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Clinical Investigation

Four-Year Outcomes From a Prospective Phase II Clinical Trial of Moderately Hypofractionated Proton Therapy for Localized Prostate Cancer

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Summary

Although large randomized trials have reported the efficacy of photon-based hypofractionated therapy, hypofractionated proton therapy (HFPT) has not been extensively studied. A prospective phase II study was performed to determine the clinical and patient reported outcomes of men treated with HFPT (70 Gy in 28 fractions). HFPT for the treatment of prostate cancer is associated with transitory low rates of urologic and gastrointestinal toxicity and low rates of patient-reported urinary and sexual bother after treatment.

Purpose: Moderately hypofractionated radiation therapy represents an effective treatment for localized prostate cancer (PC). Although large randomized trials have reported the efficacy of photon-based hypofractionated therapy, hypofractionated proton therapy (HFPT) has not been extensively studied. This study was performed to determine the clinical and patient-reported outcomes for patients with PC treated with HFPT.

Methods and Materials: Between 2010 and 2017, 184 men were enrolled on a trial of 70 Gy in 28 fractions of HFPT for low- to intermediate-risk PC. Acute and late toxicity was evaluated using National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Patient-reported outcomes were measured by International Prostate Symptom Score, International Index of Erectile Function Questionnaire, and Expanded Prostate Cancer Index Composite scores.

Results: Median follow-up was 49.2 months. Enrolled patients had low-risk (n = 18), favorable intermediate-risk (n = 78), and unfavorable intermediate-risk (n = 88) PC. Four-year rates of biochemical-clinical failure-free survival were 93.5% (95% confidence interval, 89%-98%), 94.4% (89%-100%), 92.5% (86%-100%), and 93.8% (88%-100%) in the overall group and the low-risk, favorable intermediate-risk, and unfavorable intermediate-risk cohorts, respectively (log-rank $P > .4$). The incidence of acute grade 2 or higher gastrointestinal (GI) and urologic toxicities were 3.8% and 12.5%, respectively. The 4-year incidence of late grade 2 or higher urologic and GI toxicity was 7.6% (4%-13%) and 13.6% (9%-20%), respectively. One late grade 3 GI toxicity was reported. All late toxicities were transient. Patient-reported

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International Prostate Symptom, International Index of Erectile Function, and Expanded Prostate Cancer Index Composite scores had no significant long-term changes after completion of HFPT (Supplementary Table 1, available at https://doi.org/10.1016/j.ijrobp.2019.05.069).

Conclusions: HFPT is associated with low rates of toxicity and does not appear to negatively affect 4-year patient reported urinary and bowel health. Further comparative analyses are warranted to better understand differences between proton and photon HFRT.

Introduction

Definitive external beam radiation therapy is a treatment option for many men with localized prostate cancer.[1] Technological advances in radiation treatment planning have allowed for the delivery of more conformal treatments, with the use of intensity modulated radiation therapy (IMRT) and proton therapy (PT). Such treatment modalities have allowed for the study of dose escalation with conventionally fractionated radiation therapy (1.8-2 Gy/fraction) in patients with prostate cancer (PC). Although dose escalation has been found to improve biochemical control, it results in longer treatment package times for patients.[2-4]

Radiobiological investigations have found that prostate cancer cells proliferate relatively slowly and respond to radiation in a manner typical of normal tissues.[5] As such, larger fraction sizes with fewer treatments (hypofractionation) are postulated to provide a therapeutic advantage in prostate cancer radiation.[6] Studies of moderately hypofractionated (HF) photon radiation (2.5-4 Gy/fraction) have reported similar disease control and late toxicity rates compared with conventionally fractionated regimens.[7-10] These clinical outcomes, along with the logistical advantages and lower costs of such a treatment approach, have led to greater adoption of HF radiation therapy for patients with prostate cancer in recent years.[11]

PT typically offers dosimetric advantages compared with IMRT to reduce low- and moderate-range radiation dose to neighboring organs at risk.[12] Although the use of conventionally fractionated PT (CFPT) for prostate cancer has been studied, there are less robust data on long-term outcomes for PC patients treated with hypofractionated proton therapy (HFPT). The purpose of this study was to determine the acute and long-term outcomes for patients with localized prostate cancer treated with HFPT.

Methods and Materials

Between April 2010 and April 2017, 184 men were enrolled on a prospective institutional review board–approved trial of moderately hypofractionated proton therapy for prostate cancer. The trial was registered on clinicaltrials.gov. Informed consent was obtained from all patients. Eligibility criteria included histologically confirmed prostatic adenocarcinoma with no clinical or pathologic evidence of extraprostatic disease or lymph node involvement. Patients with prior pelvic radiation, active diverticulitis, ulcerative colitis, or Crohn's disease were not eligible. Patients were staged with clinical TNM staging, the National Comprehensive Cancer Network Risk Categories, and the favorable versus unfavorable classification proposed by Zumsteg et al.[1,13] Only low- and intermediate-risk patients were allowed.

