European Journal of Cancer 59 (2016) 142–151

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Stereotactic body radiation therapy for low and intermediate risk prostate cancer—Results from a multi-institutional clinical trial☆

Raquibul Hannan [a], Vasu Tumati [a], Xian-Jin Xie [b], L. Chinsoo Cho [c], Brian D. Kavanagh [d], Jeffrey Brindle [e], David Raben [d], Akash Nanda [f], Susan Cooley [a], D.W. Nathan Kim [h], David Pistenmaa [i], Yair Lotan [g], Robert Timmerman [a,*]

[a] *Department of Radiation Oncology, University of Texas Southwestern Medical Center, USA*
[b] *Department of Clinical Sciences, University of Texas Southwestern Medical Center, USA*
[c] *Department of Radiation Oncology, University of Minnesota, USA*
[d] *Department of Radiation Oncology, University of Colorado, USA*
[e] *Department of Radiation Oncology, Prairie Lakes Hospital, USA*
[f] *Department of Radiation Oncology, Orlando Health, USA*
[g] *Department of Urology, University of Texas Southwestern Medical Center, USA*
[h] *Texas Oncology-Waco, USA*
[i] *Radiation Research Program, NCI, USA*

Received 19 November 2015; received in revised form 28 January 2016; accepted 13 February 2016

KEYWORDS
Stereotactic body radiation therapy;
SBRT;
Prostate cancer;
Dose constraints

Abstract ***Background:*** We report the outcome of a phase I/II clinical trial of stereotactic body radiation therapy (SBRT) for low (LR) and select intermediate risk (IR) prostate cancer (PCa) patients.

Patients and methods: Eligible patients included men with prostate adenocarcinoma with Gleason score 6 with PSA $\leq$ 20 or Gleason 7 with PSA $\leq$ 15 and clinical stage $\leq$ T2b. For the phase I portion of the study patients in cohorts of 15 received 45, 47.5, or 50 Gray (Gy) in five fractions. Since the maximally tolerated dose was not met in the phase I study, an additional 47 patients received 50 Gy in five fractions in the phase II study. Toxicity using Common Toxicity Criteria for Adverse Events v. 3.0, quality of life, and outcome data was collected.

Results: A total of 91 patients are included for analysis; 63.7% had NCCN IR and 36.3% had

☆ Supported by a Clinical Trial Award from the US Department of Defense (grant no. PC061629; R.T., principal investigator). Registered at Clinicaltrials.gov study number NCT00547339.

* *Corresponding author*: Department of Radiation Oncology, University of Texas Southwestern Medical Center, 5801 Forest Park Road, Dallas, TX 75390, USA.
E-mail address: Robert.Timmerman@utsouthwestern.edu (R. Timmerman).

http://dx.doi.org/10.1016/j.ejca.2016.02.014

LR PCa. At a median follow up of 54 months the actuarial freedom from biochemical failure was 100% at 3 years and 98.6% at 5 years. Actuarial distant metastasis free survival was 100% at 3 and 5 years. Overall survival was 94% at 3 years and 89.7% at 5 years with no deaths attributed to PCa. Acute and late urinary grade ≥ III toxicity occurred in 0% and 5.5% of patients, respectively. Gastrointestinal (GI) acute and late toxicity of grade ≥ III occurred in 2% and 7% of patients, respectively. A total of four men experienced grade IV toxicity (three GI, one genitourinary).

Conclusion: SBRT treatment results in excellent biochemical control rates at 5 years for LR and IR PCa patients although doses greater than 47.5 Gy in five fractions led to increased severe late toxicity.

1. Introduction

Radiation therapy for organ-confined prostate cancer (PCa) involves protracted courses of external beam radiation delivered over multiple weeks daily. Several groups have attempted to reduce the course of treatment through hypofractionation. Lloyd-Davies and colleagues reported 22-year results with acceptable toxicity [1], although the study was performed in the pre-prostate specific antigen (PSA) and pre-computed tomography (CT) scan era, and many patients had high-risk features. Recent hypofractionation studies have used stereotactic body radiation (SBRT) treatments ranging from 33.5 Gy to 36.25 Gy in five fractions [2,3]. These studies reported acceptable toxicity with limited follow up. Dose selection for these studies was based on a mathematical model, the linear-quadratic equation, which correlates *in vitro* cellular events to biologic outcomes using two major parameters, 'alpha' and 'beta.' More recently, however, it has been shown the true alpha and beta of PCa is lower than previously thought [4–6]. Several studies have suggested a benefit of hypofractionation in the treatment of PCa [4]. Moreover, the linear-quadratic equation may overestimate the biological effects of highly hypofractionated regimens, and doses of 33.5–36.25 maybe inadequate for PCa [7,8]. Therefore, a traditional dose escalation trial was designed to determine the maximally tolerated dose (MTD) of SBRT in this setting.

Our group initially explored the rationale for SBRT in animal models, showing dose responses in clinically relevant ranges [9]. Considering previous brachytherapy trials indicating acceptable toxicity with doses as high as 9.5 Gy per fraction in four fractions [10,11], we initiated a multi-centre prospective phase I/II clinical trial of dose escalated SBRT for National Comprehensive Cancer Network (NCCN) low (LR) and intermediate risk (IR) PCa using 45 Gy in five fractions. We determined and evaluated the MTD of SBRT for PCa treatment. We have previously reported a phase I dose escalation toxicity study [12] and, more recently discussed rectal SBRT dose constraints [13]. The current article reports our 5-year PCa control study and an update on toxicity outcomes.

2. Materials and methods

2.1. Patients and eligibility

Patients were enrolled on a multi-institutional institutional review board approved phase I/II dose escalation trial between 2006 and 2011. The phase I study was open to three sites, while two additional sites were later added to phase II. Inclusion criteria were previously reported, although immunosuppressed patients were excluded from the phase II study [12]. Hormonal therapy (androgen deprivation therapy [ADT]) was allowed for up to 9 months prior to SBRT to downsize the prostate gland, concurrent ADT was not allowed. CT or magnetic resonance imaging (MRI) was performed to ensure absence of regional metastases.

