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## Long-term outcomes following proton therapy for prostate cancer in young men with a focus on sexual health

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### ABSTRACT

**Background:** We investigated long-term outcomes for men  $\leq 60$  years old treated with proton therapy (PT).

**Methods:** Of 254 men  $\leq 60$  years old were treated with proton therapy alone for prostate cancer. Risk stratification included 56% with low-, 42% with intermediate- and 2% with high-risk disease. Patients received 76–82 Gy at 2 Gy/fraction or 70–72.5 Gy at 2.5 Gy/fraction. Before treatment and every 6–12 months for 5 years, patients were evaluated by a physician, answered health-related quality of life surveys, including the EPIC, IIEF and IPSS, and had PSA evaluated.

**Results:** Median follow-up for the cohort was 7.1 years; 7-year biochemical-free survival was 97.8%. Eight men (one high-risk; five intermediate-risk and two low-risk) experienced biochemical progression, including one who died of disease 9 years after treatment. Potency (erections firm enough for sexual intercourse) was 90% at baseline and declined to 72% at the first-year follow-up, but declined to only 67% at 5 years. Only 2% of patients developed urinary incontinence requiring pads. The bowel habits mean score declined from a baseline of 96 to 88 at 1 year, which improved over the following years to 93 at 5 years.

**Conclusions:** Young men with prostate cancer continue to have excellent results with respect to 7-year biochemical control and 5-year erectile function, without clinically significant urinary incontinence 5 years after proton therapy. Comparative effectiveness studies of proton therapy with surgery and IMRT are needed.

### ARTICLE HISTORY

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### Introduction

Prostate cancer is the most common non-cutaneous malignancy diagnosed among men in the United States [1] and the second most common cancer-related death [1]. Recent reports show that the proportion of younger men diagnosed with prostate cancer continues to rise [2]. While many effective treatment options are available, surgery and radiation therapy are considered standard of care with similar rates of biochemical-free survival, but distinctly different risks of toxicities and effects on health-related quality of life (HRQOL) [3–6].

In general, practice patterns have identified that younger, healthier men more frequently undergo prostatectomy while older men with more co-morbidities more frequently receive radiation therapy. It has been suggested that the discrepancy in utilization of radiation in younger patients has been due to the lack of consultation or second opinion by a radiation oncologist [7] or due to concerns of higher risk of second cancers if younger men are irradiated [8].

Since similar local control and overall survival have been observed for surgery and radiation, HRQOL has emerged as an

increasing focus in men considering their treatment options. Several investigations have reported fear of incontinence was a decision-making factor in men [9,10], while a more recent study reported that younger men placed more importance on sexual function when choosing treatment options [11].

Proton therapy is a radiation modality that may help reduce the moderate- and low-dose radiation exposure to the pelvis [12], which may reduce the risk of bowel urgency/frequency, second cancers and possibly sexual function [13,14]. Our group has previously reported excellent outcomes with respect to erectile dysfunction and urinary incontinence during the first 2 years of survival after proton therapy treatment in young men [15]. The objective of this study is to evaluate long-term disease-specific and patient-reported HRQOL outcomes following proton therapy at our institute for young men with prostate cancer, evaluate potency using the increasingly more common definition of having an erection, that is, 'firm enough for intercourse' and provide data on sexual desire, orgasms and frequency and quality of erections that can be used to help counsel patients.

## Material and methods

This study included men with prostate cancer treated with definitive proton therapy. Eligible patients were 60 years old or younger and treated on an institutional review board-approved outcome tracking protocol and/or on one of three institutional review board-approved treatment protocols open between August 2006 and January 2010. Patients who received hormone therapy ( $n=28$ ) or those lacking baseline HRQOL data ( $n=8$ ) were excluded. In total, 254 patients were eligible for analysis.

HRQOL parameters were captured prospectively using the 50-item expanded prostate cancer index composite (EPIC) questionnaire before the start of definitive treatment, every 6 months for the first year, and then every 6–12 months annually following treatment [16]. The questionnaire was mailed to the patient, completed electronically through a secure online medical record portal or obtained by patient interview for patients who could complete >5-year forms. The EPIC summary and subscales were reported and calculated using a scale of 0–100, where higher scores indicated better outcomes. Potency was defined as having erections firm enough for intercourse based on EPIC question 59. Patient-based characteristics and medical comorbidities were extracted from the initial consultation history.