All patients, regardless of risk group, received 70 Gy_{RBE} in 28 fractions. This regimen is thought to be dose equivalent to a conventionally fractionated regimen of 79.2 Gy in 44 fractions, assuming an α/β of 2.4 Gy for PC, and has been used in other contemporary studies.[8-10] As per institutional standard, patients with unfavorable intermediate-risk prostate cancer were allowed to receive short-term androgen deprivation therapy (ADT). ADT with leuprolide was generally administered neoadjuvantly and concurrently with radiation therapy.

Radiation treatment planning

Before computed tomography (CT) simulation, patients were implanted with 3 fiducial markers into the prostate under ultrasound guidance. Patients received bowel preparation before simulation and had an endorectal balloon placed for simulation and for subsequent daily treatments. Patients were requested to have a comfortably full bladder at the time of simulation and for daily treatments. Patients were immobilized in the supine position and had a CT simulation scan. On the day of simulation, patients also had 1.5 T magnetic resonance imaging performed, with endorectal balloon in place. CT and MR images were fused together to enhance the accuracy of target localization for all patients.

As previously described by Fang et al,[12] an initial volume consisting of the prostate and proximal 1 cm of the seminal vesicles was contoured as clinical target volume 1 (CTV1) and prescribed 52.5 Gy in 21 fractions. A cone down volume, CTV2, consisted of the prostate alone. CTV2 received an additional 17.5 Gy, to a cumulative dose of 70 Gy in 28 fractions. Either a passive scatter or pencil beam technique, consisting of 2 parallel-opposed proton treatments, was used for all patients.

Treatment plans were selected based on the completeness of coverage and homogeneity within the CTV and avoidance of normal structures. Dose constraints used for treatment planning can be seen in Supplementary Materials (available at https://doi.org/10.1016/j.ijrobp.2019.05.069).

Sixteen and 28 patients had minor deviations (<5%) on bladder V61 and rectum V61 dose constraints, respectively. Five and 2 patients had minor deviations (<5%) for global maximum dose of 72.1 Gy in the bladder and rectum, respectively. Orthogonal kilovoltage imaging with alignment on implanted intraprostatic gold fiducial markers was used for daily image-guided treatment delivery. To minimize treatment delivery uncertainties, patients requiring significant shifts on the treatment table had CT verification scans to assess bladder and rectal positioning.

Clinical assessment

Toxicities were prospectively scored by GU radiation oncology nurses using Common Terminology Criteria for Adverse Events, version 4.0, weekly during treatment, 1 month after treatment, and at 3-month to 6-month follow-up visits thereafter. Acute toxicities were defined as occurring within 90 days after completion of radiation therapy. In addition to a toxicity evaluation, follow-up visit included a complete history and physical examination, prostate-specific antigen (PSA) laboratory draw, and completion of the International Prostate Symptom Score (IPSS) survey, International Index of Erectile Function (IIEF-5) questionnaire, and Expanded Prostate Cancer Index Composite (EPIC) questionnaire. Results from these surveys and questionnaires were compared with baseline results.

Biochemical-clinical failure (BCF) was defined as the first occurrence of clinical failure (local recurrence, regional recurrence, or distant metastasis) or biochemical failure by the Phoenix definition (PSA $\geq$ 2 ng/mL over the nadir PSA). At the time of BCF, patients typically underwent magnetic resonance imaging pelvis, bone scan, or radionuclide scan for identification of sites of active disease.

Statistical analysis

All statistical tests were based on a 2-sided significance level, and a P value of $<$ .05 was considered statistically significant. Fisher exact test, univariate, and multivariate logistic regression were used to determine disease, treatment, and patient-related factors associated with the development of acute and late toxicity. Survival analysis was performed using the Kaplan-Meier method and equality of survival across risk groups was assessed with log-rank test. Generalized estimating equation (GEE) was used to compare patient-reported outcomes based on different patient and disease-associated variables over time. All statistical tests were performed with R version 3.5.2.

Results

Patients

As shown in Table 1, the 184 men enrolled on the institutional review board–approved protocol had low- (n = 18), favorable intermediate- (n = 78), and unfavorable intermediate-risk (n = 88) PC. Forty-eight percent of men with unfavorable intermediate-risk disease received ADT, with a median duration of 6 months (range, 4-9 months). A significant proportion of men across all 3 risk groups had other comorbidities, including heart disease (27%) and diabetes (16%). Given the limited exclusion criteria for the present study, patients on anticoagulation (18%) and with prior transurethral resection of prostatic tissue (TURP; 7%) were also represented.

