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Patient reported outcomes following proton pencil beam scanning vs. passive scatter/uniform scanning for localized prostate cancer: Secondary analysis of PCG 001-09

Mark V. Mishra [a,*], Rahul Khairnar [b], Søren M. Bentzen [c], Gary Larson [d], Henry Tsai [e], Christopher Sinesi [f], Carlos Vargas [g], George Laramore [h], Carl Rossi [i], Lane Rosen [j], Kai Sun [a], William Hartsell [k]

[a] Department of Radiation Oncology, University of Maryland School of Medicine, Baltimore, MD, United States
[b] Pharmaceutical Health Services Research, University of Maryland School of Pharmacy, Baltimore, MD, United States
[c] Department of Epidemiology & Public Health, Greenebaum Cancer Center, University of Maryland School of Medicine, Baltimore, MD, United States
[d] ProCure Proton Therapy Center, Oklahoma City, OK, United States
[e] ProCure Proton Therapy Center, Somerset, NJ, United States
[f] Hampton University Proton Therapy Institute, Hampton, VA, United States
[g] Department of Radiation Oncology, Mayo Clinic Arizona, Phoenix, AZ, United States
[h] University of Washington, Department of Radiation Oncology, Seattle, WA, United States
[i] California Protons Cancer Therapy Center, San Diego, CA, United States
[j] Willis-Knighton Proton Therapy Center, Shreveport, LA, United States
[k] Northwestern Medicine Chicago Proton Center, Warrenville, IL, United States

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ABSTRACT

Background: Although pencil beam scanning (PBS) is the most conformal method for proton beam therapy (PBT) delivery, it is unknown if outcomes differ compared to treatment with passive scatter/uniform scanning (PS/US). This analysis compares patient reported outcomes (PROs) following PBS and PS/US for prostate cancer (PC) in a prospective multicenter registry study.

Methods: We evaluated PROs with the Expanded Prostate Cancer Index Composite (EPIC) instrument for men with localized PC enrolled in PCG 001-09 (NCT01255748). PROs were assessed at baseline and through 12 months of follow-up. We compared mean changes in EPIC scores, as well as the proportions of men experiencing a one- and two-fold minimally important difference (MID) in domain scores, between PBS and PS/US. Multivariate analyses (MVAs) were performed to further evaluate the association between proton modality and PRO changes.

Results: Three-hundred-and-four men completed EPIC at baseline; 72 received PBS and 232 received PS/US. The average quality-of-life (QOL) declines from baseline through 12 months did not significantly differ between the two groups. The proportion of men reporting a 1-MID decline at 12 months for PBS and PS/US was 34.3% and 27.4%, respectively, for urinary QOL ($P = 0.27$); 40. 1% and 40.9% for bowel QOL ($P = 0.36$); and 30. 1% and 36.6% for sexual QOL ($P = 0.94$). Corresponding 2-MID declines for PBS and PS/US were observed in 26.9% and 13.2% of men for urinary QOL ($P = 0.01$), 35.3% and 29.1% for bowel QOL ($P = 0.33$); and 16.4% and 18.1% for sexual QOL ($P = 0.76$). The association between proton modality and 2-MID changes in urinary QOL at 12-months remained significant on MVA (P = 0.007).

Conclusions: The results of this analysis show differences between PBS and PS/US with regards to two-fold MID changes in urinary function at 12 months, but no differences for average score declines over time. Future studies evaluating PRO measures between the two PBT modalities are warranted.

1. Introduction

Prostate cancer remains one of the most common indications for proton beam therapy in the United States [1]. Given the rapid increase in the number of operational proton centers worldwide,

* Corresponding author at: Department of Radiation Oncology, University of Maryland School of Medicine, 22 S. Greene Street, GGK 0101, Baltimore, MD 21201, United States.
E-mail address: mmishra@umm.edu (M.V. Mishra).

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the number of prostate cancer patients who have access to proton beam therapy is expected to increase substantially [2].

