Original Article

Comparative Effectiveness Study of Patient-Reported Outcomes After Proton Therapy or Intensity-Modulated Radiotherapy for Prostate Cancer

Bradford S. Hoppe, MD, MPH[1]; Jeff M. Michalski, MD[2]; Nancy P. Mendenhall, MD[1]; Christopher G. Morris, MS[1]; Randal H. Henderson, MD[1]; Romaine C. Nichols, MD[1]; William M. Mendenhall, MD[1]; Christopher R. Williams, MD[3]; Meredith M. Regan, ScD[4]; Jonathan J. Chipman, MS[4]; Catrina M. Crociani, MPH[5]; Howard M. Sandler, MD[6]; Martin G. Sanda, MD[7]; and Daniel A. Hamstra, MD, PhD[8]

BACKGROUND: Data continue to emerge on the relative merits of different treatment modalities for prostate cancer. The objective of this study was to compare patient-reported quality-of-life (QOL) outcomes after proton therapy (PT) and intensity-modulated radiation therapy (IMRT) for prostate cancer. **METHODS:** A comparison was performed of prospectively collected QOL data using the Expanded Prostate Cancer Index Composite (EPIC) questionnaire. QOL data were collected during the first 2 years after treatment for men who received PT and IMRT. PT was delivered to 1243 men at a single center at doses from 76 grays (Gy) to 82 Gy. IMRT was delivered to 204 men who were included in the Prostate Cancer Outcomes and Satisfaction with Treatment Quality Assessment (PROSTQA) study in doses from 75.6 Gy to 79.4 Gy. The Wilcoxon rank-sum test was used to compare EPIC outcomes by modality using baseline-adjusted scores at different time points. Individual questions were assessed by converting to binary outcomes and testing with generalized estimating equations. **RESULTS:** No differences were observed in summary score changes for bowel, urinary incontinence, urinary irritative/obstructive, and sexual domains between the 2 cohorts. However, more men who received IMRT reported moderate/big problems with rectal urgency ($P = 0.02$) and frequent bowel movements ($P = 0.05$) than men who received PT. **CONCLUSIONS:** There were no differences in QOL summary scores between the IMRT and PT cohorts during early follow-up (up to 2-years). Response to individual questions suggests possible differences in specific bowel symptoms between the 2 cohorts. These outcomes highlight the need for further comparative studies of PT and IMRT. ***Cancer* 2014;120:1076–82**.

KEYWORDS: proton therapy, intensity-modulated radiotherapy, prostate cancer, outcomes, genitourinary.

INTRODUCTION

Conformal radiotherapy (RT) techniques for prostate cancer are expected to reduce urinary and rectal toxicity[1] and improve disease control through facilitation of dose escalation.[2] The increased costs associated with these techniques[3] have led payors and insurers to demand clinical data demonstrating improved disease control and/or less toxicity.

Corresponding author: Bradford Hoppe, MD, MPH, University of Florida Proton Therapy Institute, 2015 North Jefferson Street, Jacksonville, FL 32206; Fax: (904) 588-1300; bhoppe@floridaproton.org

[1]University of Florida Proton Therapy Institute, Jacksonville, Florida; [2]Department of Radiation Oncology, Washington University, St. Louis, Missouri; [3]Department of Urology, University of Florida, Jacksonville, Florida; [4]Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Boston, Massachusetts; [5]Division of Urology, Department of Surgery, Beth Israel Deaconess Medical Center, Boston, Massachusetts; [6]Department of Radiation Oncology, Cedars Sinai Medical Center, Los Angeles, California; [7]Department of Urology, Emory University, Atlanta, Georgia; [8]Department of Radiation Oncology, University of Michigan, Ann Arbor, Michigan

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Several comparative-effectiveness studies of conventional radiation therapy, 3-dimensional conformal radiation therapy (3DCRT), intensity-modulated RT (IMRT), and proton therapy (PT) have been reported. Those studies have in common a reliance on Medicare claims as surrogates for actual clinical outcomes, but they differ somewhat in their findings.[4-7] The use of Medicare claims rather than medical records may be a weakness, because medical claims codes identify interventions that may not reflect the relevant endpoints of disease control, specific treatment-related toxicity, or patient-reported quality of life (QOL). Some of the reports have attracted considerable criticism,[8,9] and the authors of 1 study acknowledge the limitations of the Medicare database and the need for patient-reported QOL outcomes.[7] A randomized trial comparing PT and IMRT has been opened, but the comparative impact on late effects will not be known for some years (registered as National Clinical Trial NCT01617161). We compared prospectively collected QOL outcomes of >1400 men from 2 databases who received treatment with PT or IMRT.