2.2. Treatment planning and delivery

Treatment planning, dose constraints, simulation, setup, and treatment delivery parameters were previously reported [12,13]. Briefly, the prostate was expanded uniformly by 3 mm to create the planning target volume (PTV). The dose was prescribed to cover ≥ 95% of the PTV. Tissue heterogeneity correction was used in all cases.

The anterior wall was allowed to receive no more than 105% of the prescription dose. No more than 3 cm^3 of the lateral walls were allowed to receive 90% of the prescription dose. The posterior rectal wall maximum dose was limited to ≤ 45% of the prescription dose. The bladder wall (outer 5 mm of the entire bladder contour) was limited to 105% of the prescription dose with no more than 10 cm^3 receiving 18.3 Gy or greater. The maximum prostatic urethra dose was limited to ≤ 105% of the prescription dose. Patients were instructed take 4 mg of dexamethasone prior to each treatment and α-

blocker (i.e. tamsulosin) was given for 6 weeks at the start of treatment.

2.3. Toxicity assessments

Toxicity was defined using the National Cancer Institute Common Toxicity Criteria for Adverse Events v. 3.0. Acute and delayed toxicities were defined before trial activation as follows: 1) toxicity occurring less than 270 d from treatment and 2) persistent or new toxicities greater than or equal to 270 d after treatment, respectively. American Urological Association Symptom Score (AUASS) and Expanded Prostate Cancer Index Composite (EPIC) bowel, urinary, hormonal, and sexual scores were measured at each follow up and documented for a total of 18 months after treatment, through quality of life (QOL) questionnaires. After 18 months, urinary function, rectal function, and sexual function data were documented without questionnaires.

2.4. Study end-points

The design and end-points of the phase I study were previously reported [12]. The primary end-point of the phase II study was to determine late gastrointestinal (GI)/genitourinary (GU) treatment side-effects, while secondary end-points included biochemical control, disease specific survival, and overall survival (OS). Since the MTD was not reached in phase I, the phase II portion was started at 50 Gy in five fractions and designed to enrol 45 patients.

The phase II component was designed to test whether late GU/GI toxicity at 270–540 d from the start of treatment following the protocol treatment is above 10%. The sample size was determined such that the probability of rejecting the treatment because of excessive late toxicity is 90% if the true late toxicity rate is 23% or higher. Assuming an exponential distribution for time from the end of the acute period to the occurrence of late toxicity, the hazard rate for the expected 10% toxicity rate and the unacceptable 23% toxicity rate is 0.006/month and 0.015/month, respectively. Following the asymptotic property of the observed hazard and using Z-test for the logarithm of the hazard ratio, we require 12 cases with severe late GU/GI toxicity. Thus, 47 patients were required to have a statistical power of 90% with a one-sided significance level of 0.05.

PSA measurement, history, and physical examination were conducted in patients every 3 months for year 1, every 6 months for years 2 and 3, and yearly starting at 4 years after treatment. The ASTRO-Phoenix failure definition was used for biochemical control [14]. The Kaplan–Meier method was used to estimate freedom from biochemical failure (FFBF), distant metastasis free survival, and OS. Intergroup comparisons for QOL data were performed using one-way analysis of variance (ANOVA) with Tukey's correction or mixed-model ANOVAs.

3. Results

A total of 47 patients were recruited to the phase I study, although two withdrew consent before treatment. An additional patient had Gleason 9 disease upon pathology review and was excluded from the analysis. The phase II portion included 47 additional patients for a total of 91 analysable patients. Demographic information is summarised in Table 1.

3.1. Biochemical outcomes

For the phase I study, the median follow up was 74 months, 72 months, and 66 months for the 45 Gy, 47.5 Gy, and 50 Gy arms, respectively. For the phase II study the median follow up was 47.5 months with a pooled total of 54 months (range 1–90 months). Of note, a total of 15 patients (16.5%) received ADT for downsizing the prostate (Table 1). The median pre-treatment PSA for the entire cohort was 5.4 (range 0.73–16.2). Following SBRT, PSA gradually decreased with a median nadir of 0.125 at 42 months, as showed by normalised PSA kinetics (Fig. 1). Six weeks after treatment, the median PSA value for all patients was 2.19 (2.19 without ADT, 2.09 with ADT), indicating a 60% reduction. There was no difference in PSA kinetics noted between treatment cohorts. PSA bounce was noted in 19 (18.4%) patients [15]; PSA bounce was detected in 17 patients after 12 months from treatment, while the remainder exhibited it at 18 months. Four bounces occurred in the 45 Gy group, two in the 47.5 Gy group, and the remainder in the 50 Gy group.

FFBF was 100% for all patients at 3 years (Fig. 2). Actuarial FFBF was 98.6% for the entire cohort, 90.9% for the 45 Gy group with one failure, and 100% for the 47.5 Gy and 50 Gy cohorts at 5 years (Fig. 2). When parsed by the NCCN risk group, FFBF rates were 100% for LR patients ($n = 33$) and 98% for IR patients ($n = 58$) at 5 years. Using the older three-successive-rises method of biochemical failure, the FFBF remained unchanged [16].

3.2. Survival

The actuarial OS rates for the 45 Gy, 47.5 Gy, and 50 Gy arms of the phase I study were 79%, 85%, and 92%, respectively, at 3 years. The 3-year OS for the phase II study was 100% and for the entire cohort was 94%. Actuarial OS rates for the 45 Gy, 47.5 Gy, and 50 Gy arms of the phase I study were 71.5%, 85%, and 92%, respectively, at 5 years. The OS for phase II patients was 98% at 5 years, and the 5-year OS for all patients was 89.7%. PCa-specific survival was 100% for all cohorts as none of the deaths were attributed to PCa-related

Table 1
Patient characteristics.