Our institution's simulation, planning, and treatment guidelines for prostate cancer have been previously published [17,18]. Briefly, for this cohort of patients, after fiducial markers were placed within the prostate under ultrasound guidance, patients were simulated with a vacuum-locked body mold, a full bladder and a saline instilled rectal balloon to stabilize the prostate position on a Philips Brilliance computed tomography big-bore simulator (Philips Healthcare, Andover, MA, USA). A magnetic resonance imaging scan was subsequently obtained on a Philips Panorama 0.23T (Philips, Amsterdam, Netherlands) open magnetic resonance imaging system immediately after computed tomography simulation and the images were fused using the Philips Pinnacle AcQSim3 virtual simulation workstation, and imported into the Varian Eclipse treatment planning system (Varian Medical System, Palo Alto, CA, USA). Targets and normal tissues were contoured according to our institution's guidelines as previously published [15]. Briefly, a planning target volume (PTV) encompassed the prostate with or without seminal vesicles with a margin of 4 mm in the anterior–posterior and lateral directions, and 6 mm in the superior–inferior direction. Dosimetric coverage specified that 95% of the PTV receive 100% of the prescribed dose and 100% of the PTV receive at least 95% of the prescribed dose. Image-guided proton therapy was achieved using orthogonal kilovolt imaging for fiducial localization with double-scatter left and right lateral (or slightly oblique) field arrangements through customized brass apertures and compensators. Patients were treated with either 2 Gy(RBE) per fraction to a total dose of 76–82 Gy(RBE) or at 2.5 Gy(RBE) per fraction to a total dose of 70–72.5 Gy(RBE) depending on the protocol.

Patient and tumor characteristics were shown in Table 1. The median age was 56 years old (range, 41–60 years). Baseline medical conditions included body mass index,

**Table 1.** Characteristics of prostate cancer patient received proton therapy ( $N=254$ )<sup>a</sup>.

Characteristic	No of patients (%)
Marital status	
Married	194 (76)
Not married	60 (24)
Mood disorder	
Depression	19 (7)
Anxiety	19 (7)
None	216 (86)
Body-mass index	
<30	194 (76)
≥30	60 (24)
Diabetes	
Yes	14 (6)
No	240 (94)
High cholesterol	
Yes	103 (41)
No	151 (59)
Cardiac disease	
Yes	24 (9)
No	230 (91)
Smoking	
<10 pack-year	185 (73)
≥10 pack-year	69 (27)
T classification	
T1c	200 (79)
T2a	42 (16)
T2b	9 (4)
T2c	2 (1)
T3a	1 (0)
Gleason score	
<7	157 (62)
7	92 (36)
>7	5 (2)
Prostate-specific antigen	
≤10	224 (88)
10.1–20	28 (11)
>20	2 (1)
Risk group	
Low	142 (56)
Intermediate	106 (42)
High	6 (2)

<sup>a</sup>Median age: 56 (range, 41–60) years.