MATERIALS AND METHODS

Materials and Patients

The Expanded Prostate Cancer Index Composite (EPIC)-26 questionnaire is a validated instrument that has 5 domains, including urinary incontinence (UI) (4 questions), urinary irritative/obstructive (UO) (4 questions), bowel function (BS) (6 questions), sexual function (SS) (6 questions), and hormonal function (HF) (5 questions); each subscale is scored from 0 to 100, in which 100 represents no problems and 0 represents substantial and significant problems with the specific subscale.[10] Prospectively collected data from EPIC questionnaires from 2 patient cohorts that received PT and IMRT, respectively, were compared.

The University of Florida Institutional Review Board approved the study, which included 1482 men with localized prostate cancer who were treated at the University of Florida with passively scattered PT between 2006 and 2010. Patients were excluded if they failed to complete treatment (n = 6), did not consent to study inclusion (n = 19), or received hypofractionated PT at 2.5 cobalt gray equivalent per fraction or weekly docetaxel on treatment protocols (n = 71), or pelvic lymph node irradiation (n = 45), leaving a total of 1243 men in the PT cohort. The EPIC questionnaires were collected on paper forms (before March 2009) or by a secure online medical records portal accessed over the Internet (after March 2009) at 6 months, 1 year, then annually.

Specific details of the PT simulation and treatment have been previously reported.[11] Patients received 1.8 to 2 grays (Gy) per fraction, and the majority (99%; n = 1226) received between 78 Gy and 82 Gy (relative biologic effectiveness) at 2 Gy (relative biologic effectiveness) per fraction.

The second cohort included 204 men from the previously reported Prostate Cancer Outcomes and Satisfaction with Treatment Quality Assessment (PROSTQA) study who were treated at 9 university-affiliated hospitals with IMRT and who had completed EPIC-26 questionnaires before treatment and then at 2 months, 6 months, 12 months, and 24 months after treatment. These patients received treatment between March 2003 and March 2006, according to individual institutional policies, which consisted of IMRT to the prostate, with or without seminal vesicles, without pelvic RT, at doses from 75.6 to 79.2Gy at 1.8 to 2.0 Gy per fraction.[12] Data on actual doses delivered to the IMRT patients were not available, but minimum and maximum doses to the planning target volume (PTV) were available for comparison with the same dose parameters in the PT cohort. Because of variability in hormone use between the cohorts, differences in hormonal function or hormonal questions were not investigated.

Statistics

SAS and JMP software were used for all statistical analyses (SAS Institute, Cary, NC). Differences between the 2 cohorts of patients in pretreatment patient-specific, disease-specific, and treatment-specific characteristics were assessed using the Fisher exact test for categorical variables and the Wilcoxon rank-sum test for continuous variables (Table 1). Scores for the EPIC were calculated as previously described.[13,14] The 6-month, 1-year, and 2-year post-treatment scores for each modality were compared with the baseline data for that modality using the Wilcoxon signed-rank sum test, which is a nonparametric analog to a *t* test for paired data. Differences from pretreatment values >50% of the standard deviation[15] at any point in time were considered to represent the minimally detectable difference. Differences in pretreatment scores for the various subscales between the 2 cohorts were assessed with the Wilcoxon rank-sum test. The same method was used to compare baseline-adjusted outcomes between the 2 modalities at 6 months, 1 year, and 2 years after treatment; baseline adjustment for each patient and each domain was accomplished by subtracting the

TABLE 1. Patient-Specific, Cancer-Specific, and Treatment-Specific Characteristics

