we evaluated early tolerance outcomes of a large number of patients delivered with higher SBRT dose levels than what has been used traditionally.

2. Patients and methods

2.1. Treatment protocol

Between 2012 and 2017, 551 clinically localized prostate cancer patients were treated at a single institution with high-dose SBRT directed to the prostate and seminal vesicles with PTV prescription doses of 37.5 or 40 Gy delivered on alternating days at the Memorial Sloan Kettering Cancer Center. National Comprehensive Cancer Network risk stratification criteria were used to categorize patients.

Clinical target volume (CTV) represented prostate and bilateral seminal vesicles based on CT or MRI scans. The PTV applied a 5-mm margin around the anterior and lateral aspects of the CTV, with a 3-mm margin posteriorly and a 2-mm margin for its superior and inferior aspects. Organs at risk, including the rectum, bladder, femoral heads, large bowel, small bowel, bladder trigone, and urethra, were contoured.

The treatment planning approach for these patients has been described previously [8,11]. In brief, all patients underwent either electromagnetic transponder or fiducial marker placement under transrectal ultrasound guidance. These markers were used to confirm and monitor the prostate position before and during each SBRT treatment. Patients prior to 2015 received either electromagnetic transponders or fiducial placement. Subsequent to 2015, transponders were discontinued, and fiducial markers were placed in all patients. Beginning in November 2016, patients routinely underwent placement of hydrogel rectal spacer at the same time as fiducial marker placement (SpaceOAR; Augmenix Inc., Waltham, MA, USA).

Patients were simulated with an empty rectum and full bladder 1 wk after placement. While details of these guidelines varied slightly over the study, the main components remained the same. Patients were instructed to take an enema the day prior to and the day of simulation, and on the day of treatment. During simulation, patients underwent Foley catheter insertion for urethral visualization. Patients were immobilized in the supine position with a custom thermoplastic mold extending from the abdomen to mid-thigh and ankle support (Aquaplast; Shippert Medical Technologies, Centennial, CO, USA). Starting in early 2015, CT simulation was performed with a 2-mm slice thickness extending from L1 to well below the ischial tuberosities. Starting in early 2015, CT simulation was followed by magnetic resonance (MR) simulation on a 3 Tesla scanner (Siemens Medical Solutions, Malvern, PA, USA) in the treatment position, incorporating patient immobilization via the use of an indexed, flat tabletop. Since June 2016, we have routinely used MR-only simulation and planning for prostate SBRT [12,13]. MR-based contouring was performed in 346 patients (63%) using T2-weighted MRI.

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Dose-volume constraints for target and normal tissue structures used in treatment planning have been described previously [8]. The standard PTV D95 was 90–100% of the prescription dose; the maximum PTV dose did not exceed 112% of the prescription dose, and the mean dose to the PTV was 99–104% of the prescription, while meeting normal tissue constraints. In general, patients were treated with three or four volumetric arcs (volumetric modulated arc therapy [VMAT]).

SBRT was initiated within 2 wk following simulation. A treatment regimen, including a full bladder without a catheter and an empty rectum, was carried out before each treatment day. Matching of fiducial markers was checked using a kilovoltage on-board imaging for interfraction target position correction. A pretreatment cone beam CT (CBCT) scan was obtained prior to each fraction. A rectal catheter was used to remove gas if the cone beam imaging detected excessive air. CBCT images were shifted until completely overlaid with the simulated target; another CBCT scan was acquired for verification. Motion during treatment delivery was assessed by tracking electromagnetic transponders, or, for patients with implanted fiducials, kilovoltage imaging between VMAT arcs, once every three IMRT fields, or triggered kilovoltage on-board imaging every 20° was used for assessment. Beginning in 2016, a custom-developed approach combining triggered kilovoltage imaging with megavoltage short-arc digital tomosynthesis was used [14].

