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Original Article

Comparative Toxicity Outcomes of Proton-Beam Therapy Versus Intensity-Modulated Radiotherapy for Prostate Cancer in the Postoperative Setting

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BACKGROUND: Despite increasing utilization of proton-beam therapy (PBT) in the postprostatectomy setting, no data exist regarding toxicity outcomes relative to intensity-modulated radiotherapy (IMRT). The authors compared acute and late genitourinary (GU) and gastrointestinal (GI) toxicity outcomes in patients with prostate cancer (PC) who received treatment with postprostatectomy IMRT versus PBT. **METHODS:** With institutional review board approval, patients with PC who received adjuvant or salvage IMRT or PBT (70.2 gray with an endorectal balloon) after prostatectomy from 2009 through 2017 were reviewed. Factors including combined IMRT and PBT and/or concurrent malignancies prompted exclusion. A case-matched cohort analysis was performed using nearest-neighbor 3-to-1 matching by age and GU/GI disorder history. Logistic and Cox regressions were used to identify univariate and multivariate associations between toxicities and cohort/dosimetric characteristics. Toxicity-free survival (TFS) was assessed using the Kaplan-Meier method. **RESULTS:** Three hundred seven men (mean ± SD age, 59.7 ± 6.3 years; IMRT, n = 237; PBT, n = 70) were identified, generating 70 matched pairs. The median follow-up was 48.6 and 46.1 months for the IMRT and PBT groups, respectively. Although PBT was superior at reducing low-range (volumes receiving 10% to 40% of the dose, respectively) bladder and rectal doses (all P ≤ .01), treatment modality was not associated with differences in clinician-reported acute or late GU/GI toxicities (all $P \geq .05$). Five-year grade ≥2 GU and grade ≥1 GI TFS was 61.1% and 73.7% for IMRT, respectively, and 70.7% and 75.3% for PBT, respectively; and 5-year grade ≥3 GU and GI TFS was >95% for both groups (all P ≥ .05). **CONCLUSIONS:** Postprostatectomy PBT minimized low-range bladder and rectal doses relative to IMRT; however, treatment modality was not associated with clinician-reported GU/GI toxicities. Future prospective investigation and ongoing follow-up will determine whether dosimetric differences between IMRT and PBT confer clinically meaningful differences in long-term outcomes. *Cancer* 2019;0:1-16. © 2019 American Cancer Society.

KEYWORDS: adjuvant radiation, gastrointestinal toxicity, genitourinary toxicity, intensity-modulated radiation therapy, postoperative radiation, prostate cancer, proton therapy, salvage radiation.

INTRODUCTION

Prostate cancer (PC) is the most common nondermatologic malignancy among men in the United States, with approximately 164,690 estimated new cases in 2018.[1] In the postprostatectomy setting, contemporary guidelines recommend consideration of adjuvant radiotherapy (RT) for patients with positive margins or pathologic T3 disease and salvage RT for biochemical or clinical recurrence.[2] Although intensity-modulated RT (IMRT) is widely regarded as standard of care in postprostatectomy RT, proton-beam therapy (PBT) is becoming increasingly prevalent.[3,4] Proponents of PBT cite its dosimetric advantages, which are intended to minimize radiation to normal tissues of nearby organs at risk (OARs).[5] Mainly retrospective reports exist in the intact setting, reporting small advantages to PBT with respect to genitourinary (GU) and gastrointestinal (GI) toxicity; however, these studies are limited

by confounding and misclassification bias.[6,7] One case-matched analysis demonstrated that, when compared to IMRT, definitive treatment of PC with PBT was not associated with significant differences in acute or late GU/GI toxicities—although a shorter median follow-up of 29 months post-PBT limited the assessment of long-term toxicities.[8]

Relative to the intact setting, literature on postprostatectomy PBT is sparse. We recently reported 2-year GU/GI toxicity outcomes of patients treated with postprostatectomy PBT, demonstrating its safety and feasibility.[9] However, no data exist to date directly comparing the dosimetric characteristics or toxicity profiles of PBT with those of IMRT in the postprostatectomy setting. To assess whether the dosimetric features of these distinct radiation modalities are associated with differences in subsequent toxicities, we performed a comparative case-matched cohort analysis of GU/GI toxicity outcomes in patients with PC who underwent postoperative IMRT versus PBT.