There are currently two alternative forms of proton beam therapy that are in clinical-use: passive scattering/uniform scanning (PS/US) or pencil-beam scanning (PBS). PBS allows for spot-weighted dose delivery, which has been shown to result in a more conformal dose-distribution [3,4]. The clinical significance of the differences between the two alternative proton approaches is not well-understood.

If there are significant differences in the toxicity profiles between the two modalities, this could have an impact on the results of ongoing randomized studies comparing protons to photons [5]. This analysis compares PRO changes associated with PBS and PS/US techniques for localized PC in a prospective multicenter registry study. A secondary objective of the study was to compare the two modalities in the context of different statistical approaches that can be used to analyze PROs.

2. Methods

2.1. Study design and setting

The Proton Collaborative Group (PCG) 001-09 (NCT01255748) is a prospective observational study for patients treated with protons at participating PBT centers across the US. Patients are enrolled after signing informed consent and are prospectively followed to collect outcomes on tumor control, toxicity, and PROs.

2.2. Patient population

This analysis was limited to the subset of men enrolled on PCG 01-009 with low- to intermediate-risk PC treated with PBT to the prostate ± seminal vesicles with conventionally-fractionated radiation to a dose of >75 Gy using PBS or PS/US. Patients on androgen deprivation therapy were excluded from the analysis, as were patients with a history of prior pelvic radiation. Analyses included patients with complete data on at least one of the Expanded Prostate Cancer Index Composite (EPIC) domains of interest at baseline and all subsequent follow-up assessments.

2.3. Measurements

The Expanded Prostate Cancer Index Composite (EPIC) questionnaire was utilized to evaluate PROs (bowel, urinary, and sexual QOL) after receipt of PBS or PS/US. EPIC is a comprehensive instrument designed to evaluate patient function and bother after prostate cancer treatment. EPIC has 4 domains: urinary, bowel, sexual, and hormonal. Each of these scales has measureable function and bother subscales. Additionally, urinary domain has 2 more subscales: urinary incontinence, urinary irritative/obstructive. Each domain and subscale is scored from 0 to 100, in which 100 represents no problems and 0 represents substantial and significant problems with the specific subscale. PROs were assessed at 0 months (baseline), 3 months, 6 months, and 12 months.

2.4. Statistical analysis

Baseline patient characteristics for patients receiving PBS and PS/US were compared using *t*-tests or Wilcoxon rank sum tests for continuous variables and chi-squared tests for categorical variables. *T*-tests were utilized to compare changes in EPIC domain scores from baseline across the radiation types. To determine whether changes in EPIC domain scores from baseline across the radiation types changed significantly over time, a generalized estimated equation (GEE) model with an identity link and a normal distribution was applied.

Minimally important differences (MIDs) in the EPIC summary scores were evaluated according to previously published thresholds: bowel (5 points), urinary (6 points), and sexual (11 points) [6,7]. MIDs were also defined as a half standard deviation difference from the mean baseline domain score. Additionally, pre-planned cut-points of 2 MID thresholds were also evaluated. The proportions of patients experiencing 1 and 2 MID declines in EPIC domains at time-points of interest were reported. Each binary MID variable was modeled using a generalized estimating equation model with a logit link to estimate the odds of experiencing a 1-MID/2-MID for each proton modality at time-points of interest, as well as to account for the repeated surveys for each patient over time. All GEE models applied above were adjusted for the following covariates: baseline EPIC domain score, race, Gleason score, and clinical T-stage. Statistical analysis was performed using SAS, version 9.4 (SAS Institute, Cary, NC). All statistical tests were performed at a significance level of 0.05.

3. Results

3.1. Patient characteristics

A total of 304 patients completed at least one of the EPIC domains (urinary, bowel, or sexual) at all study time-points, and were considered for this analysis. PBS was received by 72 patients (23.7%) while the remaining 232 patients (76.3%) received PS/US. Pre-treatment patient characteristics are summarized in Table 1. Median age of patients receiving PBS and PS/US was 66.0 years and 65.1 years, respectively.

Table 1
Baseline characteristics by proton treatment modality.

