Patient-Reported Long-term Outcomes After Conventional and High-Dose Combined Proton and Photon Radiation for Early Prostate Cancer

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Patient-Reported Long-term Outcomes After Conventional and High-Dose Combined Proton and Photon Radiation for Early Prostate Cancer

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Context Increased radiation doses improve prostate cancer control but also increase toxicity to adjacent normal tissue. Proton radiation may attenuate adverse effects.

Objective To determine long-term, patient-reported, dose-related toxicity.

Design, Setting, and Patients We performed a post hoc cross-sectional survey of surviving participants in the Proton Radiation Oncology Group (PROG) 9509—a randomized trial comparing 70.2 Gy vs 79.2 Gy of combined photon and proton radiation for 393 men with clinically localized prostate cancer (stage T1b-T2b, prostate-specific antigen <15 ng/mL, and no radiographic evidence of metastasis). The estimated 10-year biochemical progression rate for patients receiving standard dose was 32% (95% confidence interval, 26%-39%) compared with 17% (95% confidence interval, 11%-23%) for patients receiving high dose ($P<.001$). We surveyed 280 of the surviving 337 patients (83%) from April 2007 to September 2008.

Main Outcome Measures Prostate Cancer Symptom Indices, a validated measure of urinary incontinence, urinary obstruction and irritation, bowel problems, and sexual dysfunction, and related quality-of-life instruments.

Results At a median of 9.4 years after treatment (range, 7.4-12.1 years), participants' demographic and clinical characteristics were similar. Patient-reported outcomes were reported as mean (SD) scale score for standard dose vs high dose: urinary obstruction/irritation (23.3 [13.7] vs 24.6 [14.0]; $P=.36$), urinary incontinence (10.6 [17.7] vs 9.7 [15.8]; $P=.99$), bowel problems (7.7 [7.8] vs 7.9 [9.1]; $P=.70$), sexual dysfunction (68.2 [34.6] vs 65.9 [34.7]; $P=.65$), and most other outcomes were also similar, although patients receiving standard dose whose cancers had more often progressed expressed less confidence that their cancers were under control (mean [SD] scale score for standard dose, 76.0 [25.4] vs high dose, 86.2 [17.9]; $P<.001$). Many patients characterized their urinary and bowel function as normal despite reporting symptoms that, for other prostate cancer patients before and early after cancer treatment, caused substantial distress.

Conclusion Among men with clinically localized prostate cancer, treatment with higher-dose radiation compared with standard dose was not associated with an increase in patient-reported prostate cancer symptoms after a median of 9.4 years.

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PROSTATE CANCER IS THE MOST common nonskin cancer and the second leading cause of cancer death in US men. Empirical evidence indicates that increasing the radiation therapy dose improves local control rates.[1] However, irradiation of nearby nonprostate tissue, which increases in parallel with treatment doses, produces urinary, bowel, and sexual dysfunction.[2,3] Investigators have attempted to reduce toxicity to adjacent normal tissue with conformal approaches to photon radiation, which use 3-dimensional computed tomographic images to improve target localization, and radiation blocks that protect normal tissue.[4,5] One randomized trial has found that conformal radiation therapy reduces physician-reported toxicity compared with conventional approaches.[6] Proton therapy reduces the radiation to nontargeted adjacent tissue compared with standard photon (x-ray) radiation by limiting the dose distal to the target volume, potentially limiting toxicity from increased radiation doses.[7,8] Uncon-

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trolled studies have found that proton radiation allows increased radiation doses with modestly increased physician-reported toxicity.[9,10]

The Proton Radiation Oncology Group (PROG) 9509 is a randomized trial performed at Massachusetts General Hospital, Boston, and the Loma Linda University Medical Center, Loma Linda, California, that assigned 393 patients with early prostate cancer to a total dose of either 70.2 Gy (standard-dose) or 79.2 Gy (high-dose) comprising both photon and proton radiation. Improved biochemical recurrence was evident at a median 5.5-year follow-up,[11] and the benefit persisted at a median 8.9-year follow-up (10-year estimated biochemical recurrence, 17% [95% confidence interval {CI}, 11%-23%] vs 32% [95% CI, 26%-39%]; $P<.001$).[12] Physician-reported acute and late genitourinary and gastrointestinal toxicity, measured using the Radiation Therapy Oncology Group criteria,[13] was low for both groups.[14]