MATERIALS AND METHODS

Retrospective Review

We conducted a retrospective review of all patients with histologically proven prostate adenocarcinoma who received adjuvant or salvage IMRT or PBT to the prostate bed after radical prostatectomy between January 1, 2009 and December 31, 2017. Patient information was directly pulled from the electronic medical record by the Clinical Registry Program Manager of the Abramson Cancer Center at the University of Pennsylvania. To qualify for study inclusion, patients were required to have provider-reported toxicity data that were prospectively collected as part of either our departmental program registry or a clinical protocol. No retrospectively collected toxicity data were included in this study.

Patients were excluded if they: 1) had received combined IMRT and PBT, 2) had other concurrent malignancies, or 3) had an incidental PC diagnosis after cystoprostatectomy for bladder cancer. Final recommendations regarding modality were based on oncologic/anatomic suitability, patient preference, scheduling needs, machine availability, and insurance coverage. All protocols were approved before study initiation by the University of Pennsylvania Institutional Review Board.

RT Planning and Technique

Bowel and bladder preparation, patient immobilization, endorectal balloon placement, computed tomography (CT) simulation, clinical target volume (CTV) and OAR delineation, IMRT and PBT treatment planning, and daily image-guided RT were conducted as previously described.[9-12] In brief, for either treatment modality, patients were instructed on adequate presimulation bowel and bladder preparation, ie, dietary recommendations, anti-gas medications, 2 self-administered enemas with the goal of achieving an empty rectum, and drinking at least 500 mL of water 20 to 30 minutes before simulation with the goal of achieving a full bladder. During treatment, daily enemas were not required, but patients were instructed to ensure an empty rectum and full bladder before treatments. At the time of simulation and treatment, patients were immobilized in the supine position using Knee and Foot-Lok cushions (CIVCO), and an indexed lumen 9-cm endorectal balloon (RadiaDyne, LLC), which was placed into the rectum and inflated with 100 mL of water. Patients were simulated using a CT simulator (Siemens), with 1.5-mm slice thickness obtained at the level of the prostate bed and the isocenter placed in the center of the prostate bed.

For each patient, the CTV was contoured as the prostate bed according to Radiation Therapy Oncology Group guidelines. Planning target volumes (PTVs) were 10-mm, uniform expansions to the CTV, except posteriorly, where they expanded to 6 mm. The OARs evaluated included bladder, rectum, in-field rectum (rectum 1 cm above and below the CTV), and anterior rectal wall (3 mm of anterior rectal wall circumference). For postprostatectomy patients who required adjuvant or salvage RT without gross residual disease, the total prescribed dose to the CTV generally ranged from 66.0 to 70.2 gray (Gy) (relative biologic effectiveness [RBE]) in 1.8-Gy to 2.0-Gy fractions. The RBE for all proton dose distributions was considered to be 1.1. Further details regarding prescription dose and institutional dose constraints for patients requiring adjuvant or salvage RT postprostatectomy are summarized in Supporting Tables 2A and 2B. In select circumstances, OAR dose variations were allowed if they were consistent with dose level 3 of Radiation Therapy Oncology Group study 9406 or were within 5% of institutional constraints. Centralized review of dose-volume histogram parameters was performed for all patients.

IMRT and PBT plans were created using Eclipse Treatment Planning (Varian Medical Systems). IMRT plans consisted of 7 to 9 coplanar fields (with 4 or more posterior oblique fields traversing the rectum), using 6-megavolt (MV) and/or 15-MV photon beams, or volumetric-modulated arc therapy using two 6-MV coplanar arcs, all treated on Varian linear accelerators (Varian 2300IX; Varian Medical Systems). In patients

treated with PBT, radiation was delivered for most using the pencil-beam scanning technique, consisting of 2 parallel-opposed fields. A margin of 3.5% of the beam's range in the direction of the beam was applied to correct for proton beam range uncertainty when converting from Hounsfield units to proton stopping power, with another 1-mm margin allowing for beam calibration uncertainty. Pencil-beam scanning target volumes were generated for treatment planning optimization. Image-guided RT was used to ensure setup accuracy, with daily cone-beam CT or kV-kV imaging for patients who received IMRT, and daily kV-kV imaging for those who received PBT, matched to the endorectal balloon with 10 mL of diluted contrast filling for alignment of CTV and anterior rectal wall.

