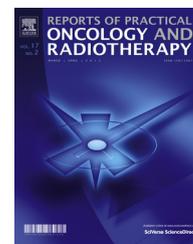




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Original research article

Image-guided hypofractionated proton beam therapy for low-risk prostate cancer: Analysis of quality of life and toxicity, PCG GU 002



Carlos Enrique Vargas^{a,*}, William Fred Hartsell^b, Megan Dunn^c,
Sameer Ramchandra Keole^a, Lucius Doh^d, John Chang^b,
Gary Lynn Larson^d

^a Department of Radiation Oncology, Mayo Clinic Hospital, Phoenix, AZ, USA

^b CDH Proton Center, Warrenville, IL, USA

^c Proton Collaborative Group, Warrenville, IL, USA

^d Radiation Medicine Associates, PC, Radiation Oncology, Oklahoma City, OK, USA

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ABSTRACT

Aim: This interim analysis evaluated changes in quality of life (QOL), American Urological Association Symptom Index (AUA), or adverse events (AEs) among prostate cancer patients treated with hypofractionation.

Background: Results for hypofractionated prostate cancer with photon therapy are encouraging. No prior trial addresses the role of proton therapy in this clinical setting.

Materials and methods: Forty-nine patients with low-risk prostate cancer received 38-Gy relative biologic effectiveness in 5 treatments. They received proton therapy at 2 fields a day, magnetic resonance imaging registration, rectal balloon, and fiducial markers for guidance pre-beam. We evaluated AEs, Expanded Prostate Index Composite (EPIC) domains, and AUA at pretreatment and at 3, 6, 12, 18, and 24 months. An AUA change >5 points and QOL change of half a standard deviation (SD) defined clinical significance.

Results: Median follow-up was 18 months; 17 patients reached follow-up of ≥ 24 months. For urinary function, statistically and clinically significant change was not seen (maximum change, 3). EPIC urinary QOL scores did not show statistically and clinically significant change at any end point (maximum, 0.45 SD). EPIC bowel QOL scores showed small but statistically and clinically significant change at 6, 12, 18, and 24 months (SD range, 0.52–0.62). EPIC sexual scores showed small but statistically and clinically significant change at 24 months (SD, 0.52). No AE grade ≥ 3 was seen.

Conclusions: Patients treated with hypofractionated proton therapy tolerated treatment well, with excellent QOL scores, persistently low AUA, and no AE grade ≥ 3 .

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Abbreviations: AE, adverse event; AUA, American Urological Association Symptom Index; EPIC, Expanded Prostate Index Composite; OTV, optimization target volume; RBE, relative biologic effectiveness; RT, radiation therapy; SD, standard deviation.

* Corresponding author at: Department of Radiation Oncology, Mayo Clinic Hospital, 5777 E Mayo Blvd, Phoenix, AZ 85054, USA.

Tel.: +1 480 342 1262; fax: +1 480 342 3972.

E-mail address: vargas.carlos@mayo.edu (C.E. Vargas).

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1. Background

Proton therapy is a radiation modality that uses particles to deliver large doses to the tumor with high accuracy and low doses to surrounding normal tissue. However, with standard doses for image-guided proton radiation therapy (RT) or intensity-modulated RT, daily treatments for 8–9 weeks are typically used. Patients who are ideal candidates for external RT or proton therapy may elect alternative modalities because of the extended treatment time. Therefore, in the present protocol, we proposed to combine a hypofractionated approach that benefits from the low α/β ratio of prostate cancer and the conformality achieved with proton therapy to deliver an abbreviated course of therapy for low-risk prostate cancer.^{1–6}

All patients required image guidance with fiducial placement and magnetic resonance imaging registration. The rationale of this image guidance approach for proton therapy has been reviewed previously.^{7,8}

2. Aim

To evaluate changes in quality of life (QOL), American Urological Association Symptom Index (AUA), or adverse events (AEs) among prostate cancer patients treated with hypofractionation over time.

3. Materials and methods

3.1. Design overview

This report corresponds to first analysis of the hypofractionated arm. The main objective was to evaluate initial rectal and bladder toxicity and quality-of-life metrics at different time intervals. Statistical calculations for toxicity were done using a double-sided $\alpha < .05$ for significance.