However, patient-reported outcomes are the most sensitive and valid measures of treatment-related morbidity. To better evaluate the toxicity from these treatments, we performed a post hoc survey to determine long-term (≥8 years), patient-reported quality-of-life outcomes. We report the results of that survey.

METHODS

Patient Population

PROG 9509 is a randomized controlled trial to compare 2 different radiation doses delivered by conformal techniques. All patients received conformal photon (x-ray) therapy to a fixed dose of 50.4 Gy, with the planned boost dose, delivered using proton therapy, to either 19.8 Gy or 28.8 Gy, using a radiobiological effectiveness proton-to-photon ratio of 1.1, for total doses of 70.2 Gy (conventional dose) or 79.2 Gy (high dose), respectively. No patients received neoadjuvant, concurrent, or adjuvant androgen-deprivation therapy.

Patients were enrolled at 2 centers (previously mentioned). Eligible patients had clinically localized adenocarcinoma of the prostate (defined as stage T1b through T2b tumors [using 1992 American Joint Committee on Cancer criteria]), serum prostate-specific antigen (PSA) levels less than 15 ng/mL, and no radiographic evidence of metastatic disease. Between January 1996 and December 1999, 393 patients were randomized centrally without blocks and stratified by pretreatment serum PSA levels (<4 ng/mL vs 4-15 ng/mL) and nodal status (NX vs N0). The clinical target volume for the proton boost was the prostate with a 5-mm margin with an additional 7 to 10 mm added for a planning target volume, according to the technical requirements of the treating devices at the 2 participating institutions.

Data Collection and Outcome Measures

PROG 9509 was designed to have 80% power to detect a 20% improvement in freedom from biochemical failure at 5 years, with additional follow-up contingent on additional funding. The initial protocol specified physician-reported monitoring of toxicity, which is less sensitive than patient-reported measures. To address this deficiency, the current study attempted to contact all living patients who had been enrolled in PROG 9509. After receiving institutional review board approval, patients were mailed a cover letter explaining the study, its voluntary nature, the requirements for participation, the study questionnaire, and a postpaid opt-out card to indicate the choice not to participate. The returned survey was accepted documentation of informed consent. Data were collected through the staff of the Center for Outcomes Research at Massachusetts General Hospital. Data management was performed at quality assurance office of clinical trials, the data management center for all studies of the Dana Farber/Partners Cancer Care.

Patients were asked to complete self-administered questionnaires, which included previously validated assessments of sexual function, urinary and bowel complications of treatment, and disease-focused quality of life.[15,16]

Urinary, Sexual, and Bowel Function

Study questionnaires included the 4 prostate cancer symptom indices (PCSI) to assess urinary incontinence, urinary obstruction and irritation, bowel dysfunction, and sexual dysfunction. The urinary incontinence index contains 3 questions gauging the degree of urinary control. The urinary obstruction and irritation index contains 5 questions assessing hesitancy, frequency, nocturia, dysuria, and urgency. The bowel problems index includes questions regarding diarrhea, urgency of bowel movements, rectal pain, bleeding, passing mucus, abdominal cramping, and tenesmus. Sexual dysfunction questions assess patients' reports of their erections (firmness and difficulty acquiring and maintaining them), orgasm, and ejaculation. In addition, we administered the 5-item sexual function and quality-of-life scale developed in the Medical Outcomes Study.[17]