Table 1 Patient and disease characteristics

	Low risk	Favorable intermediate risk	Unfavorable intermediate risk
	n = 18	n = 78	n = 88
	No. (Range or %)	No. (Range or %)	No. (Range or %)
Median age	64 (53-75)	67 (50-80)	68 (50-83)
Clinical stage			
T1c	16 (89)	67 (86)	69 (78)
T2a	2 (11)	10 (13)	12 (14)
T2b	0 (0)	1 (1)	7 (8)
PSA			
<10	18 (100)	69 (88)	64 (73)
≥10 but <20	0 (0)	9 (12)	24 (27)
Gleason Score			
6 (3 + 3)	18 (100)	8 (10)	4 (5)
7 (3 + 4)	0 (0)	70 (90)	38 (43)
7 (4 + 3)	0 (0)	0 (0)	46 (52)
Race			
White	14 (78)	64 (82)	61 (69)
Black	1 (6)	9 (12)	18 (21)
Other	3 (17)	5 (6)	9 (10)
ADT			
Yes	0 (0)	5 (6)	42 (48)
Smoking history			
Active	2 (11)	6 (8)	12 (14)
Former	7 (39)	38 (49)	35 (40)
No	9 (50)	34 (43)	41 (46)
Blood thinner use			
Yes	2 (11)	14 (18)	18 (21)
History of TURP			
Yes	4 (22)	4 (5)	5 (6)
Heart disease			
Yes	6 (33)	22 (28)	21 (24)
Diabetes			
Yes	5 (28)	8 (10)	16 (18)

Abbreviations: ADT = androgen deprivation therapy; TURP = transurethral resection of the prostate.

Biochemical-clinical failure

Median follow-up was 49.2 months (interquartile ratio, 27.6-73.2). Overall 4-year BCF-free survival was 93.5% (95% confidence interval [CI], 89%-98%). Four-year BCF-free survival for low-, favorable intermediate-, and

unfavorable intermediate-risk cohorts were 94.4% (89%-100%), 92.5% (86%-100%), and 93.8% (88%-100%) (log-rank $P > .4$), as seen in Figure 1A. Median time to BCF was 51 months (range, 18-86 months).

Four patients with BCF had no evidence of active disease on subsequent imaging workup, as seen in Table 2. One patient had evidence of recurrent disease within the prostate gland and metastatic disease in bones at the time of BCF and was started on ADT. Three patients with BCF had evidence of isolated disease in the prostate gland and had normal prostate biopsy results, with no indication of prostate adenocarcinoma. Two of these patients had salvage brachytherapy with ADT, whereas the other had salvage cryoablation and irreversible electroporation with ADT. All 3 patients treated with local salvage therapy are alive and with no evidence of disease.

Overall survival

Overall survival at 4 years was 95.8% (92%-100%), as seen in Figure 1B. There was no statistically significant difference in overall survival by risk group (log-rank $P > .7$). All 5 deaths were unrelated to PC and instead attributable to