Characteristic	45 Gy		47.5 Gy		50 Gy		Phase II		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%
Number of patients	15	16.5%	15	16.5%	14	15.4%	47	51.6%	91	100.0%
Follow up, months										
Median	74		72		66		47.5		54	
Range	4–94		1–90		3–73		1–64		1–90	
Age, years										
Median	67		67		67		65		66	
Range	55–82		58–76		53–78		52–80		53–80	
Prostate size cm^3										
Median	31		38		30		35		33	
Range	19–60		17–52		17–55		12–59		12–59	
AUA score										
Median	4.5		4		7		5		5	
Range	0–15		0–13		2–12		5–14		0–15	
PSA										
Median	6.4		5.7		4.5		5.3		5.4	
Range	3.3–12.4		1.3–11.5		0.2–7.9		0.73–16.2		0.2–16.2	
T-stage										
T1c	11	73.3%	13	86.7%	8	57.1%	31	66.0%	63	69.2%
T2a	1	6.7%	1	6.7%	4	28.6%	14	29.8%	20	22.0%
T2b	3	20.0%	1	6.7%	2	14.3%	3	6.4%	8	8.8%
Gleason										
6 (3 + 3)	4	26.7%	8	53.3%	9	64.3%	22	46.8%	43	47.3%
7 (3 + 4)	8	53.3%	5	33.3%	3	21.4%	17	36.2%	33	36.3%
7 (4 + 3)	3	20.0%	2	13.3%	2	14.3%	8	17.0%	15	16.5%
ADT use										
Yes	4	26.7%	2	13.3%	4	28.6%	5	10.6%	15	16.5%
No	11	73.3%	13	86.7%	10	71.4%	42	89.4%	76	83.5%
NCCN risk										
Low	3	20.0%	8	53.3%	7	50.0%	15	31.9%	33	36.3%
Intermediate	12	80.0%	7	46.7%	7	50.0%	32	68.1%	58	63.7%
Treatment site										
A	14	93.3%	8	53.3%	9	64.3%	27	57.4%	58	63.7%
B	1	6.7%	4	26.7%	4	28.6%	11	23.4%	20	22.0%
C	0	0.0%	3	20.0%	1	7.1%	0	0.0%	4	4.4%
D	0	0.0%	0	0.0%	0	0.0%	7	14.9%	7	7.7%
E	0	0.0%	0	0.0%	0	0.0%	2	4.3%	2	2.2%

A –University of Texas Southwestern Medical Center, B – University of Minnesota, C – Prairie Lakes Hospital, D – University of Colorado, E – Orlando Health, AUA – American Urology Association, ADT – Androgen Deprivation Therapy.

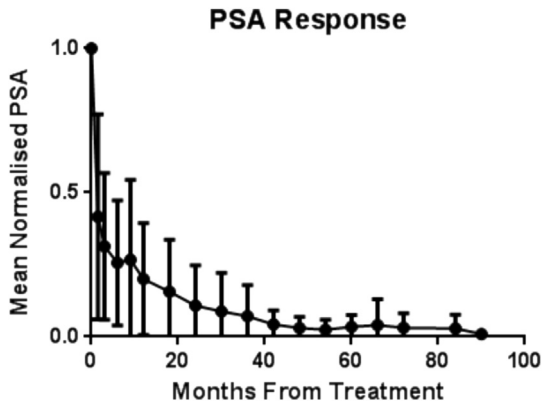


Fig. 1. Mean normalised PSA. PSA values were normalised against respective pre-treatment levels; the mean of the normalised PSA value is presented for each time point. PSA measurements were taken at initial treatment, 6 weeks after treatment, then every 3 months for the first year, every 6 months for years 2 through 4, and yearly thereafter. Median time to nadir was 42 months, with a nadir value of 0.125.

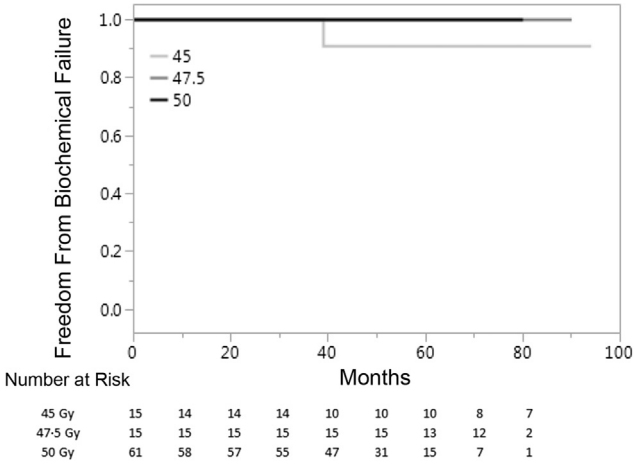


Fig. 2. FFBF Kaplan-Meier curves for individual dose levels. A single biochemical failure was observed in the 45 Gy arm after 3 years, resulting in actuarial rates of 100% and 98.6% at 3 and 5 years, respectively. No deaths in the study were attributed to prostate cancer or treatment related illnesses. FFBF = freedom from biochemical failure.

Table 2
Cumulative acute and late GU and GI toxicities by dose levels.