In addition, we measured patient assessments of other aspects of their medical condition and treatment choices. The informed decision scale ($\alpha=.79$) assesses perceptions of having sufficient information when choosing a treatment, being fully informed by one's physicians, and experiencing satisfaction with one's choices.[16] The decision regret scale is a 5-item scale that asks patients to reflect on their specific treatment decision. Patients are asked if they made the right decision, whether they would make the same choice if necessary, and whether they thought their decision caused them harm. The cancer control scale assesses confidence that one's cancer is under control, worries about recurrence, and misgivings about the efficacy of treatment based on patient understanding of clinical events.[16]

Each PCSI function or bother index was scored by summing responses to the component items and then standardizing that value to vary from 0 (no

reported symptoms) to 100 (maximum possible dysfunction reported on each scale item). All other scales also ranged from 0 to 100 scores, but with the exception of the regret scale, for which higher scores indicated greater regret, higher scores indicated better quality of life (eg, for informed decision, higher scores indicate greater confidence that one's decision making was well informed). For the function scales, scores were calculated only if participants responded to all scale items, while the remainder required responses to at least half the scale items. To assist interpretation of numerical scale scores, we parsed the PCSI results as normal, intermediate, or poor function for each PCSI scale, using our previously described method[18] based on patient-reported distress or bother for each functional scale item. The method characterizes a patient's function as normal only if the patient's response to each scale item was associated with little or no distress in other prostate cancer patients, poor if any response was associated with great distress, and intermediate for all other patients.

The questionnaire also assessed age, race, marital status, and education, with all response options defined by the investigators. We included race because of published data suggesting that patient-reported outcomes may be influenced by race.[19,20]

Table 1. Patient-Reported Sociodemographic and Clinical Characteristics[a]

Characteristic	No. (%)[b] Standard Dose	High Dose	All Patients	*P* Value[c]
No. of patients	139	141	280	
Age at time of treatment, median (range), y	66.5 (45.2-79.5)	66.8 (47.6-77.0)	66.6 (45.2-79.5)	.63
Age at time of survey, median (range), y	76.0 (55.1-87.4)	76.1 (56.8-87.8)	76.0 (55.1-87.8)	.55
Time since treatment at time of survey, median (range), y	9.3 (7.4-12.1)	9.5 (7.4-12.1)	9.4 (7.4-12.1)	.30
Race/ethnicity				
White	125 (91)	132 (95)	257 (93)	
African American	9 (7)	2 (1)	11 (4)	
Asian	2 (1)	1 (1)	3 (1)	.19
Hispanic	2 (1)	4 (3)	6 (2)	
Gave no response	1	2	3	
Marital status				
Never married	2 (1)	2 (1)	4 (1)	
Currently married	117 (84)	121 (86)	237 (85)	.85
Separated, divorced, or widowed	20 (14)	17 (12)	37 (13)	
Gave no response	0	1	1	
Educational attainment				
≤High school	25 (18)	27 (19)	52 (19)	
Attended college	66 (47)	78 (56)	144 (52)	.19
Attended graduate school	48 (35)	34 (24)	82 (30)	
Gave no response	0	2	2	
PSA ever increased after treatment				
Yes	51 (38)	19 (14)	70 (25)	
No	69 (51)	107 (77)	176 (64)	<.001
Don't know	16 (12)	13 (9)	29 (11)	
Gave no response	3	2	5	
Received another local prostate cancer treatment				
Radical prostatectomy	3 (2)	0	3 (1)	
Cryotherapy	11 (8)	1 (1)	12 (4)	.001
No local therapy	125 (90)	140 (99)	265 (95)	
Received hormonal therapy for prostate cancer after radiation treatment	18 (13)	9 (6)	27 (10)	.05

Abbreviation: PSA, prostate-specific antigen.
[a] Self-reported responses are for 289 patients with early prostate cancer who underwent treatment under the Proton Radiation Oncology Group (PROG) 9509 and completed the quality-of-life survey.
[b] Values are shown as No. (%) unless otherwise indicated.
[c] Standard-dose vs high-dose patients, Wilcoxon rank-sum (Mann-Whitney) test or Fisher exact test.