Patient Characteristic	Pencil Beam Scanning N = 72	Passive Scatter/Uniform Scanning N = 232	*P* Value
Age (in years)			0.11
Mean (standard deviation)	66.2 (6.0)	64.7 (7.6)	
Baseline PSA			0.5
Median	5.3	5.7	
Q1–Q3	4.2–7.3	4.3–8.0	
Dose (Gy)			0.77
Mean (standard deviation)	79.4 (0.5)	79.4 (0.4)	
Fractions			0.42
Median	44	44	
Q1–Q3	44.0–44.0	44.0–44.0	
Race			0.0015
Non-Hispanic White N (%)	46 (63.9)	193 (83.2)	
Non-Hispanic Black N (%)	7 (9.7)	14 (6.0)	
Other N (%)	19 (26.4)	25 (10.8)	
Gleason Score			0.3
6 N (%)	30 (41.7)	113 (48.7)	
7 N (%)	42 (58.3)	119 (51.3)	
T Stage			0.27
T1 N (%)	27 (37.5)	69 (30.5)	
T2 N (%)	45 (62.5)	157 (69.5)	
Baseline IPSS/AUA			0.21
0–7 N (%)	44 (61.1)	166 (71.6)	
8–19 N (%)	24 (33.3)	59 (25.4)	
20–35 N (%)	4 (5.6)	7 (3.0)	

3.2. Quality of life

Table 2A shows the baseline EPIC domain scores as well as average change in urinary, bowel, and sexual QOL over 1-year for each modality. Patient undergoing PS/US experienced a decline of 1.9 points (p = 0.009) in summary urinary scores from baseline to 1-year following treatment, and PBS patients experienced a decline of 3.0 points (0.0795). Summary bowel scores significantly decreased 1-year after treatment for patients treated with both proton modalities (PBS: −9.2, p < 0.0001; PS/US: −6.6 < 0.0001). Significant declines were also noted for sexual function scores at 1-year (PBS: −8.9, p = 0.0018; PS/US: −9.7, p < 0.0001).

Table 2B shows the results comparing mean changes in urinary, bowel, and sexual function over 1-year between each modality at 3-, 6, and 12- months following treatment (i.e. p-values correspond to comparisons between each modality at different time points). Statistically significant differences were observed in the urinary scores between both proton modalities at baseline (p < 0.001).Significant differences were found in the mean change in urinary scores from baseline to 3 months (p < 0.038) between PBS and PS/US, but were not different for any other EPIC domain scores. The average changes QOL scores from baseline to 6- and 12 months following treatment for urinary QOL, bowel QOL, and sexual QOL were not significantly different between PBS and PS/US (Table 2B). There were no significant differences between proton treatment modalities on multivariate analysis when modeling changes in average EPIC domain scores from baseline to 3-, 6-, and 12-months (Supplementary Table 1) or when modelling the changes from baseline through the entire follow-up period (Supplementary Table 2).

MIDs defined as half standard deviation difference from the mean baseline domain score were found to be similar to previously published thresholds: bowel (4.5 points), urinary (6.35 points), and sexual (13.1 points), and were used in the MID analysis [6,7]. The percentages of men reporting a 1-MID decline at 12 months for PBS and PS/US were 34.3% and 27.4%, respectively, for urinary QOL (P = 0.27); 40.1% and 40. 9%, respectively, for bowel QOL (*P* = 0.36); and 30.1% and 36.6%, respectively, for sexual QOL (*P* = 0.94) (Table 3A). Corresponding 2-MID declines were observed in 26.9% and 13.2% for urinary QOL (*P* = 0.01), 35.3% and 29.1% for bowel QOL (*P* = 0.33); and 16.4% and 18.1% for sexual QOL (*P* = 0.76).