3.2. Patients

We enrolled 85 patients between 2011 and 2014. Three patients withdrew consent, and the 82 other patients were assessable. Forty-nine were randomly assigned to receive 38-Gy relative biologic effectiveness (RBE). No major violations were seen for any patient. Patients were stratified by pre-enrollment initial prostate-specific antigen level (<4 ng/mL vs ≥ 4 to <10 ng/mL), positive cores (1–4 vs ≥ 5), and stage (T1 vs T2). All patients were required to have a Gleason score of 6. A prepopulated,

block randomization sheet was used for assignment by the protocol research office.

3.3. Radiation therapy

Briefly, planning for proton therapy involved the fusion of 1.5 T magnetic resonance images to computed tomography images. Patients were positioned supine. The clinical target volume contained the prostate only; the planning target volumes were 2 mm posteriorly and 3 mm elsewhere.⁹ The constructed optimization target volume (OTV) included an additional 5 mm in the beam direction distally and proximally. Proton-specific expansions accommodated changes in dose deposition and improved treatment delivery robustness. The proton beams were oriented laterally left and right, and expansions were in the lateral direction only and appropriately. The plan was optimized, normalized, and evaluated on the basis of the OTV. Two beams were used every day, and image guidance was done before each beam. Rectal balloon was used every day before treatment.

We believed that it was a safe assumption to define the α/β ratio for normal tissue first on the basis of available literature. On the basis of published data, the dose to achieve rectal isototoxicity between the 2 arms^{10–12} was defined. In this manner, 38-Gy RBE in 5 treatments was equivalent to 79.2-Gy RBE in 44 treatments, for a rectal α/β ratio of 3.5 Gy (Tables 1 and 2). The dose to the target was 38-Gy RBE. If prostate α/β ratio is <3.5 -Gy RBE, the resulting biologic equivalent dose will be >79.2 -Gy RBE in 44 treatments.

3.4. Toxicity assessment

Protocol toxicity was measured with the Common Terminology Criteria for Adverse Events version 4.0.

3.5. Statistical analysis

The primary end point was the cumulative incidence of an adverse event (AE) grade 3 or higher. Adverse bowel and urinary events were analyzed through incidence and prevalence. Prevalence was calculated at 3, 6, 12, 18, and 24 months after RT. For incidence, we considered AEs of grade 2 or higher occurring for each arm for 3 years. All analyses were carried out in the intention-to-treat population through Fisher exact test and 2-sided .05 significance levels. Patients completed the Expanded Prostate Index Composite (EPIC)¹³ and American Urological Association Symptom Index (AUA)¹⁴ before treatment and during routine follow-up visits at 3, 6, 12,

Table 1 – Dose constraints in 38-Gy relative biologic effectiveness.

Structure	Goal	Minor deviation	Major deviation
Rectum	V24 $<35\%$	V24 $<40\%$	V24 $\geq 40\%$
	V33.6 $<10\%$	V33.6 $<20\%$	V33.6 $\geq 20\%$
Bladder	V39 <8 cc	V39 <12 cc	V39 ≥ 12 cc
Femoral heads	V23 <1 cc	V23 <2 cc	V23 ≥ 2 cc
PTV	Min dose	99.5% >36.1 Gy	
OTV	PTV coverage	95% to 38 Gy	

Abbreviations: min, minimum; OTV, optimization target volume; PTV, planning tumor volume.

Table 2 – Characteristics of the 49 patients receiving 38-Gy relative biologic effectiveness in 5 fractions.

Characteristic	Value ^a
Age, median (range), y	65 (52–75)
Stage	
T1c	41
T2a	8
GS 6	49
PSA	11
0–4 ng/mL	
PSA	38
>4–10 ng/mL	
AUA score	
0–10	45
11–17	4
AUA, median (range)	4.69 (0–13)

Abbreviations: AUA, American Urological Association Symptom Index; GS, Gleason score; PSA, prostate-specific antigen.
^a Values are presented as number of patients unless specified otherwise.

Table 4 – Grade 2 urinary and bowel adverse events.