In general, patients were followed at 3 mo following radiotherapy (RT), and subsequently for every 3–6 mo for the first 5 yr and annually thereafter. Patients were evaluated for rectal and urinary toxicities according to the Common Terminology Criteria for Adverse Events, version 3.0, grading system. Acute toxicities were defined as those that occurred within 3 mo following RT, and late toxicities were those observed after 3 mo [15]. PSA levels were obtained at 3 mo following RT and 6 mo thereafter. Patients who reached 2 yr of follow-up after treatment were encouraged to undergo post-treatment prostate biopsy. The median follow-up was 17 mo, and 53% of those with at least 2 yr of follow-up (103/193) had a biopsy performed. Patients who were over the age of 80 yr and those on anticoagulants were not evaluated with post-treatment biopsies. Biochemical failure was assessed using the Phoenix definition (PSA nadir plus 2 ng/ml).

2.2. Statistical analysis

Toxicity rates were estimated by grade. For grade 2 toxicity estimates, binomial exact confidence intervals (CIs) were provided. The duration of each late toxicity event was calculated from the time of toxicity until resolution. Patients with unresolved toxicities at the end of follow-up were censored. Kaplan-Meier methods were used to estimate the median duration of late grade 2 toxicities with 95% CIs. We estimated the duration of toxicities only where at least 10 patients were observed to experience an event. Associations between baseline characteristics, including age, prostate volume, International Prostate Symptom Score (IPSS) score (for genitourinary [GU]), RT dose, and use of rectal spacer with any gastrointestinal (GI) and any GU grade 2–3 events, were assessed with univariable logistic regression. If more than one factor was significant on univariable analyses at $p < 0.05$, multivariable analyses were built. IPSS scores were dichotomized into <15 and ≥ 15. The IPSS constraint was recommended only for our prior phase 1 study, but subsequently treated patients were deemed eligible for SBRT even at higher IPSS scores [8].

PSA failure was estimated from the start of RT until biochemical relapse. Death without recurrence was treated as a competing risk; patients without biochemical recurrence who survived were censored. Cumulative incidence indicated PSA failure. No estimates were provided since no distant metastases occurred at the end of follow-up. The rate of positive biopsies after RT was provided. Associations between positive biopsy and baseline characteristics were assessed with univariable logistic regression.

Two-sided p values of <0.05 were considered statistically significant. All analyses were performed with SAS 9.4 (The SAS Institute, Cary, NC, USA).

3. Results

3.1. Patient characteristics

The median age of the 551 patients was 70 yr (range: 47–89 yr; Table 1). The median initial PSA was 6.4 ng/ml (range: 0.3–19.6 ng/ml), and the majority of patients were Gleason group 1 (3 + 4; 63.3%; 349/551) and clinical stage T1c (72.8%; 401/551). Of those patients with available prostate volume data ($n = 529$), the median was 38 cc (interquartile range [IQR]: 28–53). Fifty-three patients (9.6%) were at low risk, 226 (41%) at favorable intermediate risk, and 272 (49.4%) at unfavorable intermediate risk. The percentage of positive biopsy cores per patient was as follows: $\leq$20%: 126 (23%); >20–50%: 271 (49%); and >50%: 154 (28%). There was a small percentage of low-risk patients (10%), and patients with intermediate-risk disease had three or more positive biopsy cores routinely; most of our patients had 50% or higher core involvement. All 551 patients had percent positive biopsy core information available; the median percent was 33.3% with an IQR of 21.4–50.0. Extraprostatic extension was present in 4% (22/551; a T3 category was based on MRI), and seminal vesical invasion was noted in 0.5% of patients (three/551). The IPSS median score, available in 547 patients, was 6 (IQR: 3–11).

Most patients received 40.0 Gy (85.5%; 471/551) in 8 Gy fractions. Approximately half of the patients received a rectal spacer (48.8%; 269/551) when it became available after the approval of the Food and Drug Administration in 2016. Androgen deprivation therapy (ADT) was given to 151 patients (27.4%); of those with available data ($n = 133$), the median duration of hormone therapy was 5.9 mo (IQR: 4.1–6.2 mo; Table 1).