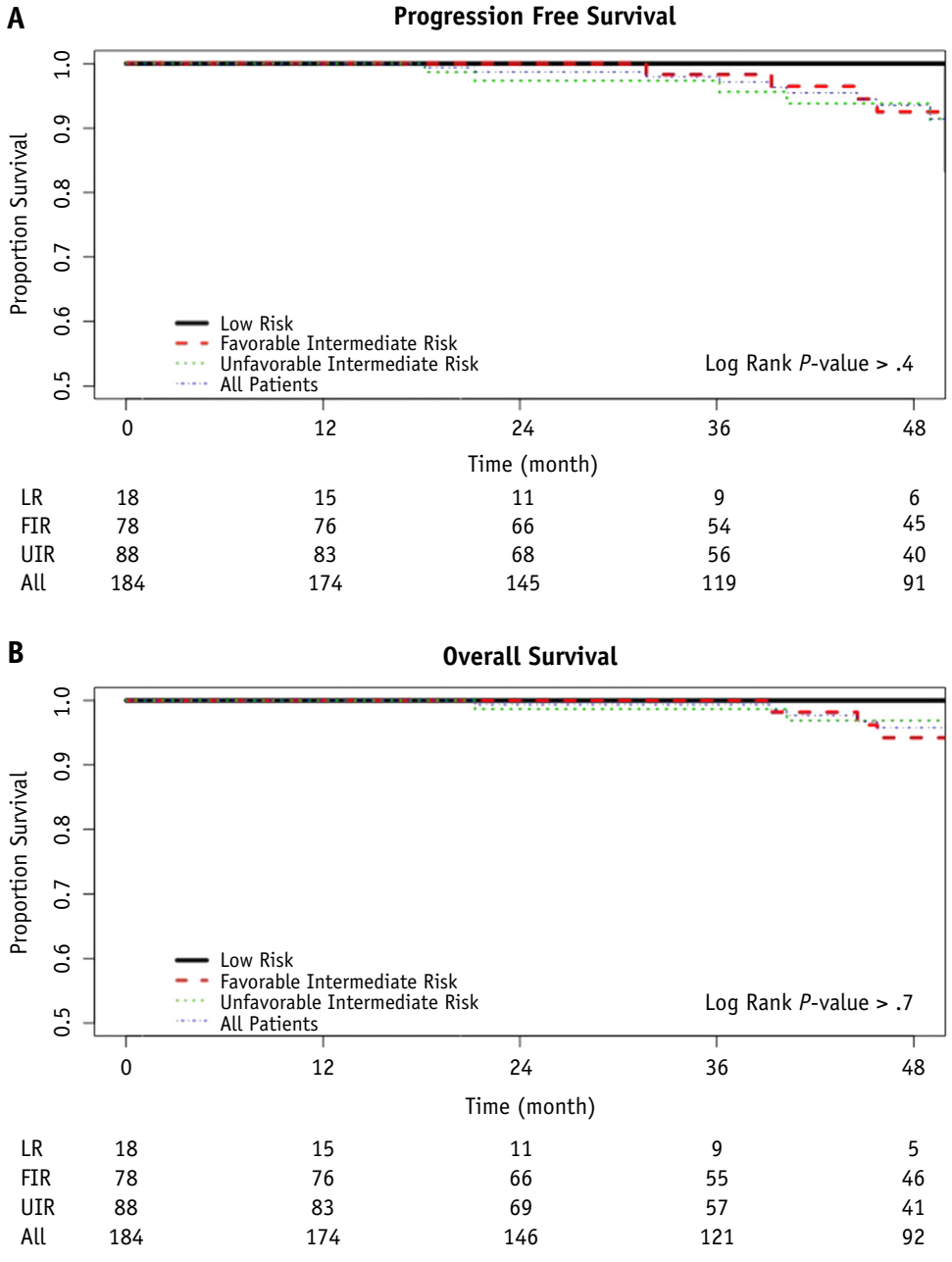

Fig. 1. (A) Progression-free survival. (B) Overall survival. *Abbreviations:* FIR = favorable intermediate risk; LR = low risk; UIR = unfavorable intermediate risk.

Table 2 Patterns of failure

Type of progression	Low risk n = 18 No. (%)	Favorable intermediate risk n = 78 No. (%)	Unfavorable intermediate risk n = 88 No. (%)
PSA failure with normal prostate biopsy results	1 (6)	1 (1)	1 (1)
PSA failure with normal prostate biopsy results and distant metastatic disease	0 (0)	0 (0)	1 (1)
PSA failure without radiographic evidence of disease	0 (0)	0 (0)	4 (5)

Abbreviation: PSA = prostate-specific antigen.

lung, esophageal, and neuroendocrine cancers; Lewy body dementia; and heart disease.

Acute toxicity

The incidence of acute Common Terminology Criteria for Adverse Events version 4.0 grade 2 or higher gastrointestinal (GI) and urologic toxicities were 3.8% (7 events) and 12.5% (23 events), respectively. Only one acute grade 3 GI toxicity was reported, in a patient who experienced profuse diarrhea and received a diagnosis of *Clostridium difficile* infection. The most common acute grade 2 GI and urologic toxicities were diarrhea (4 of 6 events) and urinary frequency (17 of 23 events).

Late toxicity

The estimated cumulative 4-year incidence of late grade 2 or higher GI toxicity was 13.6% (25 events; 95% CI, 9%-20%), as seen in Table 2. Most late toxicities occurred within the first 2 years after proton therapy, as seen in Figure 2. The one late grade 3 GI toxicity occurred in a patient on clopidogrel who was admitted for hematochezia 15 months after radiation. The patient was found to have radiation proctitis and had complete resolution of hematochezia after Argon beam coagulation. The predominant late grade 2 GI toxicity was rectal bleeding, accounting for 79% of the 24 events. All late grade 2 GI events were transient.

The estimated cumulative 4-year incidence of late grade 2 or higher urologic toxicity was 7.6% (14 events; 95% CI, 4%-13%), with no grade 3 or 4 events reported. Urinary frequency was the most common grade 2 urologic toxicity, accounting for 57% of the events. All late grade 2 urologic toxicities resolved, with a median time to resolution of 6 months.

On univariate logistic regression, seen in Table 3, a history of diabetes was associated with the development of a late grade 2+ urologic toxicity ($P = .04$); anticoagulation use ($P < .01$), a history of heart disease ($P = .04$), and Charlson Comorbidity Index ($P = .01$) were associated with the development of a late grade 2+ GI toxicity. On multivariate logistic regression, diabetes, heart disease and Charlson Comorbidity Index were no longer found to be independent predictors for late toxicity, and anticoagulation use remained the only independent predictor for the development of a late GI toxicity ($P < .01$). Prostate volume and radiation dose to rectum and bladder were not significantly associated with the development of late grade 2+ urologic or GI toxicity, as seen in Table 4 and Supplementary Material (available at https://doi.org/10.1016/j.ijrobp.2019.05.069).