Clinical Assessment

Baseline patient-reported GU, GI, and erectile functions were scored using the International Prostatic Symptom Scale (IPSS), the Expanded Prostate Cancer Index Composite-derived Bowel Symptom Score (EPIC-BASS), and the International Index of Erectile Function, respectively. All associated toxicities were prospectively scored by GU providers weekly during radiation, 1 month post-treatment, and at 3-month to 6-month intervals thereafter using the Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0. Discrepancies between CTCAE scores and qualitative provider descriptions were resolved case-by-case through manual chart review and random audits to ensure accuracy. Because of low rates of grade ≥2 GI toxicities (Table 1), grade 1 GI toxicities were included to improve detection of differences between modalities. Follow-up was completed through August 2018. Median follow-up from treatment initiation was 48.6 months (range, 2.1-117.4 months) for IMRT and 46.1 months (range, 13.4-76.3 months) for PBT.

Study Design

Our primary objective was to compare rates of acute and late GU and GI toxicity in patients who received either IMRT or PBT. A case-matched cohort approach was used to help minimize the impact of confounders and patient selection bias. By using the MatchIt routine (R Foundation for Statistical Computing), we performed 3-to-1 nearest neighbor matching for age at diagnosis (±5 years) and GU/GI disorder history, given the association of pre-RT symptoms with related toxicities.[13] Seventy matches across 267 patients (70 patients who received PBT and 197 who received IMRT) were generated.

Our statisticians were blinded to toxicity outcomes during the matching process.

Statistical Analysis

Patient characteristics and GU/GI toxicity frequencies were reported using descriptive statistics. Differences were compared between treatment groups using the Wilcoxon rank-sum test and the Pearson chi-square test for continuous and categorical variables, respectively. Conditional logistic regression identified associations between acute and late GU and GI toxicities, patient and disease characteristics, and dosimetric parameters. Variables with univariate associations ($P < .10$) were considered in multivariate models using either all selected variables or forward-stepwise variable selection. Associations between specific toxicities and given variables were measured using odds ratios (ORs) and 95% CIs. Toxicity-free survival (TFS) curves were estimated using the Kaplan-Meier method with events of interest as late grade ≥2 GU or grade ≥1 GI toxicity, starting 90 days post-treatment. P values <.05 were statistically significant. Patients without late grade ≥2 GU or grade ≥1 GI toxicity were censored at date of last follow-up. Most patients in the IMRT (>93%) and the PBT (>95%) groups had complete prospective toxicity data (Table 1). Patients with missing GU/GI toxicity data were excluded from univariate analyses (UVAs) and multivariate analyses (MVAs). Statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc) and Stata version 15 (StataCorp).

RESULTS

Patient and Disease Characteristics

In the prematched cohort, patients who received PBT had higher pathologic tumor (T) classification (≥T2; $P = .01$) and a greater frequency of positive margins ($P = .003$). There were no significant differences in age, concurrent androgen-deprivation therapy (ADT), history of GU or GI disorders, comorbidities (ie, hypertension, diabetes mellitus), or lymph node positivity between treatment groups (see Supporting Table 1). In the matched cohort, there were no significant differences with respect to matching variables (age and GU/GI disorder history) and pathologic T classification; however, patients in the PBT group still had higher rates of positive margins ($P = .02$) (Table 2). In addition, there were significant differences for several nonmatching variables: patients in the IMRT group had higher preoperative PSA levels (IMRT, 9.3 ± 8.6 ng/mL; PBT, 6.7 ± 5.4 ng/mL;