Statistical Methods

Analyses were performed using Stata version 8.1 (Stata Institute, College Station, Texas). All reported *P* values are 2-sided. To adjust for multiple testing, we defined a significant *P* value as ≤.01. For categorical variables, we used Fisher exact test, and for continuous variables, the Wilcoxon rank-sum test (Mann-Whitney). Using the mean (SD) bowel score of 8, an α of .05, 2-sided tests, and the observed number of cases provided information to calculate bowel problems scores (134 and 137), the power is as follows: 0.54 for detecting the difference in mean scores of 2 (SD, 0.25), 0.87 for detecting the difference in mean scores of 3 (SD, 0.375), and 0.98 for detecting the difference in mean scores of 4 (SD, 0.5). Using the conservative Chebycheff Inequality analysis,[21] our study had adequate power (81%) to detect group differences of 0.375 SDs; a marginally clinically significant difference in bowel problems, the symptom most specific to external beam radiation; and excess power (92%) to detect a difference of 0.5 SD.

RESULTS

Between August 2007 and December 2008, we attempted to survey the 393 patients enrolled in PROG 9509. Of these, 1 patient had withdrawn consent before treatment and we confirmed 55 deaths, leaving 337 patients eligible for study. Of these, 14 patients could not be contacted despite multiple efforts, and 43 were contacted but did not participate in the study (27 patients refused because they were uninterested [15 patients], too ill [8 patients], or declined for other reasons [4 patients], and the remaining 16

patients expressed interest but did not return questionnaires). Although living nonparticipants were similar to participants in age, deceased patients were older (mean difference, 7.0 years; $P<.001$). The 280 respondents represented 83% of eligible enrolled patients not known to have died. Of these, 139 patients had been randomized to the standard-dose treatment group and 141 patients to the high-dose group.

Pretreatment Characteristics

The median follow-up for the entire group was 9.4 years (range, 7.4-12.1 years) (TABLE 1). Median participant age at survey completion was 76.0 years (range, 55.1-87.8 years). Patients were demographically similar and highly educated with 257 patients (93%) being of white race, 237 (85%) currently married, 144 (52%) attended college, and another 82 (30%) attended graduate school. Reflecting the benefit of high-dose treatment, patients in the standard-dose group more often reported post-treatment elevation of PSA (51 patients [37%] vs 8 patients [14%]; $P<.001$) and subsequent local therapy with either radical prostatectomy or cryotherapy (14 patients [10%] vs 3 patients [1%]; $P=.002$). Cancer progression, indicated by either PSA increase or salvage therapy, was more frequent in standard-dose patients (63 patients [45%]; vs 30 patients [21%]; $P<.001$).

Functional Outcomes

Using the PCSI scales, there was little evidence of added urinary, bowel, or sexual dysfunction in the high-dose treatment group (TABLE 2). Patient-reported urinary obstruction and irritation (mean scale score: standard dose, 23.3 vs high dose, 24.6; $P=.36$), urinary incontinence (10.6 vs 9.7; $P=.99$), bowel problems (7.7 vs 7.9; $P=.70$), sexual dysfunction (68.2 vs 65.9; $P=.65$) were similar, as were other quality-of-life measures. Other measures of aspects of sexual and marital functioning were also similar. As for the numerical functional scale results, we found no differences between treatment groups when results were reported by level of function (normal, intermediate, or poor) (TABLE 3).

Perceived Health and Attitudes Toward Treatment Decisions

Using measures we developed to evaluate patient appraisals of their prostate cancer course over time, we found no evidence that treatment groups differed in either their worry about health or their attentiveness to the PSA test (TABLE 4). Patients in the standard-dose group, who had more often progressed, were less confident that their prostate cancer was under control (mean score, 76.0 vs 86.2; $P<.001$). Treatment groups had similar confi-

Table 2. Patient Responses for Urinary, Bowel, and Sexual Function and Bother or Distress[a]