Characteristic	No. of Patients (%) IMRT (n = 204)	PT (n = 1243)	P
Age: Mean [range], y	69 [46–84]	66 [40 to >89]	< .001
Body mass index: Mean ± SD, kg/m^2	28.6 ± 5.5	28.2 ± 4.3	.64
Prostate size: Mean ± SD, mL	49.5 ± 27.2	41.5 ± 20.7	.001
Race			< .001
White	166 (81)	1132 (91)	
Black	34 (17)	77 (6)	
Other	4 (2)	34 (3)	
PSA, ng/mL			.12
<4	37 (17)	205 (17)	
4-10	128 (63)	862 (69)	
>10	39 (19)	176 (14)	
Gleason score			.28
<7	104 (51)	659 (53)	
7	86 (42)	466 (37)	
>7	14 (7)	118 (10)	
Clinical tumor classification[a]			.61
T1	148 (73)	922 (74)	
T2	56 (27)	317 (26)	
T3	0 (0)	3 (<1)	
Overall risk level			.41
Low	83 (41)	567 (46)	
Intermediate	94 (46)	532 (43)	
High	27 (13)	143 (11)	
ADT	49 (24)	181 (15)	.001
PTVmin: Median [range], Gy	70.9 [40.7-90.2]	74.1 [40.0-80.7]	< .001
PTVmax: Median [range], Gy	81.5 [45.0-107.0]	83.2 [60.5-93.3]	< .001

Abbreviations: ADT, androgen-deprivation therapy; Gy, grays; IMRT, intensity-modulated radiotherapy; PSA, prostate-specific antigen; PT, proton therapy; PTVmin, minimum dose to the planned target volume; PTVmax, maximum dose to the planned target volume; SD, standard deviation.
[a] One patient who received proton therapy had no tumor classification information available.

baseline score from the 6-month, 1-year, and 2-year scores. Patients without a baseline score were excluded from the analysis. Because multiple domains were assessed for each patient, a post hoc Bonferroni adjustment was applied to the resulting *P* values (Tables 2 and 3). An adjusted *P* value $<.05$ was considered statistically significant.

Two approaches were used to analyze dichotomized responses to each question covering urinary, bowel, and sexual function, as previously reported.[16] Baseline differences in individual question responses between the 2 modalities were assessed with the Fisher exact test. Six-month, 1-year, and 2-year responses were assessed simultaneously using repeated-measures generalized estimating equations with unstructured correlation through PROC GENMOD in SAS (Table 4). The primary prognostic

TABLE 2. Raw Expanded Prostate Cancer Index Composite (EPIC) Scores With Adjusted *P* Values (Absolute Shift Compared With Baseline)

EPIC Domain at Follow-Up	EPIC Score: Proton Therapy Median	Min	Max	IMRT Median	Min	Max	P[a]
Bowel summary							
6 mo	0	−83	46	0	−63	58	.17
1 y	−4	−83	46	0	−71	58	.92
2 y	−4	−71	29	0	−79	67	.99
Urinary incontinence							
6 mo	0	−67	60	0	−71	46	.31
1 y	0	−100	52	0	−71	34	.99
2 y	0	−100	56	0	−56	44	.99
Urinary irritative/obstructive							
6 mo	0	−88	56	0	−94	38	.99
1 y	0	−75	50	0	−63	50	.27
2 y	0	−75	50	0	−50	38	.99
Sexual summary[b]							
6 mo	0	−100	100	0	−94	58	.99
1 y	0	−100	92	0	−96	58	.99
2 y	0	−100	100	0	−83	71	.99

Abbreviations: EPIC, Expanded Prostate Cancer Index Composite; IMRT, intensity-modulated radiotherapy; Max, maximum; Min, minimum.
[a] *P* values were determined using the Wilcoxon rank-sum test with Bonferroni adjustment.
[b] Sexual summary scores were calculated for men who did not receive androgen-deprivation therapy.