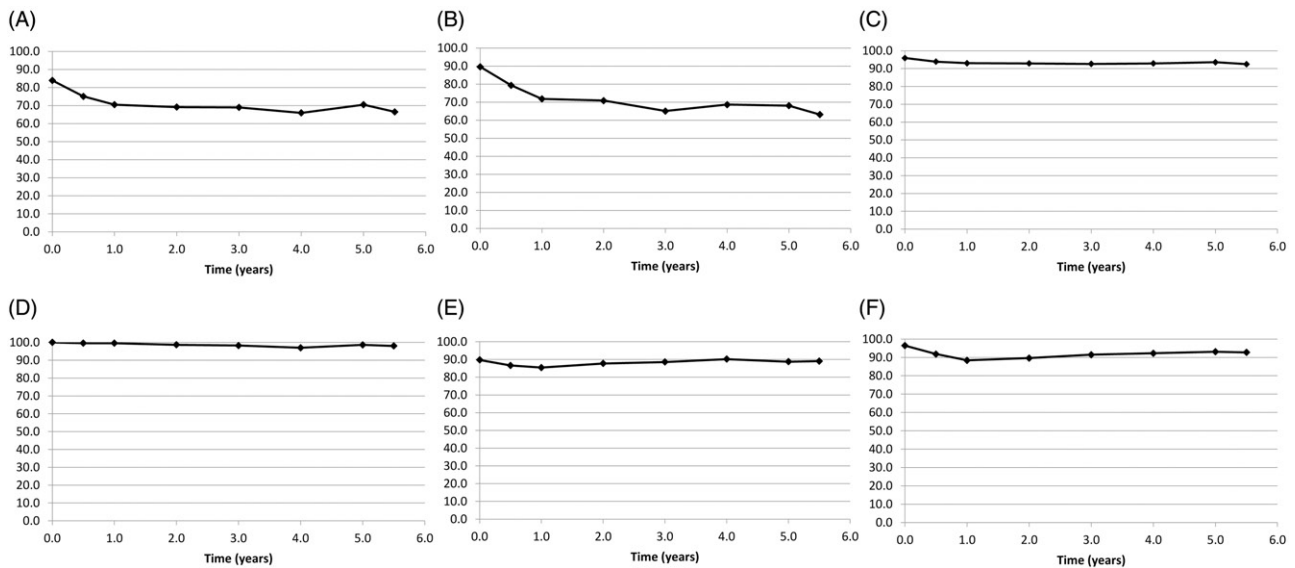
mood disorder, hyperlipidemia, cardiac disease and diabetes. Risk group stratification included 56% with low-, 42% with intermediate- and 2% with high-risk disease. The EPIC response rate changed over time with 91, 87, 67, 66 and 57% of patients responding at years 1, 2, 3, 4 and 5, respectively, but with 80% of patients completing five or more years of EPIC response data.

## Statistics

SAS and JMP software were used for all statistical computations (SAS Institute, Cary, NC, USA). Scores for patient-reported HRQOL outcomes from EPIC were calculated as described previously [15]. The nonparametric version of the chi-squared test (Fisher exact test) was used for the analysis of the categorical end-points of potency and two dichotomized versions of delta change from the baseline EPIC sexual summary score. Multiple logistic regression was used to simultaneously assess the ability of several prognostic factors to predict for potency.

## Results

The median follow-up for this cohort was 7.1 years with a 7-year biochemical-free survival rate of 97.8%. Eight men



**Figure 1.** Results of the patient-reported expanded prostate cancer index composite (EPIC) questionnaire in men 60 years old and younger over time. This data shows the baseline 0-, 0.5-, 1-, 2-, 3-, 4-, 5- and  $\geq 5$ -year data (A) sexual summary score, (B) incidence of potency, (C) urinary incontinence score, (D) percentage of men pad-free on a daily basis, (E) urinary irritative score and (F) bowel summary score.

(one high-risk [T3a G8 PSA33], five intermediate-risk and two low risk) experienced biochemical progression. Retrospective re-review of the prostate MRI with a radiologist (DK) specializing in prostate MRI was available for six of the seven recurrences among men with low- or intermediate-risk disease and demonstrated presence of extracapsular extension in four of the men prior to treatment. The 7-year biochemical-free survival for low risk was 99.2% and intermediate risk was 97.7%. The 7-year overall survival rate was 98.7%, including five deaths, one prostate cancer-related, two suicides (one with history of depression and alcoholism), a cardiac arrest and an asthma attack.

At 1 year of follow-up, the mean sexual summary score had declined by 13.4 points from a baseline of 83.9, but it then stabilized for the subsequent 4 years (Figure 1(A)). Potency, defined by the EPIC questionnaire as an erection firm enough for sexual intercourse in the prior month, was 89.7% at baseline and declined to 71.9% at 1 year of follow-up, but subsequently leveled off to 68.1% at 5 years (Figure 1(B)). Table 2 describes the outcomes at different follow-up times for specific sexual function items, including sexual desire, orgasm and frequency and quality of erections. For all outcomes, the biggest decline occurred in the first year of follow-up and then remained relatively stable at last follow-up 5 years or more following treatment.