Grade	45 Gy						47.5 Gy						50 Gy					
	Genitourinary				Gastrointestinal		Genitourinary				Gastrointestinal		Genitourinary				Gastrointestinal	
	Acute		Late		Acute		Late		Acute		Late		Acute		Late		Acute		Late	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
0	8	53·3%	8	53·3%	8	53·3%	14	93·3%	6	40·0%	9	60·0%	7	46·7%	9	60·0%	13	21·3%	28	45·9%	21	34·4%	39	63·9%
I	2	13·3%	4	26·7%	6	40·0%	1	6·7%	8	53·3%	1	6·7%	4	26·7%	5	33·3%	34	55·7%	17	27·9%	24	39·3%	5	8·2%
II	5	33·3%	3	20·0%	1	6·7%	0	0·0%	1	6·7%	4	26·7%	4	26·7%	1	6·7%	14	23·0%	12	19·7%	14	23·0%	11	18·0%
III	0	0·0%	0	0·0%	0	0·0%	0	0·0%	0	0·0%	1	6·7%	0	0.0%	0	0·0%	0	0·0%	3	4·9%	1	1·6%	4	6·6%
IV	0	0·0%	0	0·0%	0	0·0%	0	0·0%	0	0·0%	0	0·0%	0	0.0%	0	0·0%	0	0·0%	1	1·6%	1	1·6%	2	3·3%
V	0	0·0%	0	0·0%	0	0·0%	0	0·0%	0	0·0%	0	0·0%	0	0.0%	0	0·0%	0	0·0%	0	0·0%	0	0·0%	0	0·0%

GU = genitourinary. GI = gastrointestinal.

illness. The actuarial metastases-free survival rate for all patients was also 100% at 3 and 5 years.

3.3. Toxicity

Acute and late toxicities are reported in Table 2. No acute grade III or higher GU toxicities were noted. Late grade III GU toxicity consisting of grade III cystitis was noted in 4.4% of patients. A single late grade IV urinary toxicity consisting of cystitis requiring ureteroileal diversion was observed. Actuarial toxicity for late grade $\geq$ III GU toxicity at 5 years for all patients is 6% (Fig. 3). Grade III or higher acute GI toxicity was detected in 2% of patients. One patient experienced rectal pain requiring diverting colostomy; toxicity occurred 212 d after treatment and continued into the late period counting as both acute and late toxicity. Another patient was admitted for rectal bleeding and diagnosed with Dieulafoy's lesion on the posterior wall of the rectum. It was unclear whether this was related to radiation treatment or a solitary ulcer from rectal prolapse. Collectively, grade III or greater late GI toxicity was observed in 6.8% of patients (Fig. 3). Only one grade IV GI toxicity, requiring intensive care unit admission for rectal bleeding, was observed out of the 15 patients treated in the phase I 50 Gy arm. Actuarial late grade $\geq$ III toxicity at 5 years is estimated at 8% (Fig. 3). Grade II or higher erectile dysfunction (ED) was reported in 25.6% of men with potency before treatment at 55 months follow up; median time to onset was 296 d. Grade III ED was only detected in two men.

3.4. Quality of life

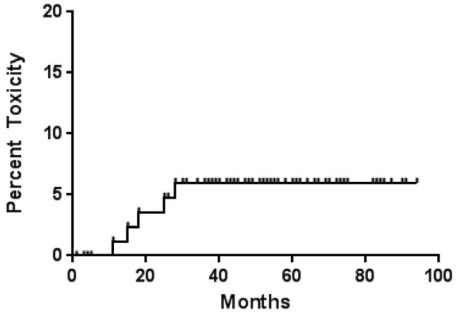
QOL data were assessed using the AUASS and EPIC bowel, urinary, hormonal, and sexual function scoring systems. Patient compliance with EPIC and AUASS questionnaires was initially greater than 90%, but decreased significantly by 18 months after treatment. Repeated measures mixed-model ANOVAs were performed to account for data loss, revealing a significant decrease in all four EPIC domains and AUASS over time. Intergroup comparisons were also performed at each time point; no differences were noted among dose levels for the EPIC domain or AUASS (Fig. 4A–D).

4. Discussion

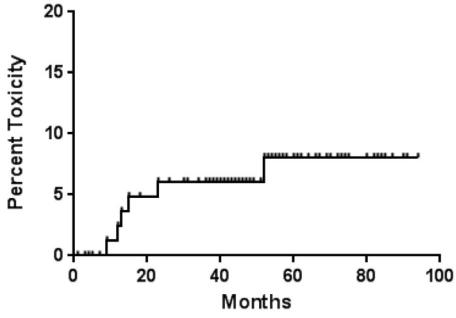
SBRT has become increasingly common to treat men with PCa despite the lack of long-term follow up prospective trials demonstrating its efficacy. We report 5-year results of a phase I/II prospective study of SBRT in men with LR and IR PCa.

We found a 3-year actuarial FFBF of 100% with a median follow up of 54 months for the entire cohort (Fig. 2) by either using the ASTRO-Phoenix definition or the older three-successive-rises method [16]. We

A.



C.



B.

Genitourinary Toxicity				
	Acute		Late	
Grade	No.	%	No.	%
0	24	26.4%	46	50.5%
1	44	48.4%	22	24.2%
2	20	22.0%	19	20.9%
3	0	0	4	4.4%
4	0	0	1	1.1%
5	0	0	0	0

D.

Gastrointestinal toxicity				
	Acute		Late	
Grade	No.	%	No.	%
0	37	40.7%	50	54.9%
1	34	37.4%	23	25.3%
2	19	20.9%	12	13.2%
3	1	1.1%	4	4.4%
4	1	1.1%	2	2.2%
5	0	0.0%	0	0.0%

Fig. 3. Actuarial (A) and crude (B) genitourinary and gastrointestinal (C,D) toxicity. Actuarial grade III or greater GU toxicity was found to be 6% at 5 years whereas the crude rate of toxicity was found to be 5.5%. Actuarial grade III or greater late GI toxicity was found to be 8% whereas the crude rate was 6.6%. GU = genitourinary; GI = gastrointestinal.

acknowledge that 5 year efficacy outcomes may be overestimated by our short follow up, but report a 98.6% FFBF. OS was lower than anticipated in the 45 Gy cohort but none of the deaths were attributable to treatment or PCa. Likely the low OS is related to chance and the older age of the treatment cohorts. The majority (64%) of the patients enrolled in this study were found to have IR PCa with 100% and 98% at 3 and 5 year FFBF rates. It is important to note that percent core positivity was not recorded and not all IR patients were enrolled in this trial; many of these patients may have been considered favourable IR, but 16% of patients were Gleason 4 + 3. Only 14 (24%) of IR patients received a short course of ADT prior for prostate volume reduction. This outcome was favourable even in conventionally fractionated radiation therapy treated-patients who received a short course of ADT [17,18]. Prospective randomised trials are needed to assess if single modality SBRT treatment provides sufficient control for IR patients.