TABLE 3. Percentage of Men With Minimally Detectable Differences From Their Baseline Expanded Prostate Cancer Index Composite Scores[a]

EPIC Domain at Follow-Up Periods	PT, %	IMRT, %	P[b]
Bowel summary			
6 mo	25	39	.002
1 y	41	37	.99
2 y	37	38	.99
Urinary incontinence			
6 mo	22	28	.36
1 y	31	29	.99
2 y	32	34	.99
Urinary irritative/obstructive			
6 mo	18	25	.99
1 y	23	20	.99
2 y	17	18	.99
Sexual summary			
6 mo	27	31	.99
1 y	36	36	.99
2 y	40	41	.99

Abbreviations: EPIC, Expanded Prostate Cancer Index Composite; IMRT, intensity-modulated radiotherapy; PT, Proton Therapy.
[a] These represent declines in scores >50% from baseline.
[b] *P* values were determined using the Wilcoxon rank-sum test with Bonferonni adjustment.

factor in each model was treatment modality, but baseline response, use of androgen-deprivation therapy (ADT), age (<65 years vs ≥65 years), and prostate size were entered into the models as covariates to control. A post

TABLE 4. Outcomes by Specific Expanded Prostate Cancer Index Composite Question

Question	Baseline			6 Months		1 Year		2 Years			
	IMRT, %	PT, %	P^a	IMRT, %	PT, %	IMRT, %	PT, %	IMRT, %	PT, %	P^b	P^c
No. of patients answering EPIC[d]	204	1212		192	1115	191	1093	177	963		
Urinary irritation/obstruction											
Dysuria	1	0	.35	6	3	2	5	1	2	.50	.99
Hematuria	1	0	.04	2	1	1	1	2	1	.33	.99
Weak stream	15	9	.03	12	7	15	11	11	8	.07	.99
Frequency	15	13	.38	17	12	15	14	13	11	.48	.99
Urinary incontinence											
Leaking > daily	6	3	.02	10	3	9	5	7	5	.008	.16
Frequent dribbling	2	2	.72	2	3	4	4	3	4	.25	.99
Any pad use	1	2	.5	4	3	3	4	5	4	.58	.99
Leaking problem	2	1	.33	5	2	5	3	5	4	.06	.99
Overall urinary problem	10	8	.32	11	8	13	11	11	10	.68	.99
Bowel function											
Urgency	3	2	.45	9	5	13	8	15	7	.001	.02
Frequency	2	1	.39	8	3	8	6	10	4	.003	.05
Fecal incontinence	1	1	.98	4	2	3	3	3	3	.28	.99
Bloody stools	2	0	.04	2	2	6	8	7	8	.06	.99
Rectal pain	3	1	.02	5	2	3	3	6	2	.19	.99
Overall bowel problem	3	2	.09	8	4	10	9	11	7	.21	.99
Sexual function[e]											
Poor erections	36	25	.003	46	33	49	41	53	42	.24	.99
Difficulty with orgasm	31	21	.003	40	27	45	32	42	32	.06	.99
Erection not firm	47	33	< .001	56	39	59	47	59	49	.21	.99
Erections not reliable	45	34	.01	51	41	58	47	60	48	.19	.99
Poor sexual function	34	29	.18	43	35	46	41	47	44	.71	.99
Overall sexuality problem	17	21	.29	29	29	30	36	33	35	.36	.99

Abbreviations: EPIC, Expanded Prostate Cancer Index Composite; IMRT, intensity-modulated radiotherapy; PT, proton therapy.
[a] These *P* values were determined using the Fisher exact test.
[b] These *P* values were determined using a generalized estimating equation with the values adjusted for baseline difference, androgen-deprivation therapy, age, and prostate size.
[c] These *P* values also were determined using a generalized estimating equation with the values adjusted for baseline difference, androgen-deprivation therapy, age, and prostate size but included the addition of a Bonferroni adjustment for 21 questions.
[d] These were recorded in absolute numbers.
[e] Sexual function was reported for patients who did not receive androgen-deprivation therapy.

hoc Bonferroni adjustment also was included to adjust for the 21 questions evaluated (excluding the hormone function questions, which were not used).