3.2. Grade 2 and 3 toxicity estimates

Acute grade 2 GI toxicities occurred in 1.8% (95% CI: 0.9–3.3%) of patients ($n = 10$); no grade 3 acute GI toxicities were noted. Late grade 2 and 3 GI toxicities were observed in

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Table 1 – Patient and clinical characteristics.[a]

		N (%)
Patients, *n*		551
Age at SBRT (yr)	Median (IQR; *N* = 551)	70 (65–74)
Clinical T stage	T1a	3 (0.5)
	T1c	401 (72.8)
	T2a	104 (18.9)
	T2b	34 (6.2)
	T2c	9 (1.6)
Initial PSA (ng/ml)	Median (range; *N* = 551)	6.4 (0.3–19.6)
Gleason score	Group 1 (3 + 3)	67 (12.2)
	Group 2 (3 + 4)	349 (63.3)
	Group 3 (4 + 3)	135 (24.5)
Prostate volume	Median (IQR; *N* = 529)	38.0 (28.0–53.0)
Prognostic risk group	Low	53 (9.6)
	Favorable-intermediate	226 (41)
	Unfavorable-intermediate	272 (49.4)
ECE	Unknown	18 (3.3)
	Negative	363 (65.9)
	Possible	71 (12.9)
	Suspicious	77 (14)
	Positive	22 (4)
SVI	Unknown	18 (3.3)
	Negative	527 (95.6)
	Possible	1 (0.2)
	Suspicious	2 (0.4)
	Positive	3 (0.5)
Lymphadenopathy	Unknown	18 (3.3)
	Negative	533 (96.7)
% Positive cores	Median (IQR; *N* = 551)	0.3 (0.2–0.5)
IIEF baseline score	Median (IQR; *N* = 530)	9.0 (2.0–25.0)
IPSS baseline score	Median (IQR; *N* = 547)	6.0 (3.0–11.0)

ECE = extracapsular extension; IIEF = International Index of Erectile Function; IPSS = International Prostate Symptom Score; IQR = interquartile range; PSA = prostate-specific antigen; SBRT = stereotactic body radiotherapy; SVI = seminal vesicle invasion.
[a] Numbers in parentheses represent frequency with percent of total unless otherwise stated.

19 (3.4%) and two (0.4%) patients, respectively, for a total grade 2+ rate of 3.8% (95% CI: 2.4–5.8%). Acute grade 2 GU toxicities occurred in 55 (10%) patients, and grade 3 acute GU toxicities were observed in four patients (0.7%), for a grade 2+ rate of 10.7% (95% CI: 8.3–13.6%). Late grade 2 and 3 GU toxicities were observed in 116 (21.1%) and 14 (2.5%) patients, respectively, for a grade 2+ rate of 23.6% (95% CI: 20.1–27.4% Tables 2, 3).

We used time-to-event methods for late toxicity duration estimates in those with at least 10 events since some toxicity events remained unresolved. The median estimate for late grade 2 GI hemorrhage was 3.4 mo (95% CI: 0.2–8.6). The median estimates for late grade 2 GU toxicity were 9.7 mo (95% CI: 6.4–15.2) for retention, 9.1 mo (95% CI: 6.5–12.0) for frequency/urgency, 1.0 mo (95% CI: 0.1–1.9) for GU hemorrhage, and 9.1 mo (95% CI: 5.0–12.3) for incontinence.

3.3. *Associations between GI/GU grade 2–3 toxicities and baseline characteristics*

Older patients had lower odds of experiencing a grade 2+ acute GI toxicity (hazard ratio [HR]: 0.91; 95% CI: 0.83–0.99; $p = 0.028$). No significant association was found between prostate volume ($p = 0.31$) or hormone therapy ($p = 0.85$) with acute GI toxicity. As only 10 acute GI toxicities occurred, no multivariable models were built (Table 4).