The patient who experienced biochemical recurrence had Gleason 4 + 3, an initial PSA of 7.4, was staged clinically as T2b, and treated in the lowest dose arm. He presented a biopsy-confirmed internal iliac node with prostate adenocarcinoma. A prostate biopsy revealed two microscopic foci of a questionably viable tumour 3.4 years after treatment. Several studies have reported no improvement in outcomes with longer follow up in IR PCa patients previously treated with SBRT doses lower than 40 Gy [2,3,19,20]. Higher doses (as those reported in this study) may be needed for increased biochemical control of biologically aggressive disease. Conventionally fractionated and intensity modulated radiation therapy (IMRT) dose escalation studies reported 5-year FFBF rates between 69 and 76% [21,22]. Radical prostatectomy (RP) series indicated 5-year recurrence-free survival rates between 65 and 84% [23] for IR PCa. Modestly hypofractionated regimens report FFBF rates of 82 and 90% in LR and IR respectively [18,24]. The current study demonstrates improved results compared to previously published data, regardless of modality.

One prospective study in 40 patients reported a median follow up of 41 months and a FFBF rate of 90% after SBRT with 33.5 Gy in five fractions using the ASTRO-Phoenix definition, but only 70% using the three-consecutive-rises method [3]. A second prospective series conducted in 67 patients indicated a median follow up of 2.7 years and a 4-year FFBF rate of 94% after a five-fraction treatment dose of 36.25 Gy in LR patients [2]. Prospective registry and retrospective studies have shed light on the efficacy of SBRT for PCa. In a series of SBRT for LR and IR PCa treated with 36.25 Gy in five fractions, Katz et al [20] reported a 7-year FFBF of 93.7% with a median follow up of 72 months. Failure rates stratified by NCCN risk groups revealed 95.9% and 89.3% FFBF rates for LR and IR, respectively. Further sub-group analysis revealed Gleason 4 + 3 patients had the lowest FFBF with a 7-year outcome of 84.3%. In a large multi-centre registry trial, Freeman et al. reported a 92% 2-year FFBF rate in a mixed population of 2000 PCa patients of mixed risk-