Patient-reported outcomes with IPSS, IIEF-5, and EPIC

Patient-reported outcomes were available for 175, 139, 104, 81, and 48 patients at baseline, 1, 2,3, and 4 years after

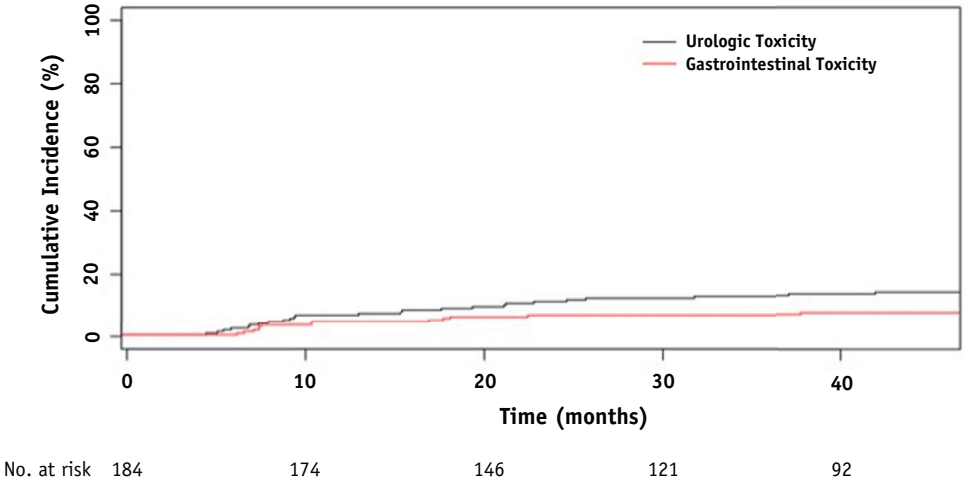

Fig. 2. Cumulative grade 2+ urologic and gastrointestinal toxicity.

Table 3 Late urologic and gastrointestinal toxicity

Late toxicity			
Urologic		Gastrointestinal	
Toxicity	No. of patients (%)	Toxicity	No. of patients (%)
Grade 2		Grade 2	
Frequency	8 (4)	Rectal bleeding	13 (7)
Urgency	3 (2)	Proctitis	10 (5)
Dysuria	1 (0.5)	Diarrhea	1 (0.5)
Cystitis	1 (0.5)	Grade 3	
Obstruction	1 (0.5)	Rectal bleeding	1 (0.5)

treatment, respectively. Median IPSS before treatment and at 1, 2, 3, and 4 years after treatment were 8.1, 8.1, 8.3, 8.8, and 8.9, respectively ($P > .9$). On GEE analysis, as seen in Table 5, age was associated with an increase in IPSS score by 0.21 points for every additional year of age ($P < .01$). In addition, patients who received ADT had a significant rise in IPSS over time, independent of years from the completion of PT ($P < .01$).

Median IIEF-5 before treatment and at 1, 2, 3, and 4 years after treatment were 15.8, 12.9, 12.3, 14.3, and 13.1, respectively ($P > .83$). On GEE, age was associated with worsening IIEF-5 score by −0.40 points for each additional year of age ($P < .001$). Diabetes and receipt of ADT were other independent variables found to be associated with worsening IIEF-5 score over time ($P = .02$ and $P < .01$, respectively).

Changes in EPIC scores in the domains of urinary incontinence, urinary irritation, bowel, sexual, and hormonal health can be visualized in Figure 3. All domains had decreases at 1 year after HFPT; however, over 4 years of follow-up there were no statistically significant rises or falls in scores in all domains, as seen in Table 5. On GEE analysis, increased age was associated with declines in the domains of urinary incontinence, urinary irritation, and sexual health. Patients on anticoagulation had worse EPIC bowel scores over time compared with patients not on anticoagulation ($P < .01$). A history of a TURP was associated with worse urinary incontinence ($P = .01$) but did not predict for worse IPSS scores over time ($P = .29$). Patients who received ADT had worse scores in the sexual and hormonal domains over time ($P = .01$ and .05, respectively). When corrected for ADT use, patient risk group had no impact on worsening scores for IPSS, IIEF, and EPIC sexual and hormonal scores.

Discussion

To the best of our knowledge, this is the first study to report objective- and patient-reported acute- and long-term outcomes of low- and intermediate-risk PC patients treated with moderately HFPT on a prospective protocol with broad eligibility criteria. Prior studies of HFPT have shown the feasibility of delivering higher dose per fraction schedules.[14,15] Nakajima et al[16] presented the acute toxicity profile of 60 to 63 Gy in 20 to 21 fractions of PT for low- and intermediate-risk prostate cancer. Delayed and chronic adverse outcomes are of even greater interest when using HF regimens, but late toxicity assessments were not reported given the limited follow-up. Regarding acute toxicity, no grade 2+ GI toxicity was identified; however, there was a 5.9% incidence of acute 2+ genitourinary toxicity. The rate of acute grade 2+ toxicities was likely underreported by Nakajima et al[16] because diarrhea was not accounted for in treatment-related toxicity. In comparison, in the present analysis, 86% of all acute grade 2+ GI toxicities were due to diarrhea.