RESULTS

Patient-specific and treatment-specific characteristics are illustrated in Table 1. IMRT patients treated were older (median age, 69 vs 66 years; $P < .001$), had larger prostate volumes (mean, 49.5 vs 41.5 g; $P = .0014$), were less likely to be white (81% vs 91% white; $P < .001$), were more likely to receive ADT (24% vs 15%; $P = .00013$), and received both a lower minimum dose to the PTV (median, 70.9 vs 74.1 Gy; $P < .001$) and a lower maximum PTV dose (median, 81.5 vs 83.2Gy; $P < .001$).

EPIC summary scores at baseline, 6 months, 1 year, and 2 years after treatment are depicted in Figure 1A-D for the PT and IMRT cohorts. After treatment, the only changes in summary scores from baseline that met the minimally detectable difference were observed for bowel summary at 6 months, 1 year, and 2 years for IMRT and for bowel summary at 1 year and 2 years for PT (Fig. 1A-D). Both groups had declines in bowel summary scores, but there were no statistically significant differences in QOL changes between groups for BS, UI, UO, or SS (SS was analyzed only among men who did not receive ADT) at any time (Table 2). When examining the percentage of men who had a minimally detectable difference at the various time points for the different summary scores, the only remarkable difference between the IMRT and PT cohorts was for the bowel summary component at the 6-month follow-up (Table 3).

An analysis of individual items comprising each domain also was planned and performed. At baseline, the only differences between the 2 cohorts were that men in the IMRT cohort were more likely to report baseline moderate/big problems with hematuria ($P = 0.04$), daily urinary leakage ($P = .02$), bloody stools ($P = .02$), and rectal pain ($P = .04$). Men in the IMRT cohort also reported more moderate/big problems within the sexual domain, including poor erections, difficulty with