The urinary incontinence mean score declined from a baseline of 95.9 to 93 after the first year, and was then stable for the following 4 years with a 5-year score of 93.6 (Figure 1(C)). Furthermore, at 5 years of follow-up, 98.6% of patients experienced no urinary leakage and required no pads on a daily basis (Figure 1(D)) compared with 99.6% at 1 year. The urinary irritative and obstructive mean score also declined initially from a baseline of 89.7 to 85.4 at 1 year, but improved over the next 4 years to 88.7 at 5 years (Figure 1(E)).

The bowel summary mean score declined initially from a baseline of 96.4 to 88.4 at 1 year, but improved over the

following years to 93.1 at the 5-year follow-up (Figure 1(F)). Table 3 reports outcomes at different follow-up times for various bowel-related items. Most of the bowel symptoms worsened within the first 6 months to 2 years and then appeared to improve over the following 3 years.

On multivariate analysis (Table 4), we investigated the patient- and treatment-related factors that might predict the rate of potency for all patients at 2 and 5 years and we also restricted our analysis to those patients who were potent at baseline. As expected, in the analysis of all patients, baseline EPIC sexual summary score was significantly associated with potency at 2 and  $\geq 5$  years. Furthermore, dose/fraction and total dose were significantly associated with potency at 2 years, but not at  $\geq 5$  years ( $p = .0621$ ). When restricted to patients who were potent at baseline, the EPIC sexual summary score remained significantly associated with potency at 2 years, but not at  $\geq 5$  years ( $p = .0629$ ). Age also appeared to be significantly associated with potency at 2 and 5 years. Additional univariate examination revealed a relationship between age and EPIC sexual summary score resulting in the conflicting findings that younger age was associated with worse potency rates at 2 years, but better potency rates at 5 years. Interestingly, dose per fraction and total dose were no longer statistically significantly associated with potency when restricted to baseline potent patients.

## Discussion

Many effective treatment options are available for men with prostate cancer, each carrying its own unique toxicity profile. As disease control and outcomes have improved with time and technological advances, prostate cancer survivors have increasingly placed more importance on HRQOL. Decision models have illustrated that patient preferences for outcomes among various treatment strategies may be an important factor that drives treatment decisions [19,20]. While men undergoing radiotherapy for prostate cancer are typically older and