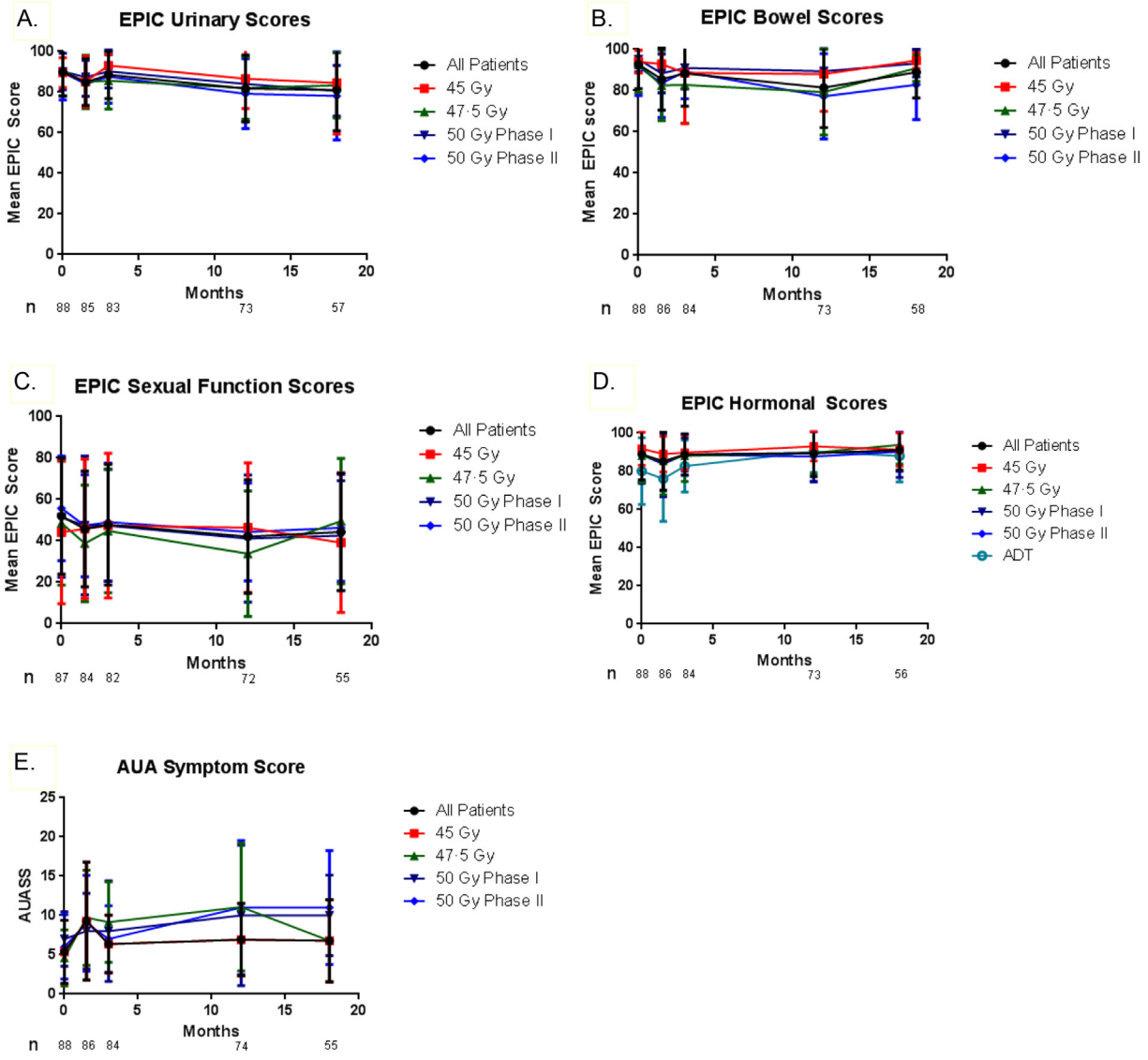


Fig. 4. EPIC urinary (A), bowel (B), sexual function (C), hormone (D), and AUA symptom (E) scores over time by treatment arm. The repeated measure mixed-model ANOVA revealed significant score decreases over time in all three EPIC domains and AUASS. Treatment comparisons were performed by dose level for all scoring domains and systems using the one-way ANOVA with Tukey's correction. No differences were found among dose levels or study phases in any domain or group. N denotes the number of questionnaires completed at each time point. EPIC = Expanded Prostate Cancer Index Composite. AUASS = American Urology Association Symptom Score. ANOVA = Analysis of Variance.

groups mostly treated with SBRT monotherapy [25]. A 2-year FFBF rate of 85% was found in the IR group. Lastly, Chen et al [19] reported a 99% FFBF with a median follow up of 2.4 years in a mixed population of 100 PCa patients treated with and without androgen suppression and SBRT of 35–36.25 Gy in five fractions.

Reported rates of acute grade II urinary toxicity were 19–35%, acute grade III toxicities were 0–6%, late grade II GU toxicities were 17–31%, and late grade III toxicities were 2–5% when doses of 35–40Gy in five fractions were used [3,15,19,26–28]. The cumulative acute grade II GU toxicity rate in this study was 22% with no reported acute grade III toxicity. Fourteen out of 20 of these toxicities were observed in the 50 Gy arm. We also report crude and actuarial late grade III GU toxicity rate of 4.4% and 6% respectively with one (1.1%) reported grade IV toxicity, all in the 50 Gy arm (Fig. 3). While our study is comparable with previously reported SBRT series, 50 Gy induced a small increase in acute GU toxicity. The GU toxicity profile in this study is modestly higher than conventionally fractionated dose escalated radiation treatments [29].

Previous SBRT studies reported acute grade II GI toxicity rates of 0–14%, grade III of 0–5%, late grade II of 0–15%, and late grade III of 0–5% using doses of 35–40 Gy [3,15,19,26–28]. Doses of 45 and 47.5 Gy are comparable to the reported toxicities but 50 Gy resulted in one (1.6%) acute and two (3.3%) late grade IV

toxicities. In all cases but one, patients developed ulceration of the rectum requiring diverting colostomy. We have extensively analysed the rectal dosimetry of all patients and demonstrated that grade III or higher rectal toxicity occurred when >3 cm^3 of the rectal wall received 50 Gy, >35% of the rectal wall circumference received 39 Gy and > 50% circumference of the rectal wall received 24 Gy [13]. When compared to dose escalation and image-guided IMRT, late GI toxicities of 45 and 47.5 Gy dose levels were modestly higher [29–32]. While the toxicity in the lower dose arms is comparable to those reported elsewhere it is important to note that the small numbers from the phase I portion may underestimate the overall toxicity rates.

Our centre has recently initiated a PCa SBRT study at 45 Gy in five fractions (NCT02353832) using a biodegradable spacer injected between the prostate and the rectum to eliminate all rectal toxicity [33]. Other approaches have been taken to avoid toxicity such as simultaneous lesion directed boosts. Initial pilot studies report acute grade III GI and GU toxicity rates of 2 and 8% respectively which are similar to whole gland techniques. It is important to note that this method is highly dependent on MRI with reported success rates between 28 and 90% in identifying lesions [34,35]. The FLAME and SPARC (NCT02145494) trials will further determine the safety and efficacy of this treatment method [36].

Reported ED rates were as high as 40% with conventionally fractionated radiation treatments [37,38]. A systematic review of RP techniques reported potency rates of 11–40% for open, 13–56% for unilateral and 31–84% for bilateral nerve sparing RP [39]. The 25.6% ED rate in this study is encouraging even when compared to other SBRT studies [17,40]. The QOL analysis of this study was limited by low questionnaire compliance. Recent studies reported that QOL can be affected up to 3 years from SBRT treatment, whereas our study was limited to 18 months [41].

In the phase I study only one patient had grade III rectal toxicity at 50 Gy for a crude rate of 6.7%. The patient was on immunosuppression and toxicity developed 9 months after treatment. The 50 Gy cohort had a similar crude rate of late GI toxicity which suggests the number of patients with toxicity is a result of the increased number of patients. The phase II was designed such that if ten or more patients had severe toxicity the trial would be stopped. Though the current analysis still did not meet the stoppage rules, we recommend using doses less than 50 Gy. The patients with toxicity required significant surgical intervention as a result of treatment and the probability of toxicity is not warranted given the safety of modest hypofractionation with ADT or lower doses of SBRT [18]. The phase I study was designed to assess late toxicity at 9 months after radiation therapy however four of six late GI toxicities occurred greater than 9 months after treatment. Radiation trials in PCa present an interesting design challenge since the time to toxicity can be long. This study underscores the inherent flaws with traditional dose escalation studies and underscores the need for rigorous multi-phase studies in evaluation of new therapies regardless of modality.