Patients who underwent rectal spacer placement experienced significantly fewer late grade 2 + GI toxicity events compared with those who did not undergo placement (odds ratio [OR]: 0.24; 95% CI: 0.08–0.71; $p = 0.010$). The incidence of grade 2+ late rectal toxicity in the hydrogel and nonhydrogel spacer cohorts was 1% and 6%, respectively ($p = 0.01$). No other variables were significantly associated with late GI toxicity ($p = 0.18$–0.55); thus, no multivariable models were built (Table 4).

No baseline factors were associated with acute grade 2 + GU toxicities ($p = 0.19$–0.42); however, patients who underwent rectal spacer placement had lower odds of developing late GU toxicity (HR: 0.37; 95% CI: 0.25–0.57; $p < 0.001$). The incidence of grade 2+ late GU toxicity in the hydrogel and nonhydrogel spacer cohorts was 15% and 32%,

Table 2 – Grade 2 toxicity estimates.[a]

Grade 2 toxicity	Timing					
	Acute			Late		
	Rate (%)	95% CI (%)	Fraction	Rate (%)	95% CI (%)	Fraction
Any GI toxicity	1.8	0.9–3.3	10/551	3.6	2.2–5.6	20/551
Diarrhea	0.2	0–1.0	1/551	0.5	0.1–1.6	3/551
GI hemorrhage	0.2	0–1.0	1/551	2.2	1.1–3.8	12/551
Hemorrhoids	0.7	0.2–1.8	4/551	1.5	0.6–2.8	8/551
Proctitis	0.9	0.3–2.1	5/551	0.5	0.1–1.6	3/551
Any GU toxicity	10.2	7.8–13.0	56/551	22.7	19.3–26.4	125/551
Cystitis	0.9	0.3–2.1	5/551	0.4	0–1.3	2/551
Frequency/urgency	8.7	6.5–11.4	48/551	14.3	11.5–17.5	79/551
Incontinence	0.9	0.3–2.1	5/551	2.9	1.7–4.7	16/551
GU hemorrhage	0.0	0–0.7	0/551	2.0	1–3.5	11/551
Retention	2.2	1.1–3.8	12/551	8.7	6.5–11.4	48/551
Urinary stricture				0.5	0.1–1.6	3/551

CI = confidence interval; GI = gastrointestinal; GU = genitourinary.
[a] Acute urinary stricture was not measured. Fifty-six patients had any grade 2 GU acute toxicity, but one of these patients also had Grade 3 toxicity. Therefore, 55 patients had a maximum grade of 2. Twenty patients had any grade 2 GI late toxicity, but one of these patients also had grade 3 toxicity. Therefore, 19 patients had a maximum grade of 2.

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Table 3 – Toxicity proportions by maximum grade.[a]

	Timing, *n* (%)					
	Acute			Late		
	Grade 1	Grade 2	Grades 3	Grade 1	Grade 2	Grades 3
Any GI toxicity	55 (10)	10 (1.8)	0 (0)	100 (18.1)	19 (3.4)	2 (0.4)
Diarrhea	20 (3.6)	1 (0.2)		28 (5.1)	3 (0.5)	
GI hemorrhage	17 (3.1)	1 (0.2)	0 (0)	34 (6.2)	12 (2.2)	2 (0.4)
Hemorrhoids	31 (5.6)	4 (0.7)		72 (13.1)	8 (1.5)	
Proctitis	6 (1.1)	5 (0.9)		3 (0.5)	3 (0.5)	
Any GU toxicity	173 (31.4)	55 (10)	4 (0.7)	196 (35.6)	116 (21.1)	14 (2.5)
Cystitis	21 (3.8)	5 (0.9)		2 (0.4)	2 (0.4)	
Frequency/urgency	160 (29)	48 (8.7)	2 (0.4)	211 (38.3)	79 (14.3)	8 (1.5)
GU hemorrhage	9 (1.6)	0 (0)	0 (0)	28 (5.1)	11 (2)	2 (0.4)
Incontinence	29 (5.3)	5 (0.9)	0 (0)	61 (11.1)	16 (2.9)	3 (0.5)
Retention	42 (7.6)	12 (2.2)	2 (0.4)	98 (17.8)	48 (8.7)	4 (0.7)
Urinary stricture					3 (0.5)	

GI = gastrointestinal; GU = genitourinary.
[a] Numbers in parentheses represent frequency with percent of total. Acute urinary stricture was not measured. Fifty-six patients had any grade 2 GU acute toxicity, but one of these patients also had grade 3 toxicity. Therefore, 55 patients had a maximum grade of 2. Twenty patients had any grade 2 GI late toxicity, but one of these patients also had grade 3 toxicity. Therefore, 19 patients had a maximum grade of 2.