**Table 2.** Sexual outcomes over time according to EPIC questions (N = 254).

EPIC question	No. of patients (%) at time points						
	Baseline	6 months	1 year	2 years	3 years	4 years	5 + years
<b>Sexual desire (Q56)</b>							
Missing	2	20	23	34	82	88	53
Fair/poor/very poor	75 (29.8%)	102 (43.6%)	99 (42.9%)	96 (43.6%)	81 (47.1%)	82 (49.4%)	98 (48.8%)
Good/very good	177 (70.2%)	132 (56.4%)	132 (57.1%)	124 (56.4%)	91 (52.9%)	84 (50.6%)	103 (51.2%)
<b>Ability to have erections (Q57)</b>							
Missing	7	26	23	35	85	89	53
Fair/poor/very poor	57 (23.1%)	91 (39.9%)	99 (42.9%)	102 (46.6%)	76 (45.0%)	79 (47.9%)	102 (50.7%)
Good/very good	190 (76.9%)	137 (60.1%)	132 (57.1%)	117 (53.4%)	93 (55.0%)	86 (52.1%)	99 (49.3%)
<b>Ability to have orgasm (Q58)</b>							
Missing	8	28	24	36	87	90	53
Fair/poor/very poor	43 (17.5%)	57 (25.2%)	82 (35.7%)	65 (29.8%)	50 (29.9%)	57 (34.8%)	67 (33.3%)
Good/very good	203 (82.5%)	169 (74.8%)	148 (64.3%)	153 (70.2%)	117 (70.1%)	107 (65.2%)	134 (66.7%)
<b>Quality erections (Q59)</b>							
Missing	2	21	23	34	82	88	53
None at all	4 (1.6%)	2 (0.9%)	3 (1.3%)	4 (1.8%)	3 (1.7%)	5 (3.0%)	8 (4.0%)
Not firm enough for sexual activity	2 (0.8%)	13 (5.6%)	20 (8.7%)	17 (7.7%)	21 (12.2%)	17 (10.2%)	21 (10.4%)
Firm enough for masturbation	20 (7.9%)	33 (14.2%)	42 (18.2%)	43 (19.5%)	36 (20.9%)	30 (18.1%)	45 (22.4%)
Firm enough for intercourse	226 (89.7%)	185 (79.4%)	166 (71.9%)	156 (70.9%)	112 (65.1%)	114 (68.7%)	127 (63.2%)
<b>Frequency of erections (Q60)</b>							
Missing	2	21	24	33	82	88	53
<50%	15 (6.0%)	26 (11.2%)	36 (15.7%)	42 (19.0%)	37 (21.5%)	47 (28.3%)	47 (23.4%)
≥50%	237 (94.0%)	207 (88.8%)	194 (84.3%)	179 (81.0%)	135 (78.5%)	119 (71.7%)	154 (76.6%)
<b>Frequency of awaking with erection (Q61)</b>							
Missing	2	20	23	33	81	87	53
< Weekly	79 (31.3%)	92 (39.3%)	96 (41.6%)	97 (43.9%)	80 (46.2%)	75 (44.9%)	98 (48.8%)
≥ Weekly	173 (68.7%)	142 (60.7%)	135 (58.4%)	124 (56.1%)	93 (53.8%)	92 (55.1%)	103 (51.2%)
<b>Frequency of sexual activity (Q62)</b>							
Missing	3	21	23	33	82	88	54
< Weekly	60 (23.9%)	69 (29.6%)	76 (32.9%)	72 (32.6%)	60 (34.9%)	69 (41.6%)	81 (40.5%)
≥ Weekly	191 (76.1%)	164 (70.4%)	155 (67.1%)	149 (67.4%)	112 (65.1%)	97 (58.4%)	119 (59.5%)
<b>Frequency of sexual intercourse (Q63)</b>							
Missing	1	21	23	33	82	87	54
< Weekly	94 (37.2%)	99 (42.5%)	110 (47.6%)	105 (48.0%)	89 (51.7%)	97 (58.1%)	118 (59%)
≥ Weekly	160 (62.8%)	134 (57.5%)	121 (52.4%)	114 (52.0%)	83 (48.3%)	70 (41.9%)	82 (41%)
<b>Ability to function sexually (Q64)</b>							
Missing	1	21	24	33	82	88	54
Fair/poor/very poor	65 (25.7%)	95 (40.8%)	105 (45.7%)	111 (50.2%)	82 (47.7%)	82 (49.4%)	101 (50.5%)
Good/very good	188 (74.3%)	138 (59.2%)	125 (54.3%)	110 (49.8%)	90 (52.3%)	84 (50.6%)	99 (49.5%)
<b>How much of a problem is sexual desire (Q65)</b>							
Missing	5	22	24	34	82	88	53
Small/very small/no problem	227 (91.2%)	196 (84.5%)	191 (83.0%)	181 (82.3%)	130 (75.6%)	130 (78.3%)	159 (79.1%)
Moderate/big problem	22 (8.8%)	36 (15.5%)	39 (17.0%)	39 (17.7%)	42 (24.4%)	36 (21.7%)	42 (20.9%)
<b>How much of a problem are erections (Q66)</b>							
Missing	7	22	25	34	82	90	53
Small/very small/no problem	224 (90.7%)	186 (80.2%)	172 (75.1%)	157 (71.3%)	116 (67.4%)	111 (67.7%)	139 (69.2%)
Moderate/big problem	23 (9.3%)	46 (19.8%)	57 (24.9%)	63 (28.6%)	56 (32.6%)	53 (32.3%)	62 (30.8%)
<b>How much of a problem are orgasms (Q67)</b>							
Missing	8	23	25	34	83	92	55
Small/very small/no problem	226 (91.9%)	201 (87.0%)	193 (84.3%)	182 (82.7%)	146 (85.4%)	138 (85.2%)	162 (81.4%)
Moderate/big problem	20 (8.1%)	30 (13.0%)	36 (15.7%)	38 (17.3%)	25 (14.6%)	24 (14.8%)	37 (18.6%)
<b>How much of a problem is sexual function (Q68)</b>							
Missing	1	21	24	33	81	88	53
Small/very small/no problem	231 (91.3%)	191 (82.0%)	174 (75.7%)	164 (74.2%)	121 (69.9%)	118 (71.1%)	155 (77.1%)
Moderate/big problem	22 (8.7%)	42 (18.0%)	56 (24.3%)	57 (25.8%)	52 (30.1%)	48 (28.9%)	46 (22.9%)