Other trials of HFPT have used more stringent eligibility criteria. Henderson et al[17] reported their prospective experience of 70 to 72.5 Gy in 28 to 29 fractions. Patients were enrolled from 2008 to 2011 and therefore did not receive ADT in the management of unfavorable intermediate-risk prostate cancer, as is typically done in the contemporary management of such patients.[1] As such, patients with unfavorable intermediate-risk disease had a lower freedom from biochemical and clinical progression compared with our study. The incidence of late grade 2 rectal bleeding (11%) was similar to that found in the present analysis (10.5%). In our study a statistically significant association was found between anticoagulation use and the development of a late grade 2 rectal bleed. Exclusion criteria on the trial by Henderson et al[17] prevented patients on anticoagulation from enrolling, thereby potentially decreasing the rate of grade 2 GI toxicity. Similarly, patients with a prostate volume >60 cm^3, IPSS > 15, with diabetes, or a history of TURP were excluded from Henderson et al[17] but permitted in our trial.

Our finding of anticoagulant use as an independent predictor for late grade 2+ GI toxicity is similar to that reported by Hamstra et al.[18] In their analysis of predictors of late rectal toxicity in patients who received dose escalated radiation therapy, the use of anticoagulants was found to independently increase the risk of grade 2+ rectal toxicity. Unlike their study, we did not find Charlson Comorbidity Index, a history of heart disease, and age as independent predictors for late grade 2+ GI toxicity. In an effort to reduce the probability of high radiation doses falling into the rectal tissue, the 2 proton beams were arranged in an opposed lateral fashion. This allowed for the distal penumbra to fall in the soft tissues on the lateral borders of the prostate gland. Dose deposition in the anterior wall of the rectum was attributed to the lateral penumbra of the proton beam, for which there is no range uncertainty association.

Patient-reported outcomes in the present study offer insight into long-term quality-of-life domains after HFPT, an important piece of information missing from the limited body of literature on HFPT. Patients noted little change in urinary incontinence, irritation, and bowel function, as reflected in IPSS and EPIC scores. As expected with the

Table 4 Univariate and multivariate analysis on late grade 2 urologic and gastrointestinal toxicity

	All patients with grade 2+ urologic toxicity		All patients with grade 2+ GI toxicity	
	No. of patients (%)	Fisher exact test *P*	No. of patients (%)	Fisher exact test *P*
Diabetes				
No	9/155 (6)	.05	18/155 (12)	.08
Yes	5/29 (17)		7/29 (24)	
Heart disease				
No	10/135 (7)	1	14/135 (10)	.05
Yes	4/49 (8)		11/49 (22)	
Smoking history				
No	4/84 (5)	.27	13/84 (15)	.52
Yes	10/100 (10)		12/100 (12)	
Anticoagulation use				
No	12/150 (8)	1	11/150 (7)	<.01
Yes	2/34 (6)		14/34 (41)	
ADT use				
No	8/137 (6)	.2	18/137 (13)	.81
Yes	6/47 (13)		7/47 (15)	
History of TURP				
No	14/171 (8)	.6	25/171 (15)	.22
Yes	0/13 (0)		0/13 (0)	
Risk group				
Low risk	2/18 (11)	.43	0/18 (0)	.21
Favorable intermediate risk	4/78 (5)		11/78 (14)	
Unfavorable intermediate risk	8/88 (9)		14/88 (16)	
Univariate logistic regression				
	Estimated effect (CI)	*P*	Estimated effect (CI)	*P*
Age	−0.02 (−0.09 to 0.06)	.67	0.04 (−0.02 to 0.10)	.25
CCI	0.19 (−0.16 to 0.49)	.19	0.35 (0.09-0.62)	.01
Prostate volume	−0.003 (−0.04 to 0.04)	.87	0.01 (−0.02 to 0.05)	.35
Diabetes	1.22 (0.15-2.29)	.04	0.88 (−0.15 to 1.84)	.07
Heart disease	0.11 (−0.89 to 1.11)	.86	0.92 (0.03-1.79)	.04
Anticoagulation use	−0.33 (−0.93 to 0.27)	.67	2.18 (1.27-3.12)	<.01
Multivariate logistic regression				
	Estimated effect (CI)	*P*	Estimated Effect (CI)	*P*
CCI	0.14 (−0.29 to 0.47)	.44	0.26 (−0.04 to 0.59)	.10
Diabetes	1.13 (−0.22 to 2.42)	.09	0.48 (−0.78 to 1.66)	.43
Heart disease	−0.23 (−1.63 to 0.99)	.72	0.66 (−0.37 to 1.67)	.20
Anticoagulation use	−0.42 (−2.34 to 0.99)	.61	2.16 (0.49-4.40)	<.01

Abbreviations: ADT = androgen deprivation therapy; CCI = Charlson Comorbidity Index; CI = confidence interval; GI = gastrointestinal; TURP = transurethral resection of the prostate.

administration of short-term ADT, an initial decline in quality-of-life in the EPIC hormonal domain was noted, which resolved at the time of 3-year follow-up. This change in score within the hormonal domain can be considered to be clinically relevant, as defined by the minimally important difference (decline in hormonal score by 4-6 points) by Skolarus et al.[19] Among all 35 patients meeting the minimally important difference, 33 received ADT. No other domains met the defined cutoffs for minimally important difference for EPIC scores. Although not meeting the definition of minimally important difference, the quality-of-life affected by sexual function dropped in patients who received ADT and did not return to baseline at 4-year follow-up. Although more often occurring in patients after cessation of long-term ADT, protracted effects on sexual functioning are possible in some men even after short-term ADT and likely reflect slow testosterone recovery.[20,21]