Symptoms grade 2	38-Gy RBE in 5 fractions, no. (%)
<i>Urinary</i>	
Pre-RT	7 (15.21)
During tx	9 (19.6)
At 3 mo	4 (10.0)
At 6 mo	7 (17.5)
At 1 y	7 (22.6)
At 2 y	2 (12.5)
Overall	17 (37.0)
<i>EPIC bowel</i>	
Pre-RT	0 (0)
During tx	2 (4.3)
At 3 mo	1 (2.5)
At 6 mo	3 (7.5)
At 1 y	1 (3.2)
At 2 y	1 (6.3)
Overall	6 (13.0)

Abbreviations: EPIC, Expanded Prostate Index Composite; RBE, relative biologic effectiveness; RT, radiotherapy; tx, treatment.

18 and 24 months after treatment completion. EPIC was used.¹³ Higher numbers corresponded to better function and decreased bother. QOL changes were assessed on the basis of pretreatment baseline scores. The t test was used to determine the significance of the change. A significant clinical difference was set as half a standard deviation (SD).¹⁵ We defined a clinically significant change in AUA scores at ≥5 points.¹⁴ The schedule of assessments is summarized in [Table 3](#).

4. Results

4.1. Patients

Median follow-up for both arms was 18 months, and more than 1 quartile of patients have been monitored for ≥2 years.

There was no difference in patients' characteristics ([Table 2](#)). No treatment has failed, and no deaths related or unrelated to treatment have occurred.

4.2. Adverse events

No toxicity of grade 3 or higher was seen in either arm. AE grading was done with Common Terminology Criteria for Adverse Events, version 4.0. Any use of a prescription or over-the-counter medication over baseline counted as a grade 2 AE. Patients tolerated treatment well, and only some of them needed a medication for AEs. The most common symptoms were frequency and urgency ([Table 4](#)).

Bowel AEs were minimal and no grade 3 AE was seen. The most common concern was blood in stool, which may have

Table 3 – Schedule of assessments.

Assessment	Screen	RT	Time, mo					
			3	6	12	18	24	36
Procedure	X							
Informed consent	X							
Consult	X							
Medications	X		X	X	X	X	X	X
Adverse events	X	Once	X	X	X	X	X	X
QOL EPIC	X		X	X	X	X	X	X
IPSS	X		X	X	X	X	X	X
Laboratory								
PSA	X		X	X	X	X	X	X
Radiation		5 txs						
Tumor								
Tumor biopsy	X							
MRI pelvis (planning)	X							
Fiducial markers (guidance)	X	Daily						
Rectal balloon		Daily						

Abbreviations: EPIC, Expanded Prostate Cancer Index Composite; IPSS, International Prostate Symptom Score; MRI, magnetic resonance imaging; PSA, prostate-specific antigen; QOL, quality of life; RT, radiation therapy; txs, treatments.

Table 5 – AUA scores, EPIC U, EPIC GI, and EPIC S by treatment arm.

Characteristic ^a	5 Fractions	SD	P-Value	Half SD	Change
<i>AUA score</i>					
Baseline	4.820	3.920		1.960	
3 mo	6.250	4.060	.09	2.030	1.430
6 mo	6.130	5.630	.20	2.815	1.310
12 mo	7.680	5.390	.008	2.695	2.860
18 mo	7.950	7.970	.03	3.985	3.130
24 mo	6.690	4.710	.12	2.355	1.870
<i>EPIC U</i>					
Baseline	91.268	8.190		4.095	
3 mo	87.000	11.120	.04	5.560	4.268
6 mo	88.690	12.440	.24	6.220	2.578
12 mo	85.910	12.550	.02	6.275	5.358
18 mo	84.000	15.610	.01	7.805	7.268
24 mo	90.922	7.300	.88	3.650	0.346
<i>EPIC bowel</i>					
Baseline	96.387	4.290		2.145	
3 mo	91.850	9.500	.003	4.750	4.537
6 mo	87.600	15.860	<.001	7.930	8.787
12 mo	87.518	13.990	<.001	6.995	8.869
18 mo	90.470	11.190	.002	5.595	5.917
24 mo	89.240	13.670	.002	6.835	7.147
<i>EPIC S</i>					
Baseline	59.980	22.750		11.375	
3 mo	57.160	24.570	.57	12.285	2.820
6 mo	55.880	27.470	.27	13.735	4.100
12 mo	52.120	25.330	.17	12.665	7.860
18 mo	47.890	25.870	.06	12.935	12.090
24 mo	46.550	25.620	.053	12.810	13.430

Abbreviations: AUA, American Urological Association Symptom Index; EPIC, Expanded Prostate Index Composite; S, sexual; SD, standard deviation; U, urinary.