have medical comorbidities that preclude them from having surgery, more younger men are considering definitive radiotherapy because of concerns about erectile dysfunction and urinary incontinence following prostatectomy [21]. Proton therapy has a dosimetric advantage of delivering a lower integral dose to the surrounding normal tissues than x-ray radiation [22]. Here, we report that young men with prostate cancer receiving proton therapy results in excellent 7-year biochemical-free survival and quality of life at 1 year and 5 years of follow-up. The results represent not only a 5-year update of our previous experience [15], with similarly excellent outcomes at 5 years as compared with the prior 2 year

results, but also utilize a more common definition for potency wherein patients describe the quality of their erections as 'firm enough for intercourse' [23]. Additionally, we provide additional sexual data that can be used to counsel patients interested in sexual outcomes following treatment, including information on sexual desire, orgasm, erections and sexual activity, which is especially of interest to younger men.

Evaluation of HRQOL outcomes with the EPIC questionnaire has gained in popularity in recent years. Utilizing the shortened EPIC-26 questionnaire, Sanda et al. [3] compared quality of life after surgery, external-beam radiotherapy

**Table 3.** Bowel outcomes over time according to EPIC questions ( $N = 254$ ).

EPIC question	No. of patients (%) at time points						
	Baseline	6 months	1 year	2 years	3 years	4 years	5 + years
Frequency of rectal urgency (Q42)							
Missing	1	22	23	33	82	86	52
≤Weekly	246 (97.2%)	213 (91.8%)	207 (89.6%)	203 (91.9%)	162 (94.2%)	161 (95.8%)	187 (92.6%)
>Weekly	7 (2.8%)	19 (8.2%)	24 (10.4%)	18 (8.1%)	10 (5.8%)	7 (4.2%)	15 (7.4%)
Frequency of uncontrolled leakage of stool (Q43)							
Missing	1	21	23	33	81	86	51
≤Weekly	252 (99.6%)	229 (98.3%)	225 (97.4%)	219 (99.1%)	171 (98.8%)	166 (98.8%)	201 (99.0%)
>Weekly	1 (0.4%)	4 (1.7%)	6 (2.6%)	2 (0.9%)	2 (1.2%)	2 (1.2%)	2 (1.0%)
Frequency of bloody stools (Q45)							
Missing	1	21	23	33	82	86	51
Never/rarely	249 (98.4%)	223 (95.7%)	200 (86.6%)	192 (86.9%)	155 (90.1%)	156 (92.9%)	192 (94.6%)
Half the time/usually/always	4 (1.6%)	10 (4.3%)	31 (13.4%)	29 (13.1%)	17 (9.9%)	12 (7.1%)	11 (5.4%)
No. of bowel movements a day (Q47)							
Missing	1	23	24	35	82	89	51
≤2	223 (88.1%)	187 (81.0%)	184 (80%)	186 (84.9%)	144 (83.7%)	131 (79.4%)	160 (78.8%)
>2	30 (11.9%)	44 (19.0%)	46 (20%)	33 (15.1%)	28 (16.3%)	34 (20.6%)	43 (21.2%)
Problem with bowel urgency (Q49)							
Missing	2	21	24	33	82	86	51
None/very small/small	251 (99.6%)	220 (94.4%)	216 (93.9%)	208 (94.1%)	164 (95.3%)	161 (95.8%)	198 (97.5%)
Moderate/big	1 (0.4%)	13 (5.6%)	14 (6.1%)	13 (5.9%)	8 (4.7%)	7 (4.2%)	5 (2.5%)
Problem with frequency of bowel movements (Q50)							
Missing	5	23	23	33	83	88	51
None/very small/small	248 (99.6%)	223 (96.5%)	218 (94.4%)	214 (96.8%)	167 (97.7%)	166 (100%)	200 (98.5%)
Moderate/big	1 (0.4%)	8 (0.03%)	13 (5.6%)	7 (3.2%)	4 (2.3%)	0 (0%)	3 (1.5%)
Problem with losing control of stools (Q52)							
Missing	5	23	24	33	84	87	53
None/very small/small	248 (99.6%)	229 (99.1%)	226 (98.3%)	218 (98.6%)	167 (98.2%)	164 (98.2%)	199 (99%)
Moderate/big	1 (0.4%)	2 (0.9%)	4 (1.7%)	3 (1.4%)	3 (1.8%)	3 (1.8%)	2 (1%)
Problem with bloody stools (Q53)							
Missing	2	23	23	33	83	87	52
None/very small/small	251 (99.6%)	226 (97.8%)	211 (91.3%)	203 (91.9%)	160 (93.6%)	165 (98.8%)	197 (97.5%)
Moderate/big	1 (0.4%)	5 (2.2%)	20 (8.7%)	18 (8.1%)	11 (6.4%)	2 (1.2%)	5 (2.5%)
How problematic are bowel movements (Q54)							
Missing	1	20	23	33	81	87	51
None/very small/small	252 (99.6%)	225 (96.2%)	214 (92.6%)	211 (95.5%)	166 (96.0%)	162 (97.0%)	199 (98.0%)
Moderate/big	1 (0.4%)	9 (3.8%)	17 (7.4%)	10 (4.5%)	7 (4.0%)	5 (3.0%)	4 (2.0%)