TABLE 1. Summary of Toxicity Outcomes

| Toxicity Onset | Outcome | No. of Patients (%) | | | P^a |
		All, n = 267	IMRT, n = 197	PBT, n = 70	
Systemic: Grade ≥2					
Overall					
Acute	No	246 (92.1)	185 (93.9)	61 (87.1)	.117
	Yes	21 (7.9)	12 (6.1)	9 (12.9)	
Late	Unknown	14 (5.2)	11 (5.6)	3 (4.3)	1.000
	No	239 (89.5)	175 (88.8)	64 (91.4)	
	Yes	14 (5.2)	11 (5.6)	3 (4.3)	
Fatigue					
Acute	No	257 (96.3)	190 (96.4)	67 (95.7)	.725
	Yes	10 (3.7)	7 (3.6)	3 (4.3)	
Late	Unknown	14 (5.2)	11 (5.6)	3 (4.3)	.685
	No	245 (91.8)	179 (90.9)	66 (94.3)	
	Yes	8 (3.0)	7 (3.6)	1 (1.4)	
Hot flashes					
Acute	Unknown	15 (5.6)	13 (6.6)	2 (2.9)	.063
	No	243 (91.0)	180 (91.4)	63 (90.0)	
	Yes	9 (3.4)	4 (2.0)	5 (7.1)	
Late	Unknown	39 (14.6)	34 (17.3)	5 (7.1)	.625
	No	223 (83.5)	160 (81.2)	63 (90.0)	
	Yes	5 (1.9)	3 (1.5)	2 (2.9)	
Radiation dermatitis					
Acute	Unknown	5 (1.9)	4 (2.0)	1 (1.4)	.625
	No	262 (98.1)	193 (98.0)	69 (98.6)	
Late	Unknown	21 (7.9)	18 (9.1)	3 (4.3)	1.000
	No	245 (91.8)	178 (90.4)	67 (95.7)	
	Yes	1 (0.4)	1 (0.5)	0 (0.0)	
GU: Grade ≥2					
Overall					
Acute	No	212 (79.4)	154 (78.2)	58 (82.9)	.492
	Yes	55 (20.6)	43 (21.8)	12 (17.1)	
Late	No	170 (63.7)	121 (61.4)	49 (70.0)	.247
	Yes	97 (36.3)	76 (38.6)	21 (30.0)	
Hematuria					
Acute	Unknown	1 (0.4)	1 (0.5)	0 (0.0)	1.000
	No	265 (99.3)	195 (99.0)	70 (100.0)	
	Yes	1 (0.4)	1 (0.5)	0 (0.0)	
Late	Unknown	14 (5.2)	11 (5.6)	3 (4.3)	1.000
	No	253 (94.8)	186 (94.4)	67 (95.7)	
	Yes	0 (0.0)	0 (0.0)	0 (0.0)	
Urinary frequency					
Acute	Unknown	2 (0.7)	2 (1.0)	0 (0.0)	.367
	No	250 (93.6)	182 (92.4)	68 (97.1)	
	Yes	15 (5.6)	13 (6.6)	2 (2.9)	
Late	Unknown	14 (5.2)	11 (5.6)	3 (4.3)	1.000
	No	247 (92.5)	181 (91.9)	66 (94.3)	
	Yes	6 (2.2)	5 (2.5)	1 (1.4)	
Urinary incontinence					
Acute	No	228 (85.4)	166 (84.3)	62 (88.6)	.436
	Yes	39 (14.6)	31 (15.7)	8 (11.4)	
Late	Unknown	14 (5.2)	11 (5.6)	3 (4.3)	.532
	No	219 (82.0)	159 (80.7)	60 (85.7)	
	Yes	34 (12.7)	27 (13.7)	7 (10.0)	
Urinary retention					
Acute	Unknown	1 (0.4)	1 (0.5)	0 (0.0)	.057
	No	262 (98.1)	195 (99.0)	67 (95.7)	
	Yes	4 (1.5)	1 (0.5)	3 (4.3)	
Late	Unknown	14 (5.2)	11 (5.6)	3 (4.3)	1.000
	No	250 (93.6)	184 (93.4)	66 (94.3)	
	Yes	3 (1.1)	2 (1.0)	1 (1.4)	
Urinary tract pain					
Acute	Unknown	1 (0.4)	1 (0.5)	0 (0.0)	.609
	No	261 (97.8)	193 (98.0)	68 (97.1)	
	Yes	5 (1.9)	3 (1.5)	2 (2.9)	
Late	Unknown	14 (5.2)	11 (5.6)	3 (4.3)	.265
	No	252 (94.4)	186 (94.4)	66 (94.3)	
	Yes	1 (0.4)	0 (0.0)	1 (1.4)	