	Prostate Cancer Symptom Indices Response Score						
	Standard Dose		High Dose		All		
Scale	No. of Patients	Mean (SD)	No. of Patients	Mean (SD)	No. of Patients	Mean (SD)	*P* Value[b]
Urinary obstruction and irritation							
Urinary obstruction and irritation[c]	132	23.3 (13.7)	132	24.6 (14.0)	264	24.0 (13.9)	.36
Urinary obstruction and irritation, bother[d]	123	12.0 (16.5)	123	11.9 (15.1)	246	12.0 (15.8)	.80
Urinary incontinence							
Urinary incontinence[c]	131	10.6 (17.7)	134	9.7 (15.8)	265	10.2 (16.7)	.99
Urinary incontinence, bother[d]	133	10.3 (19.2)	134	8.4 (15.3)	267	9.4 (17.4)	.63
Urinary incontinence quality of life[e]	129	92.2 (16.4)	134	93.3 (13.6)	263	92.7 (15.0)	.72
Bowel problems							
Bowel problems[c]	134	7.7 (7.8)	137	7.9 (9.1)	271	7.8 (8.4)	.70
Bowel problems, bother[d]	131	5.5 (10.2)	131	7.9 (12.4)	262	6.7 (11.4)	.10
Sexual function							
Sexual dysfunction[c]	132	68.2 (34.6)	127	65.9 (34.7)	259	67.1 (34.6)	.65
Sexual problems, bother[d]	124	44.5 (24.1)	122	45.1 (22.2)	246	44.8 (23.1)	.95
Sexual intimacy[f]	128	67.7 (28.8)	123	70.7 (27.4)	251	69.2 (28.1)	.44
Sexual confidence[f]	129	38.0 (30.7)	123	42.2 (31.3)	252	40.1 (31.0)	.30
Masculine self-esteem[f]	130	78.4 (23.5)	123	80.1 (20.8)	253	79.2 (22.2)	.92
Marital affect[f]	93	91.7 (17.7)	99	91.8 (17.0)	192	91.8 (17.3)	.83

[a] Self-reported responses are for 287 patients with early prostate cancer who underwent treatment under the Proton Radiation Oncology Group (PROG) 9509 and completed the study survey.
[b] Standard-dose vs high-dose patients, Wilcoxon rank-sum test.
[c] Scales assesses the frequency or severity of symptoms. Scales range from 0 (no symptoms) to 100 (maximum symptoms).
[d] Symptom bother scales assess the bother or distress patients feel from the symptoms assessed in each scale. Scales range from 0 (no bother or distress) to 100 (maximum bother or distress).
[e] Measures the impact of the symptom by inquiring about its direct consequences, such as feeling unclean or worry about public embarrassment. Scale ranges from 0 (lowest quality of life) to 100 (highest quality of life).
[f] Scale ranges from 0 (lowest quality of life) to 100 (highest quality of life).

dence that they had made a well-informed treatment decision, although patients in the standard-dose group tended to express more regret (mean score, 12.7 vs 9.2; $P=.02$).

Cancer Progression and Outcomes

To assess the affect of cancer progression on our results, we performed analysis of variance multiple regression models that controlled for progression. While progression was independently associated with urinary obstruction and irritation, greater treatment regret, reduced confidence of cancer control, and greater health worry, there was no significant association between the treatment group and any outcome variable and study group (data not shown).

Level of Function vs Perceived Level of Function

To compare the patient's level of function based on prior correlations with patient-reported bother to the patients' self-description, we asked patients to select the term that best described their function with regard to urinary incontinence, urinary obstruction and irritation, and bowel problems (TABLE 5). From 92% to 99% of patients with normal function agreed with that assessment. However, patients were much more often in disagreement when their function was rated as abnormal. For urinary obstruction and irritation, and bowel problems, more than two-thirds of patients with intermediate function described their function as normal and more than half classified as poor characterized their function as intermediate. For urinary incontinence, patients were more likely to agree that their function was abnormal; only 45% of patients whose function was classified as intermediate described it as normal. Few patients were classified as having poor function for urinary incontinence.