**Table 4.** Multivariate analysis of potency with regard to patient- and treatment-related factors of prostate cancer with proton therapy.

	All patients		Baseline potent patients	
	2 years	5 + years	2 years	5 + years
Age (<55 vs. ≥55)	0.2506	0.2431	0.0303	0.0215
Body-mass index (<30 vs. ≥30)	0.5706	0.0853	0.6009	0.1388
Diabetes or cardiac disease (yes vs. no)	0.4007	0.1656	0.191	0.1531
High cholesterol (yes vs. no)	0.0944	0.9993	0.28	0.6804
Dose/fraction and total dose (2 Gy[RBE]/fraction <80 Gy[RBE] vs. 2.5 Gy[RBE]/fraction <80 Gy[RBE] vs. 2 Gy[RBE]/fraction ≥80 Gy[RBE])	0.0335	0.0621	0.151	0.0924
Penile bulb (<30 vs. ≥30 Gy [RBE])	0.0623	0.6478	0.3328	0.8054
EPIC sexual summary score (0–67 points vs. 68–99/100 points)	0.0017	0.0004	0.0218	0.0629

Italics designate significant  $p$  values.

or brachytherapy. They observed a substantial decline in sexual summary and urinary incontinence scores from baseline to 2 years after surgery, but only a mild to moderate decline in patients treated with external-beam radiotherapy or brachytherapy. Urinary irritative symptoms and bowel symptoms were more frequent after brachytherapy and radiotherapy than with surgery. Similar findings were reported by Pardo et al. [24] at 3 years after treatment of prostate cancer. Here, we report some of the longest follow-up of patient-reported HRQOL after proton therapy [25], finding that there are only mild changes in urinary, bowel and sexual domains

following definitive treatment with proton therapy. The patient-reported EPIC sexual summary score demonstrated a slight decline from a baseline of 84 to 70 in the first year after proton therapy that sustained at year five of follow-up. This is important as it suggests that the sexual summary score at the 1-year follow-up is a good surrogate for expectations of sexual function at 5-year follow-up.