Our patient-reported outcomes are similar to those reported in other studies of outcomes after CFPT for prostate cancer. Gray et al[22] found similar immediate declines in EPIC urinary incontinence and irritation after prostate

Table 5 GEE analysis

	IPSS		IIEF		EPIC Urinary Incontinence		EPIC Urinary Irritation		EPIC Bowel		EPIC Sexual		EPIC Hormonal	
	Estimate	*P*	Estimate	*P*	Estimate	*P*	Estimate	*P*	Estimate	*P*	Estimate	*P*	Estimate	*P*
Years from PT	0.01	.97	−0.99	.83	3.51	<.01	−1.04	.29	−0.29	.73	−2.88	.08	−2.15	.48
Age*	0.21	<.01	−0.40	<.001	−0.29	.04	−0.42	.01	−0.03	.68	−0.58	.03	−0.28	.34
Smoking History*	2.53	.14	1.57	.22	0.17	.94	−1.74	.44	−0.34	.77	0.59	.88	4.40	.29
CCI*	0.94	.02	−0.75	.13	0.14	.87	−0.07	.92	−0.23	.73	−1.47	.39	1.33	.40
Heart disease*	1.31	.21	−2.04	.13	0.42	.85	0.37	.87	−2.29	.12	−0.92	.83	−1.78	.91
Anticoaguation use*	2.77	.09	1.56	.28	−4.34	.17	−7.75	.07	−5.42	<.01	−6.63	.19	−5.34	.66
Diabetes*	0.41	.79	−3.54	.02	0.97	.72	−1.06	.75	−1.53	.38	−5.29	.34	−3.75	.47
History of TURP*	−1.77	.29	−4.04	.50	4.87	.01	4.07	.08	1.09	.48	2.91	.70	18.53	.40
Prostate volume*	0.11	.29	−0.02	.98	0.00	.96	−0.01	.88	−0.04	.30	−0.18	.19	0.23	.17
ADT use*	1.91	.01	−4.68	<.01	−4.58	.11	−2.90	.35	−0.16	.90	−11.22	.01	−15.32	.05
Risk group*,†	3.21	.04	−0.59	.01	−4.41	.31	−7.98	.21	−3.90	.31	−11.89	.02	−18.78	.04
Risk group adjusted*,‡	2.29	0.35	−0.29	.11	−6.58	.29	−6.88	.41	−3.43	.52	−14.43	.25	−22.80	.38

Abbreviations: ADT = androgen deprivation therapy; CCI = Charlson Comorbidity Index; CI = confidence interval; EPIC = Expanded Prostate Cancer Index Composite questionnaire; GEE = generalized estimating equation; GI = gastrointestinal; IEFF = International Index of Erectile Function questionnaire; IPSS = International Prostate Symptom Score survey; TURP = transurethral resection of the prostate.

* Adjusted for years out from proton therapy.

† 0 = low-risk, 1 = favorable intermediate risk, 2 = unfavorable intermediate risk

‡ Risk group adjusted for ADT use.

radiation in their patients who received CFPT. At 2- year follow-up, their patients treated with CFPT and photons all had persistently lowered EPIC bowel scores, unlike our patients who had a return to baseline in EPIC bowel score. Such a return to baseline EPIC bowel scores were similarly reported by Hoppe et al[23] in 1243 patients who received CFPT for localized prostate cancer and had EPIC scores recorded for 24 months of follow-up.[23] Pugh et al[24] used EPIC scores at nonstandardized intervals in 423 men treated with CFPT to show normalization of EPIC urinary irritation scores, similar to our findings. They, however, found no return to baseline in the domains of urinary