Table 3B shows multivariate analyses for 1 and 2 MID changes in EPIC domains in patients undergoing PBS compared to PS/US at each follow-up period, adjusted for race, Gleason score, and clinical T- stage. No statistically significant differences were observed between PBS and PS/US in the proportion of men with a 1-MID change in urinary, bowel, or sexual QOL at any follow-up time point. However, compared to PBS, patients undergoing PS/US had significantly lower odds of 2-MID declines in bowel QOL at 6 months (OR = 0.44, 95%CI = 0.23, 0.84, p = 0.01) and in urinary QOL at 12 months (OR = 0.39, 95%CI = 0.20, 0.77, p = 0.007). MID differences for all other time points and domains were not significantly different. No statistically significant differences were observed between the PBS and PS/US in the proportion of men with 1- and 2-MID in urinary, bowel and sexual QOL, when the repeated surveys for each patient over the entire follow-up period were modeled (Supplementary Table 3).

4. Discussion

Patient reported outcome measures are the preferred approach for measuring treatment-morbidity in oncology clinical trials. PROs have been shown to better predict for functional independence and severe treatment-morbidity as compared to clinician-scored toxicity measures [8]. For prostate cancer patients, EPIC is one of the most widely-used PRO tools to measure quality-of-life before and after treatment [7,9], and is the PRO tool that is being used in an ongoing proton vs. photon randomized study for men undergoing PC treatment [5]. The current study represents one of the first multi-institutional studies to compare prospectively collected EPIC

Table 2A
Changes in Expanded Prostate Cancer Index Composite (EPIC) Domain Scores from Baseline to subsequent follow-up time points across proton treatment modalities.

EPIC Domain		Time Point						
		Mean Baseline Scores (SD)	Mean Change in Scores from Baseline (SD)					
			3 months	P Value	6 months	P Value	12 months	P Value
Urinary	PBS (N = 67)	85.9 (13.9)	1.6 (12.5)	0.8436	0.4 (17.2)	0.5812	−3.0 (17.2)	0.0795
	PS/US (N = 219)	89.7 (10.07)	−1.9 (11.7)	0.0084	−0.9 (11.5)	0.1203	−1.9 (11.6)	0.0090
Bowel	PBS (N = 68)	94.9 (7.2)	−2.6 (10.3)	0.0191	−4.7 (13.1)	0.0021	−9.2 (17.2)	<0.0001
	PS/US (N = 230)	94.5 (7.5)	−1.9 (8.6)	0.0006	−3.9 (13.5)	<0.001	−6.6 (4.9)	<0.0001
Sexual	PBS (N = 61)	52.8 (26.7)	−3.9 (16.7)	0.0356	−4.3 (16.9)	0.0265	−8.9 (22.9)	0.0018
	PS/US (N = 205)	60.8 (24.0)	−6.8 (17.9)	<0.0001	−7.3 (18.4)	<0.0001	−9.7 (18.5)	<0.0001

Table 2B
Change in Expanded Prostate Cancer Index Composite (EPIC) Domain Scores from Baseline to 1-year after treatment between proton treatment modalities.

EPIC Domain		Time Point						
		Mean Baseline Scores (SD)	P Value	Mean Change in Scores from Baseline (SD)				
				3 months	P Value	6 months	P Value	12 Months	P Value
Urinary	PBS (N = 67)	85.9 (13.9)	0.0005	1.6 (12.5)	0.038	0.4 (17.2)	0.55	−3.0 (17.2)	0.61
	PS/US (N = 219)	89.7 (10.07)		−1.9 (11.7)		−0.9 (11.5)		−1.9 (11.6)	
Bowel	PBS (N = 68)	94.9 (7.2)	0.74	−2.6 (10.3)	0.57	−4.7 (13.1)	0.66	−9.2 (17.2)	0.25
	PS/US (N = 230)	94.5 (7.5)		−1.9 (8.6)		−3.9 (13.5)		−6.6 (4.9)	
Sexual	PBS (N = 61)	52.8 (26.7)	0.28	−3.9 (16.7)	0.27	−4.3 (16.9)	0.26	−8.9 (22.9)	0.81
	PS/US (N = 205)	60.8 (24.0)		−6.8 (17.9)		−7.3 (18.4)		−9.7 (18.5)	

Table 3A
Minimally Important Differences for the changes in Expanded Prostate Cancer Index Composite (EPIC) domain scores from baseline to each follow-up visit between proton treatment modalities.