Several studies have reported a post-radiotherapy decline in potency rates ranging from 30 to 50% within 3 years of treatment [26–30]. Some longitudinal studies further indicate that sexual function declines in the second year after

external-beam radiotherapy [31,32]. With proton therapy, we observed only an initial 18% drop in the potency rate after the first year, and the ability to achieve an erection firm enough for intercourse declined minimally in subsequent years. By the fifth year of follow-up, the potency rate reached 67%. Most of the specific sexual items in the EPIC instrument showed the greatest decline in the first year with only minimal further decline at 5 years, contrary to suggestions that sexual dysfunction after radiation therapy becomes more of a problem for patients [33] during the second through fifth year of follow-up.

To evaluate factors that may affect potency, we collected baseline body mass index, past medical history of mood disorder, cardiac disease, hypercholesterolemia and diabetes. We further explored treatment factors like dose to the penile bulb, total prescribed dose and dose per fraction. In this cohort, patient-reported EPIC sexual summary composite scores were statistically significant or trended to be associated with potency on multivariate analysis (Table 4). Although, patients treated at 2.5 Gy(RBE)/fraction to 70–72.5 Gy(RBE) appeared to fare better than patients treated at 2 Gy(RBE)/fraction to <80 Gy(RBE) or to  $\geq 80$  Gy(RBE) among all patients, the finding was not significant when restricted to patients with baseline potency, suggesting that this finding might be weak. Furthermore, age appeared to be significantly associated with potency; however, this finding was found to interact with EPIC summary score and resulted in conflicting data at 2 and  $\geq 5$  years. Consequently, no patient- or treatment-related factors really appeared to have an impact on outcomes.

When comparing our data to those published by Alemozaffar et al. [23], we find that men 60 years old and younger treated with proton therapy have higher EPIC sexual summary and potency scores at 2 years than similar men treated with nerve-sparing surgery. Although outcomes after proton therapy appear better than those reported in the same study for external-beam radiation therapy, the patient cohorts are considerably different and, thus, not a fair comparison. A young IMRT cohort with high-level HRQOL follow-up is needed to provide a better comparative cohort to elucidate if any sexual function benefit exists.

Urinary continence levels were well maintained with only a 2.8-point decline after 1 year that remain unchanged at 5 years of follow-up. Incontinence rates after prostatectomy vary in the current literature from 20 to 80% [34,35]. Here we report that for patients treated with proton therapy, the rate of no urinary leakage is 99% and these patients remained pad-free on a daily basis even at 5 years. With respect to urinary irritative mean score, there was an initial 5-point decline from 90 after 1 year that improved by the second year and leveled at 88 at subsequent annual follow-up visits. A similar trend was noted in bowel summary score with an initial 8-point decline from 96 after 1 year that subsequently improved over the next several years to 93 at the 5-year follow-up.

A limitation of this study is that, we restrict the analysis to those patients treated until 2010 and, therefore, are unable to evaluate whether experience with planning proton therapy treatment can have an impact on HRQOL. We had previously evaluated whether rectal toxicities varied among

patients treated before 2009, but did not observe any significant difference [36]. Since 2010, numerous modifications have been made in our original treatment planning and patient set up. Owing to intrafraction motion studies, we have reduced the PTV margin [37], introduced rectal balloons for all patients instead of rectal saline and, most recently, begun to use hydrogel to separate the prostate from the rectum. Future studies that include patients treated with these modifications may reveal differences in HRQOL attributable to these changes. Another weakness of the study was that the patient-reported response rate fell to 57% at year 5; however, many of those unresponsive patients did provide follow-up at later points, which could be used at a  $\geq 5$ -year follow-up point for which we have an 80% response rate. Finally, another limitation of our study is that participants were treated a single institution, many of whom were self-referred and traveled great distances to receive proton therapy. It is possible that our patient population is not representative of the larger population of young men with prostate cancer, so these findings should be prospectively validated in a multi-institutional experience.

In summary, young men with prostate cancer experience excellent 7-year disease control and 5-year erectile function, urinary continence and bowel habits after proton therapy. These outcomes were similar to those reported at 1 year, suggesting that 1-year outcomes might be a good surrogate for longer-term outcomes among men 60 years and younger treated with proton therapy. Comparative effectiveness studies of proton therapy with surgery and IMRT are needed for younger men.

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## Disclosure statement

The authors have no conflicts of interest to declare.

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