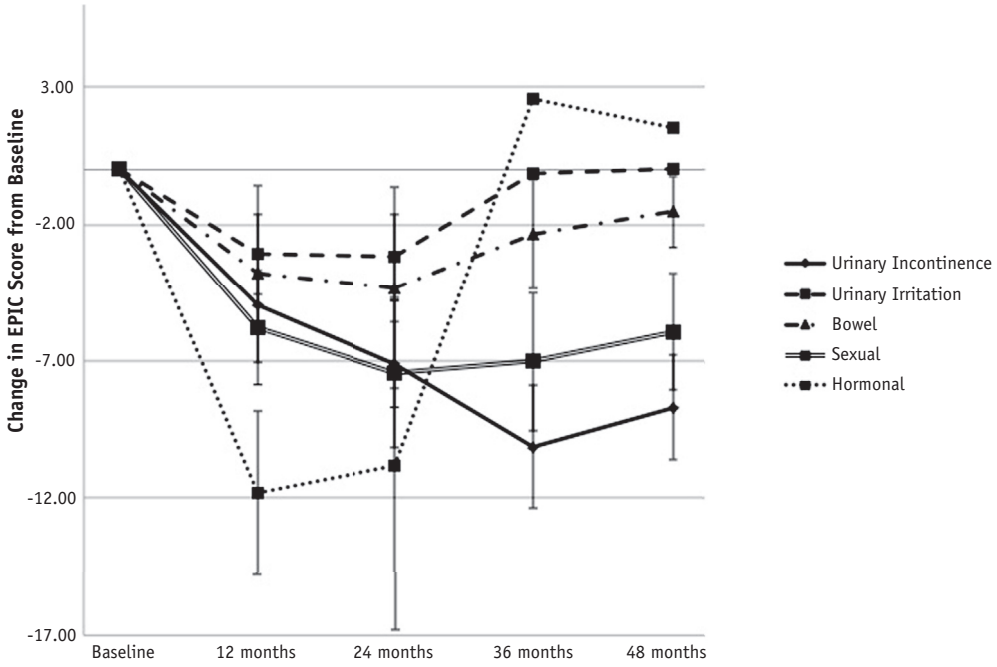

Fig. 3. Change in Expanded Prostate Cancer Index Composite scores for patients.

incontinence and bowel health. Compared with these studies, our patient-reported outcomes were collected at standardized time intervals and have a longer median follow-up period (48 months vs 24 months).

The rates of late toxicities seen in this phase II study of HFPT are similar to other studies of hypofractionated IMRT. In the CHHiP (Conventional or Hypofractionated High Dose Intensity Modulated Radiotherapy for Prostate Cancer) trial 7% to 12% and 11% to 12% of patients experienced late grade 2+ urologic and GI toxicity, respectively.[8] The NRG trial reported late grade 2+ urologic and GI toxicities in 26% and 18% of patients.[7] Similarly, PROFIT (Prostate Fractionated Irradiation Trial) reported late grade 2+ urologic and GI toxicities in 9% and 22% of patients.[10] Rates of 5-year BCF in these trials (85%-91%) are comparable to the 4-yr BCF in this study (93.5%). The rates of acute and late GI and genitourinary toxicity in this study of HFPT are also similar to those reported by Fang et al[12] for a cohort of patients who received CFPT. In their study, patients who received CFPT had acute grade 2+ GI and urologic toxicity rates of 4.3% and 21.3%, respectively, and late grade 2+ GI and urologic toxicity rates of 9.7% and 11.8%.

Patients with localized prostate cancer who have the option to receive HFPT often have surgical options as well. Although the present study does not compare prostatectomy to HFPT, prior publications have reported higher rates of urinary leakage and erectile dysfunction after open and robotic prostatectomy compared with conventionally fractionated external beam radiation therapy.[25-27] Given the similar toxicity profile between HF and conventionally fractionated radiation regimens reported in randomized trials of photon radiation and single arm studies of CFPT, it is possible that HFPT also results in less long-term urinary and sexual bother compared with prostatectomy.[7-9,12] Although quality of life regarding bowel function is often considered to be more greatly impaired after radiation therapy compared with prostatectomy, our study indicates that with modern treatment planning and delivery, bowel quality of life generally remains unchanged years after HFPT. A criticism of radiation therapy in the treatment of prostate cancer is the cost of a 9-week course of treatment, which is estimated to exceed the cost of a robotic prostatectomy.[28] Moderately hypofractionated IMRT has been found to reduce the financial toxicity of radiation therapy by decreasing the number of daily treatments, benefiting payers and patients.[29] Further hypofractionation with larger fraction sizes can be safely delivered with proton therapy given the dosimetric properties of protons.[14,15] Such HFPT regimens further reduce the total treatment package time and can help close the gap in cost between prostatectomy and radiation therapy.

This study is limited by its single arm design of HFPT, without a direct comparison with hypofractionated photon therapy. A randomized trial of hypofractionated therapy comparing these 2 treatment modalities, similar to the PARTIQoL (Proton Therapy vs. IMRT for Low or Intermediate Risk Prostate Cancer) trial for conventionally fractionated prostate radiation therapy, would allow for a direct comparison between proton and photon therapy.[30] In addition, as reflected by our patient's baseline IPSS and EPIC scores, our patients were relatively asymptomatic from a urinary standpoint. However, patients with preexisting urinary symptoms may have higher rates of late urologic toxicity, and as a result, our rates of late toxicity may not be reflective of patients with higher baseline IPSS scores.[12] However, our study was inclusive of patients with significant comorbidities and allowed for the enrollment of patients with a history of TURP and is the first to detail the outcomes of such patients after HPFT.

Conclusions

In conclusion, early results from HFPT for the treatment of PC indicate low rates of transitory urologic and GI toxicity and low posttreatment rates of patient-reported urinary, bowel, hormonal, and sexual bother, with favorable disease control. The results from this trial are similar to series of standard fractionated proton therapy. Ongoing analyses are warranted to assess long-term toxicity and understand differences between proton and photon hypofractionated radiation therapy in the treatment of organ-confined PC.

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