Table 3. Long-term Level of Function Based on Patient Distress or Bother

Treatment-Related Function and Group	Level of Function, No. of Patients (%) [95% CI][a]			*P* Value
	Normal	Intermediate	Poor	
Urinary obstruction and irritation				
Standard dose	37 (27) [19-35]	64 (46) [38-55]	38 (27) [20-36]	.27
High dose	26 (18) [12-26]	73 (52) [43-60]	42 (30) [22-38]	
All patients	63 (23) [18-28]	137 (49) [43-55]	80 (29) [23-34]	
Urinary incontinence				
Standard dose	84 (64) [55-72]	42 (32) [24-41]	5 (4) [1-9]	.97
High dose	84 (63) [54-71]	45 (34) [26-42]	5 (4) [1-8]	
All patients	168 (63) [57-69]	87 (33) [27-39]	10 (4) [2-7]	
Bowel problems				
Standard dose	39 (29) [22-38]	68 (51) [42-59]	27 (20) [14-28]	.96
High dose	42 (31) [22-39]	69 (50) [42-59]	26 (19) [13-27]	
All patients	81 (30) [24-36]	137 (51) [44-57]	53 (20) [15-25]	
Sexual function				
Standard dose	9 (7) [3-12]	24 (18) [12-26]	99 (75) [67-82]	.95
High dose	9 (7) [3-13]	25 (20) [13-28]	93 (73) [65-81]	
All patients	18 (7) [4-11]	49 (19) [14-24]	192 (74) [68-79]	

Abbreviation: CI, confidence interval.
[a] For each symptom, normal function indicates that the patient reported no bothersome symptoms on any item in the scale, intermediate function indicates at least 1 moderately bothersome symptom but no highly bothersome symptom, and poor function indicates at least 1 highly bothersome symptom.

Table 4. Measured Patient Attitudes to Their Prostate Cancer, Perceived Health Status, and Past Treatment Decisions[a]

Scale[b]	Patient Attitudes by Group, Mean (SD)[c]			*P* Value
	Standard Dose	High Dose	All	
Health worry	19.1 (20.8)	16.5 (16.6)	17.8 (18.8)	.73
PSA concern	69.0 (32.8)	69.7 (34.6)	69.3 (33.6)	.99
Cancer control	76.0 (25.4)	86.2 (17.9)	81.1 (22.5)	<.001
Informed decision	78.4 (22.5)	81.5 (21.3)	79.9 (21.9)	.14
Regret	12.7 (21.5)	9.2 (19.1)	10.9 (20.4)	.02

Abbreviation: PSA, prostate-specific antigen.
[a] Self-reported responses are for 287 patients with early prostate cancer who underwent treatment in the Proton Radiation Oncology Group (PROG) 9509 and completed the study survey.
[b] Health worry measures the patient's beliefs about his overall health; PSA concern measures the intensity of patient attention to PSA level; cancer control measures the patient's beliefs about how well cancer is under control; informed decision measures the patient's confidence that treatment decision was well-informed; and regret measures regret about treatment choice.
[c] Scores are based on a 0 to 100 scale with better quality of life indicated by higher scores, with the exception of regret.

COMMENT

This study, reporting patient-reported quality-of-life outcomes after the longest published follow-up after radiation therapy for prostate cancer, indicates that radiation at the higher doses now commonly used were not associated with increased patient-reported, long-term, treatment-related urinary, bowel, or sexual dysfunction or related quality-of-life outcomes. In particular, a 9-Gy increased boost of proton radiation sufficient to reduce estimated 10-year biochemically PSA-detected treatment failure from 32% to 17% was associated with no additional treatment-related dysfunction. Patients who received the less efficacious standard-dose radiation reported less confidence that their cancers were under control and greater regret about their treatment decisions—differences that reflected their more frequent disease progression, but no difference in other measures of their quality of life, including attitudes toward their cancers and their health.