TABLE 1. *Continued*

Toxicity Onset	Outcome	No. of Patients (%)			P^a
		All, n = 267	IMRT, n = 197	PBT, n = 70	
Urinary urgency					
Acute	Unknown	1 (0.4)	1 (0.5)	0 (0.0)	.298
	No	255 (95.5)	186 (94.4)	69 (98.6)	
	Yes	11 (4.1)	10 (5.1)	1 (1.4)	
Late	Unknown	14 (5.2)	11 (5.6)	3 (4.3)	.346
	No	247 (92.5)	180 (91.4)	67 (95.7)	
	Yes	6 (2.3)	6 (3.0)	0 (0.0)	
GI: Grade ≥1					
Overall					
Acute	No	170 (63.7)	119 (60.4)	51 (72.9)	.082
	Yes	97 (36.3)	78 (39.6)	19 (27.1)	
Late	No	199 (74.5)	146 (74.1)	53 (75.7)	.874
	Yes	68 (25.5)	51 (25.9)	17 (24.3)	
Abdominal pain					
Acute	Unknown	6 (2.3)	6 (3.1)	0 (0.0)	.419
	No	242 (90.6)	175 (88.8)	67 (95.7)	
	Yes	19 (7.1)	16 (8.1)	3 (4.3)	
Late	Unknown	14 (5.2)	11 (5.6)	3 (4.3)	1.000
	No	234 (87.6)	172 (87.3)	62 (88.6)	
	Yes	19 (7.1)	14 (7.1)	5 (7.1)	
Bloating					
Acute	No	244 (91.4)	180 (91.4)	64 (91.4)	1.000
	Yes	23 (8.6)	17 (8.6)	6 (8.6)	
Late	Unknown	15 (5.6)	12 (6.1)	3 (4.3)	1.000
	No	236 (88.4)	172 (87.3)	64 (91.4)	
	Yes	16 (6.0)	13 (6.6)	3 (4.3)	
Diarrhea					
Acute	No	226 (84.6)	163 (82.7)	63 (90.0)	.179
	Yes	41 (15.4)	34 (17.3)	7 (10.0)	
Late	Unknown	14 (5.2)	11 (5.6)	3 (4.3)	1.000
	No	231 (86.5)	170 (86.3)	61 (87.1)	
	Yes	22 (8.2)	16 (8.1)	6 (8.6)	
Fecal incontinence					
Acute	No	264 (98.9)	196 (99.5)	68 (97.1)	.169
	Yes	3 (1.1)	1 (0.5)	2 (2.9)	
Late	Unknown	13 (4.9)	10 (5.1)	3 (4.3)	.685
	No	246 (92.1)	180 (91.4)	66 (94.3)	
	Yes	8 (3.0)	7 (3.5)	1 (1.4)	
Rectal hemorrhage					
Acute	No	240 (89.9)	175 (88.8)	65 (92.9)	.489
	Yes	27 (10.1)	22 (11.2)	5 (7.1)	
Late	Unknown	14 (5.2)	11 (5.6)	3 (4.3)	.835
	No	219 (82.0)	160 (81.2)	59 (84.3)	
	Yes	34 (12.7)	26 (13.2)	8 (11.4)	
Rectal mucositis					
Acute	No	263 (98.5)	193 (98.0)	70 (100.0)	.575
	Yes	4 (1.5)	4 (2.0)	0 (0.0)	
Late	Unknown	15 (5.6)	12 (6.1)	3 (4.3)	.288
	No	248 (92.9)	183 (92.9)	65 (92.9)	
	Yes	4 (1.5)	2 (1.0)	2 (2.9)	
Rectal pain					
Acute	No	244 (91.4)	176 (89.3)	68 (97.1)	.049[b]
	Yes	23 (8.6)	21 (10.7)	2 (2.9)	
Late	Unknown	14 (5.2)	11 (5.6)	3 (4.3)	.118
	No	243 (91.0)	176 (89.3)	67 (95.7)	
	Yes	10 (3.7)	9 (54.6)	0 (0.0)	
Sexual: Grade ≥2					
Erectile dysfunction					
Acute	Unknown	124 (46.4)	97 (49.2)	27 (38.6)	.548
	No	102 (38.2)	73 (37.1)	29 (41.4)	
	Yes	41 (15.4)	27 (13.7)	14 (20.0)	
Late	Unknown	60 (22.5)	45 (22.8)	15 (21.4)	.318
	No	138 (51.7)	98 (49.7)	40 (57.1)	
	Yes	69 (25.8)	54 (27.4)	15 (21.4)	