^a Bold indicates statistically significant data.

been related to treatment vs other associated or unrelated medical conditions (Table 5). Overall, incidence of grade 2 AEs was low over the first 3 years.

4.3. AUA scores

A small increase in AUA scores was seen at 12 and 18 months. The difference was smaller than 5 points and was not considered clinically significant (Table 5). Changes in AUA scores improved after 18 months.

4.4. EPIC scores

Urinary scores declined slightly over time and improved at 2 years (Table 5). However, the change was small and less than a half SD. The maximum change over time occurred at 18 months and was 7 points. No clinically significant changes in the EPIC urinary scores were seen.

Questions also were analyzed individually. Small changes were seen over time for specific questions. Most changes seen in the domain corresponded to increased leakage of urine, weak urinary stream, and overall urinary bother.

Bowel scores decreased at 6 months, and the decline continued over 2 years. The maximum decrease occurred at 1 year and was 9 points (Table 5).

At 1 year, most of the change in the sexual domain was seen as a decrease in both the frequency and quality of an erection.

5. Discussion

Hypofractionated approaches for prostate cancer have certain relative advantages. A higher biologic effective dose to the cancer tissue may be achieved as a result of a lower α/β ratio of the cancer compared with normal tissue.^{1,10,16,17} Potentially higher doses per fraction may have additional effects over the vascular or cancer stem cells not seen with lower doses per fraction.¹⁸ Clinical results for hypofractionated photon prostate cancer treatments have also been favorable.^{3,19–31}

Many different fractionations, from 6.75 Gy in 5 treatments to 10 Gy in 5 treatments, have been used. Our design was based on data published with high-dose-rate brachytherapy for prostate cancer and the published normal tissue α/β ratio.^{1,10,11,32–34} However, our fractionation of 7.6-Gy RBE in 5 treatments is well within the dose range published for this technique. Our early clinical results are suggestive that this dose of proton therapy is safe. Toxicity seen for patients treated with similar doses of hypofractionated photon therapy also suggested that our long-term AE rate should be low. We have not seen an AE grade 3 or higher with a median follow-up of 18 months. Similarly, other publications with longer follow-up have not seen an AE grade 3 or higher.^{25,27,28} So, there is no reason to think that AEs would be seen with longer follow-up. Furthermore, most grade-3 events in the University of Texas Southwestern study¹⁹ and the Georgetown University study²¹ were seen within 12 months. With a median follow-up of 18

months, the present study should reflect most AEs for this technique. On the basis of our clinical data, doses of 38-Gy RBE in 5 treatments appear to be safe.

Literature on prostate hypofractionation suggests that most AEs are urinary in nature.^{3,20–22,24,30} In our present study, AUA scores and EPIC urinary scores had no significant change over time. Most symptoms were related to weak urinary stream that improved with medications, as reflected by an almost flat AUA score over time. Katz et al.²⁷ saw a relative large decrease in the EPIC urinary scores that recovered by 12 months. Given the lack of changes in the EPIC urinary domain and AUA scores and the relative short median time to AEs in the hypofractionated prostate published literature, major changes are unlikely to be seen.

Bowel AEs are less frequent in the literature of hypofractionated prostate treatments, and rates of grade 3 or higher are within 0% to 1% for most publications.^{3,20–25,27,28} Similarly, no AEs of grade 3 or higher were found in our study. Overall EPIC bowel scores were high during follow-up. However, they decreased slightly over time in our study. The change was about a half SD, and the largest change was seen at about 12 months' follow-up, with improvement thereafter.

EPIC sexual domain decreased at 24 months and was about a half SD. Longer follow-up would be necessary to further evaluate this decline.

6. Conclusions

No grade 3 urinary or bowel AEs were seen. No difference was seen for the EPIC urinary and AUA scores over time. Hypofractionated proton beam therapy for low-risk prostate cancer appears safe; however, longer follow-up is necessary for further evaluation.

Author contributions

All authors helped in the preparation of the manuscript and the interpretation of the data and results and have reviewed the paper. All authors have approved the final article.

Conflict of interest

None declared.

Financial disclosure

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