Several possible explanations for these unexpected results arise, which are not mutually exclusive. First, an efficacious increased radiation dose does not increase long-term toxicity to adjacent normal tissues if given using techniques that minimize dose to

nearby critical tissues, such as proton beam. In this sense, our results may be taken as validating this technology and confirm the similar physician-reported short- and long-term toxicity for standard-dose and high-dose patients initially reported.[11]

Alternatively, high-dose patients may have experienced increased toxicity earlier in their course that resolved during the nearly 10 years of follow-up. It is well recognized that rectal bleeding may resolve years after radiation, although hematuria has been reported to progressively increase.[22] Sexual dysfunction increases progressively in this age group whether they have had radiation treatment or not, and it may not be possible to detect a further increment due to the extra radiation dose against the increasing background dysfunction.

A third explanation is that standard-dose patients experienced less treatment-related toxicity, but the direct consequences of more frequent salvage therapy or the discouraging implications of cancer progression eliminated their advantage. The urinary obstruction and irritation symptom increased early after external beam radiation but not after the first year,[3] was strongly associated with cancer progression, but after adjusting for progression, not with the treatment group. Other treatment-related symptoms, including bowel problems, the adverse effect most specific to external beam radiation therapy; urinary incontinence, the adverse effect most specific to salvage surgery and cryotherapy; and sexual dysfunction, associated with surgery, cryotherapy, and androgen-deprivation therapy, were not significantly associated with progression.

Fourth, patients who underwent high-dose treatment did experience greater treatment-related toxicity but have adapted to their condition over time and no longer notice or report it. Our data documenting that patients frequently rate their function as normal, despite documented organ-specific symptoms, indirectly suggests such an adaptation to a new normal.

Table 5. Level of Urinary, Bowel, and Sexual Function vs Patient-Rated Function[a]

Functional Scale and Measured Level of Function[b]	Current Functional Level No. of Patients (%) [95% CI]			*P* Value
	Normal	Intermediate	Poor	
Urinary obstruction and irritation				
Normal	58 (92) [82-97]	5 (8) [3-18]	0 [0-6]	<.001
Intermediate	89 (69) [60-77]	37 (29) [21-37]	3 (2) [0-7]	
Poor	15 (19) [11-30]	52 (67) [55-77]	11 (14) [7-24]	
Urinary incontinence				
Normal	149 (92) [87-96]	13 (8) [4-13]	0 [0-2]	<.001
Intermediate	38 (45) [33-56]	46 (54) [43-65]	1 (1) [0-6]	
Poor	1 (10) [0-44]	3 (30) [7-65]	6 (60) [26-88]	
Bowel problem				
Normal	79 (99) [93-100]	1 (1) [0-7]	0 [0-4]	<.001
Intermediate	110 (81) [74-88]	25 (18) [12-26]	0 [0-3]	
Poor	20 (38) [25-52]	27 (51) [37-65]	6 (11) [4-23]	

Abbreviation: CI, confidence interval.
[a] Patients with early prostate cancer who underwent treatment in the Proton Radiation Oncology Group (PROG) 9509 and completed the study survey.
[b] The measured level of function was determined by same indicators as for Table 3.
Patients indicated their self-reported level of function in items asking them to consider their overall function for each symptom.

Fifth, highly motivated men may be more satisfied with the outcome of a technologically novel therapy that, in many cases, they actively researched and sought. Proton beam is undoubtedly one such therapy.

Finally, our follow-up of study participants is incomplete. Of the original 393 participants in PROG 9509, 55 (14%) died and an additional 58 patients (14.8%) did not participate in the survey, reducing study power and raising the possibility of bias. However, no differences in overall survival between treatment groups have yet emerged (78% vs 83%; $P = .41$),[12] treatment-related morbidity has little effect on survival, and our sample was balanced between study groups and adequate to detect clinically meaningful differences.