Abbreviations: IMRT, intensity-modulated radiotherapy; PBT, proton beam therapy.
[a]For all variables, *P* values compare the 2 treatments groups (IMRT and PBT). The Fisher exact test was performed based on nonmissing data.
[b]This *P* value indicates a statistically significant difference.

TABLE 2. Matched Cohort Characteristics

Characteristic	All, n = 267	IMRT, n = 197	PBT, n = 70	P^a
Patient characteristics				
Demographics				
Age at diagnosis, y				
No. of patients	267	197	70	.230
Range	42.0-77.0	45.0-77.0	42.0-74.0	
Median	60.0	60.0	62.0	
Mean ± SD	59.7 ± 6.3	59.4 ± 6.0	60.5 ± 7.0	
IQR	55.0-64.0	55.0-64.0	56.0-66.0	
PMH: No. (%)				
GU PMH				
No	149 (55.8)	110 (55.8)	39 (55.7)	.986
Yes	118 (44.2)	87 (44.2)	31 (44.3)	
GI PMH				
No	84 (31.5)	62 (31.5)	22 (31.4)	.995
Yes	183 (68.5)	135 (68.5)	48 (68.6)	
Hypertension				
No	136 (50.9)	100 (50.8)	36 (51.4)	.924
Yes	131 (49.1)	97 (49.2)	34 (48.6)	
Hemorrhoids				
No	243 (91.0)	180 (91.4)	63 (90.0)	.731
Yes	24 (9.0)	17 (8.6)	7 (10.0)	
Diabetes mellitus				
No	222 (83.1)	164 (83.2)	58 (82.9)	.940
Yes	45 (16.9)	33 (16.8)	12 (17.1)	
Baseline GI and GU function				
Baseline IPSS score				
No. of patients	240	171	69	.873
Range	0.0-29.0	0.0-23.0	0.0-29.0	
Median	5.0	6.0	5.0	
Mean ± SD	6.8 ± 5.3	6.9 ± 5.1	6.7 ± 5.7	
IQR	3.0-10.0	3.0-10.0	3.0-10.0	
Baseline IPSS QOL score				
No. of patients	221	166	55	.964
Range	0.0-6.0	0.0-6.0	0.0-6.0	
Median	2.0	2.0	2.0	
Mean ± SD	2.2 ± 1.6	2.2 ± 1.6	2.1 ± 1.6	
IQR	1.0-3.0	1.0-3.0	1.0-3.0	
Baseline IIEF score				
No. of patients	206	147	59	.681
Range	1.0-25.0	3.0-25.0	1.0-25.0	
Median	7.0	7.0	6.0	
Mean ± SD	10.4 ± 6.8	10.5 ± 6.8	10.1 ± 7.0	
IQR	5.0-16.0	5.0-16.0	5.0-15.0	
Baseline EPIC-BASS score				
No. of patients	181	131	50	.027[b]
Range	0.4-100.0	0.4-100.0	0.8-100.0	
Median	92.9	92.9	92.9	
Mean ± SD	80.6 ± 31.4	77.5 ± 34.9	88.9 ± 16.6	
IQR	82.1-96.4	82.1-96.4	89.3-100.0	
Disease characteristics				
Pathologic features				
Primary Gleason grade: No. (%)				
Unknown	1 (0.4)	0 (0.0)	1 (1.4)	.753
2	1 (0.4)	1 (0.5)	0 (0.0)	
3	153 (57.3)	116 (58.9)	37 (52.9)	
4	107 (40.1)	76 (38.6)	31 (44.3)	
5	5 (1.9)	4 (2.0)	1 (1.4)	
Secondary Gleason grade: No. (%)				
Unknown	1 (0.4)	0 (0.0)	1 (1.4)	.750
2	2 (0.7)	1 (0.5)	1 (1.4)	
3	94 (35.2)	69 (35.0)	25 (35.7)	
4	155 (58.1)	117 (59.4)	38 (54.3)	
5	15 (5.6)	10 (5.1)	5 (7.1)	
Pathological Gleason score				
No. of patients	267	197	70	.657
Range	5.0-9.0	5.0-9.0	5.0-9.0	
Median	7.0	7.0	7.0	
Mean ± SD	7.1 ± 0.7	7.1 ± 0.7	7.2 ± 0.8	
IQR	7.0-7.0	7.0-7.0	7.0-7.0	