Table 4 – Multivariable associations between baseline factors and outcomes (grades 2–3).[a,b]

			Acute					Late				
			N (%)	OR	95% CI		*p* value	*N* (%)	OR	95% CI		*p* value
Any GI toxicity	Prostate volume			0.98	0.94–	1.02	0.31		0.99	0.97–	1.02	0.55
	Age at SBRT (yr)			0.91	0.83–	0.99	0.028		0.98	0.92–	1.04	0.45
	Hormone therapy	Yes	3 (2)	1.14	0.29–	4.46	0.85	3 (2)	0.43	0.12–	1.48	0.18
		No	7 (2)	REF				18 (5)	REF			
	Rectal spacer	Yes	2 (1)	0.26	0.05–	1.22	0.09	4 (1)	0.24	0.08–	0.71	0.010
		No	8 (3)	REF				17 (6)	REF			
Any GU toxicity	Prostate volume			1.01	0.99–	1.02	0.42		1.01	1.00–	1.01	0.24
	Age at SBRT (yr)			1.02	0.98–	1.06	0.35		1.00	0.98–	1.03	0.79
	Hormone therapy	Yes	20 (13)	1.41	0.80–	2.51	0.24	34 (23)	0.92	0.59–	1.44	0.71
		No	39 (10)	REF				96 (24)	REF			
	Rectal spacer	Yes	24 (9)	0.69	0.40–	1.20	0.19	40 (15)	0.37	0.25–	0.57	<0.001
		No	35 (12)	REF				90 (32)	REF			
	IPSS baseline score			1.04	0.99–	1.09	0.09		1.09	1.05–	1.13	<0.001
	IPSS baseline score (grouped)	≥15	7 (12)	1.13	0.49–	2.61	0.78	20 (34)	1.76	0.99–	3.15	0.055
		<15	52 (11)	REF				110 (23)	REF			

CI = confidence interval; GI = gastrointestinal; GU = genitourinary; IPSS = International Prostate Symptom Score; *N* = total number for level; OR = odds ratio; REF = reference; SBRT = stereotactic body radiotherapy.
[a] Models assess probability of experiencing toxicity: OR > 1 indicates higher odds of toxicity; OR < 1 indicates lower odds of toxicity.
[b] For continuous factors, odds ratio corresponds to a one-unit increase.

respectively ($p < 0.001$). Additionally, patients with higher IPSS scores had higher odds of late GU toxicity (OR: 1.09; 95% CI: 1.05–1.13; $p < 0.001$). The association when IPSS score was dichotomized into ≥15 versus <15 approached but did not reach significance (OR: 1.76; 95% CI: 0.99–3.15; $p = 0.055$); no other factors were significantly associated with late GU toxicity ($p = 0.24$–0.79; Table 4). In a multivariable model with IPSS score and rectal spacer, both factors remained significantly associated with late grade 2 + GU toxicities; patients with higher IPSS scores had a higher odds of toxicity (OR: 1.08; 95% CI: 1.05–1.13; $p < 0.001$) and patients with rectal spacer placement had a lower odds of toxicity (OR: 0.37; 95% CI: 0.25–0.57; $p < 0.001$).

3.4. Clinical outcomes

The median follow-up in survivors ($n = 543$) was 17.0 mo (IQR: 7–29 mo). In survivors, 17% of patients ($n = 92$) had at least 3 yr of follow-up. The 5-yr cumulative incidence of PSA failure was 2.1% (95% CI: 0.6–5.3%). No patients experienced distant metastases events at follow-up.