EPIC Domain		Time Point											
		MID for decline from Baseline Scores N (%)											
		3 months		P Value		6 months		P Value		12 months		P Value	
		MID1	MID2	MID1	MID2	MID1	MID2	MID1	MID2	MID1	MID2	MID1	MID2
Urinary	PBS (N = 67)	16 (23.9%)	8 (11.9%)	0.51	0.85	18 (26.9%)	11 (16.4%)	0.83	0.86	23 (34.3%)	18 (26.9%)	0.27	0.01
	PS/US (N = 219)	61 (27.9%)	28 (12.8%)			56 (25.6%)	34 (15.5%)			60 (27.4%)	29 (13.2%)		
Bowel	PBS (N = 68)	18 (26.5%)	12 (17.7%)	0.72	0.69	25 (36.8%)	19 (27.9%)	0.14	0.02	32 (40.1%)	24 (35.3%)	0.36	0.33
	PS/US (N = 230)	56 (24.4%)	36 (15.7%)			63 (27.4%)	35 (15.2%)			94 (40.9%)	67 (29.1%)		
Sexual	PBS (N = 61)	18 (29.5%)	5 (8.2%)	0.74	0.44	14 (23.0%)	8 (13.1%)	0.33	0.63	22(30.1%)	10 (16.4%)	0.94	0.76
	PS/US (N = 205)	65 (31.7%)	24 (11.7%)			60 (29.3%)	32 (15.6%)			75 (36.6%)	37 (18.1%)		

MID – Minimally important differences, was defined as a half standard deviation difference from the mean baseline domain score. MID1 was defined as 1-MID decline; MID2 was defined as 2-MID decline.

Table 3B
Multiple logistic regression to estimate the association of MID for the changes in Expanded Prostate Cancer Index Composite (EPIC) domain scores from baseline to each visit between proton treatment modalities.[*],[**],[***]

EPIC Domain		Time Point								
		3 months			6 months			12 months		
		OR	95% CI	P value	OR	95% CI	P value	OR	95% CI	P value
Urinary	1-MID	1.14	0.60, 2.16	0.70	0.81	0.44, 1.51	0.51	0.66	0.36, 1.23	0.19
	2-MID	1.04	0.44, 2.50	0.92	0.86	0.41, 1.83	0.71	0.39	0.20, 0.77	0.007
Bowel	1-MID	0.86	0.46, 1.62	0.66	0.60	0.34, 1.08	0.09	0.76	0.44, 1.33	0.33
	2-MID	0.85	0.42, 1.75	0.66	0.44	0.23, 0.84	0.01	0.74	0.41, 1.34	0.33
Sexual	1-MID	0.95	0.48, 1.89	0.89	1.22	0.59, 2.53	0.58	0.88	0.47, 1.66	0.70
	2-MID	1.21	0.41, 3.57	0.72	0.92	0.35, 2.41	0.87	0.88	0.37, 2.11	0.78

[*] MID – Minimally important differences, was defined as a half standard deviation difference from the mean baseline domain score. MID1 was defined as 1-MID decline; MID2 was defined as 2-MID decline.
[**] All models were adjusted by the covariates of baseline EPIC domain score, race, Gleason score, and T-stage.
[***] The reference is pencil-beam scanning (PBS) treatment for the OR estimate.

scores between PBS and PS/US for men with localized prostate cancer.

There are a variety of ways to report and analyze PROs [10]. A common approach is to compare two groups based on average PRO score changes from baseline over time. While such analyses provide for valuable data, statistically significant differences may be found regardless of the magnitude—or clinical relevance—of the changes. Moreover, evaluating average PRO score changes for an entire cohort may not reflect data for the small number of patients who experience significant treatment morbidity. For example, if some individual patients experience an increase in QoL of scores following treatment, this may 'counter' the impact of patients who have large declines in QoL scores over time. An alternative approach, is to compare treatments based on the proportion of patients who experience a minimally important differences (MID), which is thought to represent the smallest change in PRO scores that is considered clinically-relevant, with a 1-MID change considered to represent a moderate decline and 2- MID change considered a large change in QoL [11].