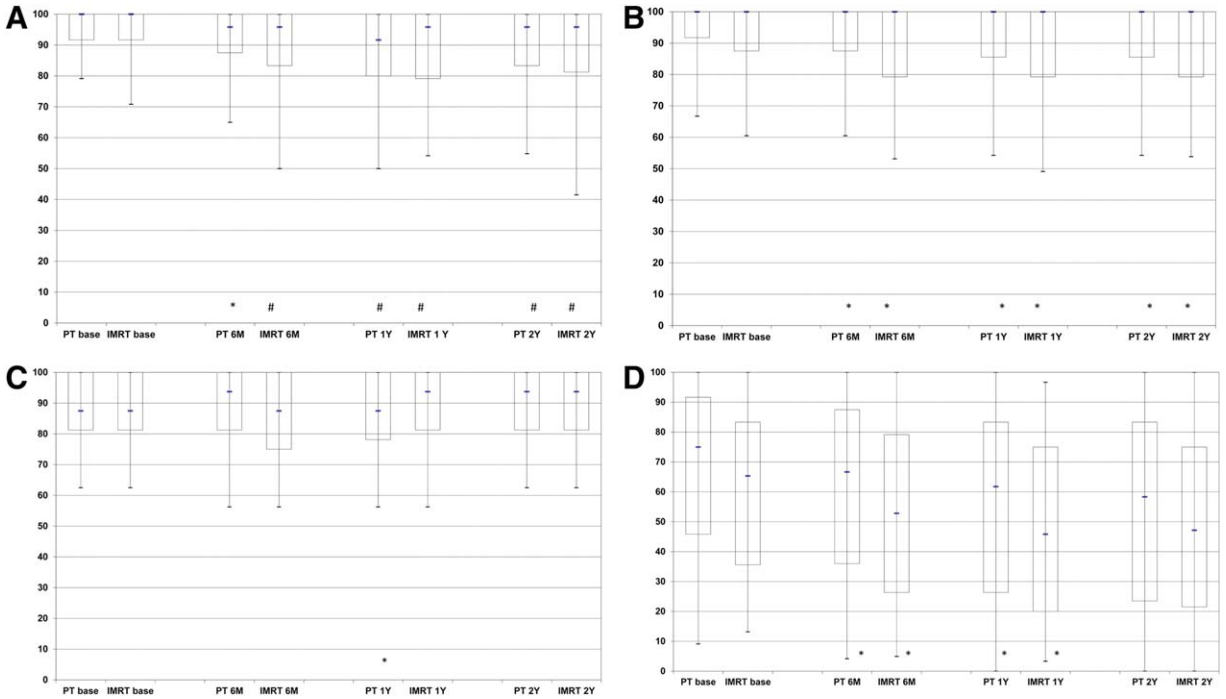

Figure 1. Expanded Prostate Cancer Index Composite (EPIC) summary scores are illustrated over time for men who received intensity-modulated radiotherapy (IMRT) or proton therapy (PT) for prostate cancer. Bar-and-whisker graphs at baseline and at 6 months (6M), 1 year (1Y), and 2 years (2Y) after proton therapy or intensity-modulated radiotherapy illustrate (A) bowel summary scores, (B) urinary incontinence scores, (C) urinary irritative/obstructive scores, and (D) sexual summary scores (no androgen-deprivation therapy). The bottom whisker represents the cutoff score for the lowest 5%, the bottom bar represents the cutoff score for the lowest quartile, the blue line represents the median score, the top of the bar represents the cutoff score for the top quartile, and the top of the whisker represents the cutoff score for the top 5%. At the bottom of the graph, an asterisk indicates a statistically significant change from baseline score for each treatment modality and time point, and a pound sign indicates a statistically significant and minimally detectable change (>50% of the baseline standard deviation) from the baseline score.

orgasms, erections not sufficient for intercourse, and unreliable erections (all $P < .01$) (Table 4). When comparisons over time were controlled for differences between groups in age, prostate size, and ADT use as well as baseline QOL, there were no significant differences between the cohorts except for more frequent reports in the IMRT cohort of "moderate" or "big problems" with rectal urgency ($P = .02$) and bowel frequency ($P = .05$).

DISCUSSION

The study reported herein compares patient-reported QOL outcomes in PT and IMRT cohorts using the EPIC questionnaire. No significant differences were observed in QOL EPIC summary scores for bowel, urinary, or sexual function between the IMRT and PT cohorts, despite higher minimum and maximum PTV doses in the PT cohort, a factor that is expected to be associated with higher toxicity.

EPIC urinary summary scores were similar between the IMRT and PT cohorts in this study, concurring with similar urinary toxicity rates between IMRT and PT suggested by surrogate data reported in the Medicare studies.[5,6,17] However, the EPIC bowel outcomes in this study did not correlate with findings in 2 of the Medicare studies,[5,6] which suggested worse bowel toxicity with PT than with IMRT. The Medicare studies have been criticized for their reliance on surrogate data rather than actual clinical data, such as using colonoscopy claims to conclude rectal toxicity. Furthermore, absence of any clinical and treatment details in the Medicare studies also may have confounded conclusions, because radiation dose, dose fractionation, and dose distribution, the most important predictive factors for gastrointestinal toxicity, were not available and could have been significantly impacted by the dose-escalation studies being performed during the study period at the 2 proton centers.[12,18] In contrast to the Medicare studies, the current study is based on prospectively collected, actual patient-reported clinical outcomes using the same QOL instrument and acquisition times between the PT and IMRT cohorts, and, as such,

should provide a more reliable comparison of functional outcomes.

In this study, bowel summary scores were similar between the groups, correlating with the findings by Yu et al,[7] who reported on a more recent Medicare patient population that included patients who received treatment at different proton centers. The results also are similar to those recently reported by Gray et al,[19] who compared QOL outcomes of 95 men who received PT at Massachusetts General Hospital using the Talcott Prostate Symptom Index[20] with men who received IMRT from the PROSTQA database using the EPIC questionnaire; those authors reported that little difference was demonstrated in bowel problems >6 months after treatment.