Of the 119 patients with a follow-up biopsy, 11.8% (95% CI: 6.6–19.0%) had a positive biopsy, 56.3% (95% CI: 46.9–65.4%) a negative biopsy, and 31.9% (95% CI: 23.7–41.1%) a treatment effect biopsy. The incidence of a positive biopsy among patients who received 37.5 Gy was 17.9% (95% CI: 6.1–36.9%), and this incidence was 9.9% (95% CI: 4.6–17.9%)

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Table 5 – Univariable associations between baseline factors and post-RT biopsy outcome ($N = 119$).[a,b]

		N (#O)	OR	95% CI		p value
Prostate volume		117 (14)	1.00	0.98–	1.03	0.82
Hormone therapy	Yes	18 (1)	0.40	0.05–	3.25	0.39
	No	101 (13)	REF			
MSK risk	Unfavorable-intermediate	57 (9)	3.19	0.38–	27.05	0.29
	Favorable-intermediate	44 (4)	1.70	0.18–	16.34	0.65
	Low	18 (1)	REF			

CI = confidence interval; MSK = Memorial Sloan Kettering Cancer Center; N = total number for level; #O = number of positive biopsies for level; OR = odds ratio; REF = reference; RT = radiotherapy.
[a] Models assess probability of experiencing toxicity: OR > 1 indicates higher odds of toxicity; OR < 1 indicates lower odds of toxicity.
[b] For continuous factors, odds ratio corresponds to a one-unit increase.

for patients who were treated with 40 Gy. The median time between RT and post-RT biopsy was 25.2 mo (IQR: 24.3–28.1); none of the baseline factors were significantly associated with post-RT biopsy results (p = 0.29-0.82; Table 5).

4. Discussion

In this trial, we evaluated early tolerance outcomes of a large number of patients delivered with higher SBRT dose levels than what has been used traditionally. The patient population we treated consisted predominantly of intermediate-risk disease (>90%), in which the overwhelming majority had three more core positive cores, and where almost 50% of patient had ≥50% positive cores often with a visible lesion noted on baseline diagnostic MRI. We found minimal incidence of acute and late grade 3 urinary or rectal toxicities in patients who received high-dose SBRT. The most common grade 2+ late toxicities were urinary-related manifestations (chronic urethritis with associated frequency or urgency and hematuria). Late rectal toxicity manifesting as grade 2 rectal bleeding was noted in 2.5% of cases, consistent with other reports using lower SBRT doses (35–36.25 Gy in five fractions). Our findings are consistent with toxicity outcomes from a multicenter study of low- and intermediate-risk patients treated with 40 Gy in five fractions [6]. The favorable toxicity profile that we report is at least comparable with what we have previously observed using high-dose IMRT and similar as well to what was reported in a recently completed phase 3 trial that compared an SBRT regimen with 78 Gy of conventionally fractionated IMRT [16,17].

The low-toxicity outcomes in this study may be attributed to using dose-volume constraints for critical normal structures and application of tight margins around the CTV. We used restrictive selection criteria, including selecting patients with prostate sizes <80 cc and IPSS scores <15 (late urinary toxicity was not significantly higher in patients with higher IPSS scores (>15).

At our institution, we routinely monitor intrafraction motion and adjust target position. We demonstrated reduced urinary toxicity rates in patients who underwent corrections of interfraction motion via delivery of conventionally fractionated external beam radiation therapy [18]. Since 2016, we have integrated MRI-based contouring and treatment planning without using CT-MRI fusion to delineate the apex and prostatic base [12,13]. Since 2016, all eligible SBRT patients have undergone hydrogel spacer placement to reduce exposure. Here, we observed lower rates of late GI- and GU-related toxicities associated with rectal spacer placement, consistent with reports that used conventionally fractionated external beam RT. Our results are consistent with the outcomes of a phase 3 trial reported by Hamstra et al [19] who found significantly improved urinary and rectal quality of life outcomes in a hydrogel spacer cohort compared with a control group. However, it should be noted that our study was not powered or designed to make definitive claims about rectal spacer benefit. In addition, as spacer placement was ubiquitous after 2016 unless contraindicated, we cannot separate out whether the association that we found was confounded by an underlying effect of time period.