We report the results of a prospective study of SBRT in men with LR and IR PCa. This study shows SBRT with doses of 45 and 47.5 Gy in five fractions results in high control rates and acceptable toxicity, however doses of 50 Gy results in high rates of late toxicity. Future studies will clarify the dose necessary to achieve appropriate balance between control and toxicity. Longer follow up and additional trials are necessary before SBRT can be accepted as a standard of care but are warranted given the promising results.

Conflict of interest statement

All authors have no conflicts of interest to disclose.

Acknowledgements

Role of funding source: The funding agency (US Department of Defense) was involved establishing guidelines for monitoring and received periodic progress reports.

The authors would like to sincerely thank Damiana Chiavolini for her assistance in preparation of this manuscript.

References

[1] Lloyd-Davies RW, Collins CD, Swan AV. Carcinoma of prostate treated by radical external beam radiotherapy using hypofractionation. Twenty-two years' experience (1962–1984). Urology 1990;36(2):107–11.

[2] King CR, Brooks JD, Gill H, Presti Jr JC. Long-term outcomes from a prospective trial of stereotactic body radiotherapy for low-risk prostate cancer. Int J Radiat Oncol Biol Phys 2012;82(2):877–82.

[3] Madsen BL, Hsi RA, Pham HT, Fowler JF, Esagui L, Corman J. Stereotactic hypofractionated accurate radiotherapy of the prostate (SHARP), 33.5 Gy in five fractions for localized disease: first clinical trial results. Int J Radiat Oncol Biol Phys 2007;67(4):1099–105.

[4] Duchesne GM, Peters LJ. What is the alpha/beta ratio for prostate cancer? Rationale for hypofractionated high-dose-rate brachytherapy. Int J Radiat Oncol Biol Phys 1999;44(4):747–8.

[5] Fowler JF, Ritter MA, Chappell RJ, Brenner DJ. What hypofractionated protocols should be tested for prostate cancer? Int J Radiat Oncol Biol Phys 2003;56(4):1093–104.

[6] Dasu A, Toma-Dasu I. Prostate alpha/beta revisited – an analysis of clinical results from 14 168 patients. Acta Oncol 2012;51(8):963–74.

[7] Puck TT, Marcus PI. Action of X-rays on mammalian cells. J Exp Med 1956;103(5):653–66.

[8] Park C, Papiez L, Zhang S, Story M, Timmerman RD. Universal survival curve and single fraction equivalent dose: useful tools in understanding potency of ablative radiotherapy. Int J Radiat Oncol Biol Phys 2008;70(3):847–52.