IMRT and PT both produce "high radiation dose" volumes that conform to the target; IMRT does so at the expense of exposing a larger volume of nontargeted tissue to "low and moderate radiation doses."[21,22] Thus, toxicities and functional outcomes related to high radiation dose exposure, such as rectal bleeding, are expected to be similar between IMRT and PT if target doses and daily doses are similar.[22,23] Conversely, the rate of toxicities related to larger volumes of nontargeted tissue receiving low-dose and moderate-dose radiation exposure might be expected to be higher with IMRT than with PT. In the current study, the rate of rectal bleeding tended to being worse in the PT cohort, which may be explained by the higher prescription doses received in the PT cohort. Studies investigating rectal toxicities other than bleeding—such as rectal syndrome (which includes rectal urgency), frequency, and incontinence—have demonstrated correlations with the volumes of the rectum receiving both high and low to moderate doses.[18,24,25] Those studies focused on patients who received 3DCRT rather than IMRT, but the dose-volume relations serve to demonstrate the type of toxicity improvements that might be expected with reductions in the volume of rectum exposed to low to moderate radiation doses using PT compared with IMRT. Therefore, a potentially important finding of the current study is the analysis that identified significantly worse bowel urgency and bowel frequency in the IMRT group, a problem that affects QOL and can persist more than 10 years after radiation.[26] Nevertheless, alternate explanations, such as differing use of image-guided therapy, differing use of aspirin or other anticoagulants, target margins, interobserver variability, older age, or larger prostate volumes in the IMRT cohort, also could influence these results.[27]

Recent research has investigated the impact of different rectal complications on global QOL after radiation therapy for prostate cancer. Krol et al[28] evaluated anorectal function in 85 men at least 1 year after conventional-dose prostate RT using the EPIC questionnaire, the Fecal Incontinence QOL scale, and anal manometry. Those authors observed that fecal incontinence and rectal urgency most greatly influenced overall QOL along with impaired anal resting pressure. It was also demonstrated that urgency of defecation has a more severe impact on patient-reported QOL than rectal bleeding, despite clinicians' greater concern with rectal bleeding, which can be treated and resolved, compared with urgency, which can worsen over time and for which there is little treatment for its symptomology.[29] Therefore, these differences in discreet rectal symptoms between PT and IMRT treatments, as assessed from patient-reported outcomes, are intriguing and warrant further evaluation.

The strengths of the current study are the prospective design for data collection, the use of patient-reported outcomes (PRO) from contemporary IMRT and PT series, the use of a common QOL instrument, and the collaborative effort between institutions that use IMRT and those that use PT. Although patients were not randomized to RT modalities, baseline information on clinical factors, QOL, and RT details permitted some adjustments for differences between the cohorts. Nevertheless, no level of statistical manipulation can account for how PT patients may have sought out (and traveled) to receive treatment in expectation of fewer side effects and better QOL. This exact criticism, however, can be made for the Medicare studies, which also were unable to statistically account for these differences. Another potential weakness is that the patients receiving PT were treated consistently at a single academic center, whereas the patients receiving IMRT were treated at 9 different academic centers; however, the same could be said for the Medicare studies, in which the vast majority of patients who were treated before 2008 would have been treated at 1 institution.[18] Additional weaknesses include that our comparative analysis plan was post hoc, although the QOL data were collected prospectively, and the difference in EPIC data collection between the cohorts—with patients who received IMRT undergoing a telephone-assisted interview whereas those who received PT read and completed their questionnaires without assistance—potentially could lead to bias in either direction.

The findings from this study provide evidence of excellent and comparable QOL outcomes for patients with prostate cancer who receive either contemporary IMRT or PT. Although similar bowel, urinary, and sexual scores were observed with IMRT and PT, potential

differences in specific functional outcomes, such as bleeding, rectal urgency, and bowel frequency, also were observed and may reflect differences in radiation dose distributions between IMRT and PT, differences in patient characteristics, or both. Further investigation will be necessary to validate these findings and to identify the underlying mechanisms that account for them.

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CONFLICT OF INTEREST DISCLOSURES

Dr. Hoppe reports receiving an honorarium from ProCure for lectures, and he serves on the board of the Proton Collaborative Group. Dr. Sandler is a board member of Eviti and he reports payment from Medivation, Millennium, Bayer Health, and Varian Health for consultant services. Dr. Sanda is a board member of Medicametrix, and he reports payment from Sanofi-Aventis for lectures. Dr. Hamstra reports payment from Myriad Health and Bayer Health for consultant services and payment from Varian Health for lectures.

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