Potential benefits of dose intensification must be balanced with risks of late normal tissue toxicity. Prospective clinical trials have demonstrated that higher doses significantly improve disease-free survival outcomes in intermediate-risk patients [20–26]. Phase 3 studies of dose intensification with three-dimensional conformal radiation therapy/IMRT or combined brachytherapy and treatment regimens have found a concomitant increase in the risk of late normal tissue toxicity [27]. The innovations used may synergistically result in the favorable toxicity profile that we observed. The relatively low toxicity observed in this cohort could possibly be related to several specific technical factors, which include careful delineation of the target with adherence to dose-volume constraints, use of tight margins around the target volume, rectal protection, and correction for intrafraction motion.

A phase 1 dose escalation study reported improved outcomes using higher radiation dose levels [8]. Although escalated doses beyond 40 Gy (45–50 Gy) have been associated with increased rectal toxicity, a recent study suggested significant reduction of toxicity in patients treated with 45 Gy in five fractions using a hydrogel spacer [28]. Current trials comparing moderate hypofractionation regimens with ultrahypofractionation have used SBRT dose levels of 35–36.25 Gy in five fractions; however, these doses may not be sufficient to eradicate intermediate-risk disease, as optimal SBRT dosing must be confirmed through trials.

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Limitations to this report include its retrospective nature and, subsequent to follow-up, the number of patients who received post-treatment biopsy. Additionally, no definitive conclusions can be made on cancer control with short-term follow-up. This study was underpowered to examine post-treatment outcomes related to the use of ADT in conjunction with SBRT. However, this study demonstrates the feasibility and early tolerance to high-dose SBRT using strict planning guidelines. We also confirmed low positive post-treatment biopsy outcomes in patients treated with 40 Gy SBRT; among patients with positive biopsies, the majority had unfavorable intermediate-risk disease, indicating that higher doses may be required for advanced disease risk [8]. The overwhelming majority of the patients in this study had intermediate-risk disease having, in most cases, at least several positive cores, generally with a visible lesion on MRI; in addition, almost half of the patients had 50% or more positive biopsy core involvement. Therefore, this population was not favorable, although not high risk.

Several randomized trials are underway comparing moderate hypofractionated regimens or conventionally fractions regimens with SBRT. Widmark et al [17] reported early toxicity results from the HYPO-RT trial comparing a conventionally fractionated regimen with SBRT in which a 6.1 Gy dose was delivered in seven weekly fractions. Nevertheless, there is no evidence to date that the ultrahypofractionated regimen is associated with higher toxicity. Despite potential limitations, our findings may validate that an ultrashort course of treatment using SBRT does not compromise tumor control and toxicity outcomes.

5. Conclusions

Favorable tumor control rates were achieved in patients with low- and intermediate-risk prostate cancer. Urinary and rectal toxicity rates were low and comparable with conventional IMRT. The 2-yr post-treatment positive biopsy rates noted among patients treated with this high-dose SBRT regimen was 17.9% for those treated with 37.5 Gy and 9.9% for those treated with 40 Gy. Given the short-term follow-up in this patient population, no definitive conclusions can be made about long-term tumor control outcomes.

Author contributions: Michael J. Zelefsky 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: Zelefsky, Pinitpatcharalert, Kollmeier, Gorovets.
Acquisition of data: Pinitpatcharalert, Varghese, Gorovets.
Analysis and interpretation of data: Zelefsky, Kollmeier, Goldman, McBride, Gorovets, Zhang, Happersett, Hunt.
Drafting of the manuscript: Zelefsky, Gorovets, Pinitpatcharalert.
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Statistical analysis: Goldman, Gorovets, Zhang.
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