To conclude that additional dose is not associated with additional toxicity, particularly when using highly sensitive patient-reported measures, runs contrary to the widely accepted association between radiation dose and toxicity. However, data comparing outcomes after different radiation doses are surprisingly sparse.[23] In one randomized trial, prostate cancer patients who received 78 Gy reported more frequent bowel movements compared with those who received 70 Gy, but no other differences in bowel or sexual symptoms.[24] In another, which compared 64 to 74 Gy after 3 to 6 months of neoadjuvant hormonal treatment, the

Table 6. Comparison of Mean Urinary, Bowel, and Sexual Function Scores[a]

PROG 9509 Dysfunction	Boston Area, All Patients	Cohort Study
No. of patients	280	97
Time of follow-up, median, y	9.4	5.9
Age at survey, median, y	76.0	75.0
Urinary obstruction and irritation, mean score (SD)	24.0 (13.9)	21.8 (14.5)
Urinary incontinence, mean score (SD)	10.2 (16.7)	11.2 (18.0)
Bowel problem, mean score (SD)	7.8 (8.4)	10.6 (13.2)
Sexual dysfunction, mean score (SD)	67.1 (34.6)	76.3 (30.8)

Abbreviation: SD, standard deviation.
[a] Patients with early prostate cancer who underwent treatment in the Proton Radiation Oncology Group (PROG) 9509 were compared with long-term follow-up of patients undergoing external beam radiation therapy (photon) in a contemporaneous prospective cohort study. Table is modified from Clark and Talcott.[28]

calculated radiation dose to the penile bulb was associated with erectile dysfunction at 2 years after treatment but not to the assigned treatment dose.[25] A trial of a hypofractionated schedule compared with a standard schedule found similar 5-year urinary and bowel symptoms, but efficacy was also identical.[26]

A further problem in assessing outcomes after proton beam or more widely available radiation modalities is that, despite their frequent use, little long-term patient-reported data are available. Most reports have at most 2-year follow-up,[3] but occasionally extend to 3 years.[27] However, at a median of 5.5 years (range, 4-8 years), patients in a contemporaneous multicenter prospective cohort study[28] who had undergone external beam photon radiation reported roughly comparable outcomes (TABLE 6).

Some data support the explanation that symptoms become less noticeable over time. Korfage et al[29] found that patients trivialized dysfunction, especially sexual dysfunction, associating it with old age, and assigned adverse effects to treatment—not disease. In their studies, disease-specific instruments detected dysfunction, but they also detected response shift as patients adapted to changed health. Yu et al[30] found a strong correlation between optimism and eating ability in Chinese patients treated for nasopharyngeal carcinoma, indicating that psychological status influenced reported function.

These data challenge the assumption that the quality-of-life impact of persisting dysfunction is stable and can be extrapolated from naive expectations or early treatment experience. Any metric that assumes a stable relationship between symptoms and quality of life over time, such as quality-adjusted life-year, requires empirical validation of the assumption of stability over time, whether or not the analysis discounts benefits over time.[31] To the extent that patients adapt to treatment-related dysfunction, the assumption that the impact of treatment-related dysfunction is stable underestimates the net benefit of treatment.

Prostate cancer is now being detected and treated at earlier ages and cured patients may live for decades with treatment adverse effects. Long-term outcomes have thus become a central factor in patient treatment decisions, but to date, long-term patient-reported data are lacking for both surgery and radiation. The experimental higher dose in PROG 9509 is now common in clinical practice. Among men with clinically localized prostate cancer, treatment with higher-dose radiation compared with standard dose was not associated with an increase in patient-reported prostate cancer symptoms after a median of 9.4 years.

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Study concept and design: Talcott, Shipley, Slater, Zietman.
Acquisition of data: Talcott, Rossi, Zietman.
Analysis and interpretation of data: Talcott, Clark, Niemierko, Zietman.
Drafting of the manuscript: Talcott, Clark, Slater, Zietman.
Critical revision of the manuscript for important intellectual content: Talcott, Rossi, Shipley, Clark, Slater, Niemierko, Zietman.
Statistical analysis: Talcott, Clark, Niemierko.
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> The first capacity of human intellect is that the mind is fitted to receive the impressions made on it, either through the senses by outward objects, or by its own operations when it reflects on them.
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> —John Locke (1632-1704)