[9] Lotan Y, Stanfield J, Cho LC, Sherwood JB, Abdel-Aziz KF, Chang CH, et al. Efficacy of high dose per fraction radiation for implanted human prostate cancer in a nude mouse model. J Urol 2006;175(5):1932–6.
[10] Martinez AA, Pataki I, Edmundson G, Sebastian E, Brabbins D, Gustafson G. Phase II prospective study of the use of conformal high-dose-rate brachytherapy as monotherapy for the treatment of favorable stage prostate cancer: a feasibility report. Int J Radiat Oncol Biol Phys 2001;49(1):61–9.
[11] Yoshioka Y, Suzuki O, Isohashi F, Seo Y, Okubo H, Yamaguchi H, et al. High-Dose-Rate Brachytherapy as Monotherapy for Intermediate- and High-Risk Prostate Cancer: Clinical Results for a Median 8-Year Follow-Up. Int J Radiat Oncol Biol Phys 2015.
[12] Boike TP, Lotan Y, Cho LC, Brindle J, DeRose P, Xie XJ, et al. Phase I dose-escalation study of stereotactic body radiation therapy for low- and intermediate-risk prostate cancer. J Clin Oncol 2011;29(15):2020–6.
[13] Kim DW, Cho LC, Straka C, Christie A, Lotan Y, Pistenmaa D, et al. Predictors of rectal tolerance observed in a dose-escalated phase 1-2 trial of stereotactic body radiation therapy for prostate cancer. Int J Radiat Oncol Biol Phys 2014;89(3):509–17.
[14] Roach 3rd M, Hanks G, Thames Jr H, Schellhammer P, Shipley WU, Sokol GH, et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. Int J Radiat Oncol Biol Phys 2006;65(4):965–74.
[15] King CR, Brooks JD, Gill H, Pawlicki T, Cotrutz C, Presti Jr JC. Stereotactic body radiotherapy for localized prostate cancer: interim results of a prospective phase II clinical trial. Int J Radiat Oncol Biol Phys 2009;73(4):1043–8.
[16] Consensus statement: guidelines for PSA following radiation therapy. American Society for Therapeutic Radiology and Oncology Consensus Panel. Int J Radiat Oncol Biol Phys 1997;37(5):1035–41.
[17] D'Amico AV, Manola J, Loffredo M, Renshaw AA, DellaCroce A, Kantoff PW. 6-month androgen suppression plus radiation therapy vs radiation therapy alone for patients with clinically localized prostate cancer: a randomized controlled trial. JAMA 2004;292(7):821–7.
[18] Dearnaley DP, S.I., Mossop H, Birtle AJ, Bloomfield DJ, Cruickshank C, et al. Comparison of hypofractionated high-dose intensity-modulated radiotherapy schedules for prostate cancer: results from the phase III randomized CHHiP trial (CRUK/06/016). in Genitourinary Cancers Symposium. 2016. San Fransico, CA. J Clin Oncol 2016;34 (suppl 2S; abstr 2).
[19] Chen LN, Suy S, Uhm S, Oermann EK, Ju AW, Chen V, et al. Stereotactic body radiation therapy (SBRT) for clinically localized prostate cancer: the Georgetown University experience. Radiat Oncol 2013;8:58.
[20] Katz AJ, Kang J. Stereotactic body radiotherapy as treatment for organ confined low- and intermediate-risk prostate carcinoma, a 7-year study. Front Oncol 2014;4:240.
[21] Michalski JM, M.J., Purdy J, Bosch W, Bahary J, Lau HY, et al. A randomized trial of 79.2Gy versus 70.2Gy radiation therapy (RT) for localized prostate cancer. J Clin Oncol 2015;33(Suppl. 7). abstr 4.
[22] Beckendorf V, Guerif S, Le Prise E, Cosset JM, Bougnoux A, Chauvet B, et al. 70 Gy versus 80 Gy in localized prostate cancer: 5-year results of GETUG 06 randomized trial. Int J Radiat Oncol Biol Phys 2011;80(4):1056–63.
[23] Han M, Partin AW, Pound CR, Epstein JI, Walsh PC. Long-term biochemical disease-free and cancer-specific survival following anatomic radical retropubic prostatectomy. The 15-year Johns Hopkins experience. Urol Clin North Am 2001;28(3):555–65.
[24] Lee WR, Dignam JJ, Amin M, Bruner D, Low D, Swanson GP, et al. NRG Oncology RTOG 0415: a Randomized Phase 3 Noninferiority Study Comparing 2 Fractionation Schedules in Patients with Low-Risk Prostate Cancer. Int J Radiat Oncol Biol Phys January 2016;94(1):3–4.
[25] Freeman D, Dickerson G, Perman M. Multi-institutional registry for prostate cancer radiosurgery: a prospective observational clinical trial. Front Oncol 2014;4:369.
[26] Oliai C, Lanciano R, Sprandio B, Yang J, Lamond J, Arrigo S, et al. Stereotactic body radiation therapy for the primary treatment of localized prostate cancer. J Radiat Oncol 2013;2(1):63–70.
[27] Tree AC, Ostler P, Hoskin P, Dankulchai P, Nariyangadu P, Hughes RJ, et al. Prostate stereotactic body radiotherapy-first UK experience. Clin Oncol (R Coll Radiol) 2014;26(12):757–61.
[28] McBride SM, Wong DS, Dombrowski JJ, Harkins B, Tapella P, Hanscom HN, et al. Hypofractionated stereotactic body radiotherapy in low-risk prostate adenocarcinoma: preliminary results of a multi-institutional phase 1 feasibility trial. Cancer 2012;118(15):3681–90.
[29] Spratt DE, Zumsteg ZS, Ghadjar P, Kollmeier MA, Pei X, Cohen G, et al. Comparison of high-dose (86.4 Gy) IMRT vs combined brachytherapy plus IMRT for intermediate-risk prostate cancer. BJU Int 2014;114(3):360–7.
[30] Yu JB, Cramer LD, Herrin J, Soulos PR, Potosky AL, Gross CP. Stereotactic body radiation therapy versus intensity-modulated radiation therapy for prostate cancer: comparison of toxicity. J Clin Oncol 2014;32(12):1195–201.
[31] Zelefsky MJ, Kollmeier M, Cox B, Fidaleo A, Sperling D, Pei X, et al. Improved clinical outcomes with high-dose image guided radiotherapy compared with non-IGRT for the treatment of clinically localized prostate cancer. Int J Radiat Oncol Biol Phys 2012;84(1):125–9.
[32] Takeda K, Takai Y, Narazaki K, Mitsuya M, Umezawa R, Kadoya N, et al. Treatment outcome of high-dose image-guided intensity-modulated radiotherapy using intra-prostate fiducial markers for localized prostate cancer at a single institute in Japan. Radiat Oncol 2012;7:105.
[33] Uhl M, van Triest B, Eble MJ, Weber DC, Herfarth K, De Weese TL. Low rectal toxicity after dose escalated IMRT treatment of prostate cancer using an absorbable hydrogel for increasing and maintaining space between the rectum and prostate: results of a multi-institutional phase II trial. Radiother Oncol 2013;106(2):215–9.
[34] Aluwini S, van Rooij P, Hoogeman M, Kirkels W, Kolkman-Deurloo IK, Bangma C. Stereotactic body radiotherapy with a focal boost to the MRI-visible tumor as monotherapy for low- and intermediate-risk prostate cancer: early results. Radiat Oncol 2013;8:84.
[35] Kirkham AP, Emberton M, Allen C. How good is MRI at detecting and characterising cancer within the prostate? Eur Urol 2006;50(6):1163–74. discussion 75.
[36] Lips IM, van der Heide UA, Haustermans K, van Lin EN, Pos F, Franken SP, et al. Single blind randomized phase III trial to investigate the benefit of a focal lesion ablative microboost in prostate cancer (FLAME-trial): study protocol for a randomized controlled trial. Trials 2011;12:255.
[37] Stanford JL, Feng Z, Hamilton AS, Gilliland FD, Stephenson RA, Eley JW, et al. Urinary and sexual function after radical prostatectomy for clinically localized prostate cancer: the Prostate Cancer Outcomes Study. JAMA 2000;283(3):354–60.
[38] Ponholzer A, Brossner C, Struhal G, Marszalek M, Madersbacher S. Lower urinary tract symptoms, urinary incontinence, sexual function and quality of life after radical prostatectomy and external beam radiation therapy: real life experience in Austria. World J Urol 2006;24(3):325–30.
[39] Dubbelman YD, Dohle GR, Schroder FH. Sexual function before and after radical retropubic prostatectomy: a systematic review of prognostic indicators for a successful outcome. Eur Urol 2006;50(4):711–8. discussion 18–20.

[40] Obayomi-Davies O, Chen LN, Bhagat A, Wright HC, Uhm S, Kim JS, et al. Potency preservation following stereotactic body radiation therapy for prostate cancer. Radiat Oncol 2013;8:256.
[41] King CR, Collins S, Fuller D, Wang PC, Kupelian P, Steinberg M, et al. Health-related quality of life after stereotactic body radiation therapy for localized prostate cancer: results from a multi-institutional consortium of prospective trials. Int J Radiat Oncol Biol Phys 2013;87(5):939–45.