In this study, we have performed analyses looking at both average changes over 1-year from treatment completion as well as the MID approach. We found that there were significant declines in average bowel and sexual function scores over 1-year for men treated with PBS and PS/US, which is consistent with a prior analysis from MD Anderson [12]. Statistically significant declines in average scores were also noted for urinary function over 1-year for PS/US, and a trend was noted for PBS. The changes in average scores for urinary and sexual function for each modality were below the MID threshold for each of these domains. However, changes for bowel function did meet the MID threshold at 1-year for patients treated with PBS and PS/US.

When comparing average changes between baseline and 1-year following treatment *between* each of the two proton modalities, we did not find a significant difference in average bowel, urinary, or sexual function quality-of-life scores. When comparing the two cohorts using the MID approach, we did not find any differences in the proportion of men experiencing a moderate decline in function (1-MID) at 3-, 6-, and 12-months following treatment in any quality-of-life measures. However, men undergoing PBS (compared to PS/US) were found to have a higher odds ratio for experiencing a large decline (twice the MID) for EPIC bowel summary scores at 6 months, and for urinary summary score changes at 12 months—a finding that has not been reported before.

A prior single-institution analysis from the MD Anderson Cancer Center [12] also showed average score declines in bowel, urinary, and sexual function following treatment with each proton modality, but did not find significant differences between both proton modalities. That study looked at MID changes in the context of average score changes, but did not compare the proportion of men with moderate (1-MID) or large (2-MID) declines following treatment with PBS or PS/US. Future studies will be necessary to validate this finding in larger cohorts, with longer-term follow-up.

It is worth noting that there were some differences in the baseline characteristics of patients treated with PBS vs. PS/US. The PS/US cohort had a greater percentage of men who were non-Hispanic white compared to the PBS cohort. Importantly, patients treated with PBS had lower baseline EPIC summary scores for urinary function (85.9 vs. 89.7, p = 0.0005). Although our analysis was

focused on change in scores from baseline, which should help account from these differences, it is possible that the findings of increased 2-MID changes in urinary function in the PBS group reflects that this cohort had poorer baseline function, which put them at a greater risk for urinary morbidity following treatment.

There are several limitations of this analysis that are worth noting. First, our analysis included a higher number of men treated with PS/US compared to PBS, which reflects the fact that PS/US has been in clinical use for a longer period of time. Second, we did not have information on use of rectal spacer during treatment, which could have had an impact on patient-reported bowel function after treatment. Moreover, the registry did not collect other vital information that would help better inform the results of this analysis, including: type of IGRT utilized, dosimetric parameters, use of margins (or parameters for robust optimization), field arrangements, or pre-treatment use of alpha-agonists. Finally, the data presented only reports changes up to one-year following treatment completion. The limitations of this study, therefore, make it difficult to definitively conclude whether the differences observed are due to inherent differences between the treatment modalities or to other patient- or treatment-specific variables. However, it is worth noting that a prior analysis comparing the two modalities also found significant differences between PBS and PS/US in terms of acute, clinician scored, urinary toxicity [13]. Future studies that report longer-term PRO changes will be necessary to better compare the two treatment modalities and the impact of other dosimetrc and planning parameters on treatment outcomes.

5. Conclusion

This represents one of the first comparisons of patient reported outcomes following PBS and PS/US in a multi-institutional setting. Although we found no differences in average quality-of-life score changes over a 1-year time period between the two proton modalities, we did find differences between the two modalities with regards to the proportion of men who experienced two-fold MID changes in bowel and urinary function at 6 and 12 months, respectively. Given that both types of analyses (average scores changes for an entire cohort and proportion of men with MID changes) provide complementary data on outcomes that would be of relevance to patients, future studies should report both outcome measures. Taken together, these data support the ongoing need for prospective evaluation of both modalities to provide patients and stakeholders with prospectively collected data that can be used to guide treatment decision-making.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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