TABLE 2. *Continued*

Characteristic	All, n = 267	IMRT, n = 197	PBT, n = 70	P[a]
Positive margins: No. (%)				
No surgery	1 (0.4)	1 (0.5)	0 (0.0)	.022[b]
No	117 (43.8)	92 (46.7)	25 (35.7)	
Yes	140 (52.4)	101 (51.3)	39 (55.7)	
Unknown	9 (3.4)	3 (1.5)	6 (8.6)	
Staging				
pT stage: No. (%)				
pT2	135 (50.6)	91 (46.2)	44 (62.9)	.055
pT3	128 (47.9)	103 (52.3)	25 (35.7)	
Unknown	4 (1.5)	3 (1.5)	1 (1.4)	
Lymph node status				
N0	256 (95.9)	190 (96.4)	66 (94.3)	.730
N1	3 (1.1)	2 (1.0)	(1.4)	
Unknown	8 (3.0)	5 (2.5)	3 (4.3)	
Other features				
Concurrent ADT: No. (%)				
No	222 (83.1)	167 (84.8)	55 (78.6)	.234
Yes	45 (16.9)	30 (15.2)	15 (21.4)	
Preoperative PSA, ng/mL				
No. of patients	221	164	57	.031[b]
Range	0.5-66.0	0.5-66.0	0.5-29.8	
Median	6.0	6.7	5.3	
Mean ± SD	8.6 ± 8.0	9.3 ± 8.6	6.7 ± 5.4	
IQR	4.5-9.8	4.9-11.0	4.1-6.7	
Pre-RT PSA, ng/mL				
No. of patients	267	197	70	.736
Range	0.0-18.3	0.0-18.3	0.0-5.2	
Median	0.2	0.2	0.3	
Mean ± SD	0.6 ± 1.7	0.6 ± 1.9	0.5 ± 1.0	
IQR	0.1-0.4	0.1-0.4	0.1-0.4	

Abbreviations: ADT, androgen-deprivation therapy; EPIC-BASS, Expanded Prostate Cancer Index Composite-derived Bowel Symptom Score; GI, gastrointestinal; GU, genitourinary; IMRT, intensity-modulated radiotherapy; IPSS, International Prostate Symptom Score; IPSS QOL, International Prostate Symptom Score Quality-of-Life Assessment; IQR, interquartile range; PBT, proton-beam therapy; PMH, past medical history; PSA, prostate-specific antigen; pT stage, pathologic tumor classification; RT, radiotherapy.
[a]For all variables, the P value compares the 2 treatment groups (IMRT and PBT). The chi-square test was used for categorical variables, and the t test was used for continuous variables.
[b]This P value indicates a significant difference.

$P = .03$) and lower baseline EPIC-BASS scores (IMRT, 77.5 ± 34.9; PBT, 88.9 ± 16.6; $P = .03$) (Table 2).

DOSIMETRY
Matched dosimetric characteristics are summarized in Supporting Table 3. For patients in both groups, the median total prescription dose was 70.2 Gy (RBE) (range, 66.0-75.6 Gy [RBE]; $P > .05$). The mean target and OAR volumes did not differ significantly between groups. Maximum, minimum, mean, and median bladder, bladderless-CTV, rectum, and in-field rectum doses were lower with PBT (all $P < .01$). PBT plans were superior at minimizing low-range dose (volumes receiving 10% to 40% of the dose, respectively) to the bladder and rectal structures (all $P < .01$) (Fig. 1C-F) and high-range dose (V50-V65) to the anterior rectal wall (all $P < .01$) (Fig. 1G); PBT rectum and in-field rectum V50 to V70 doses were significantly higher, albeit to a lower absolute degree (all $P < .01$) (Fig. 1E,F). In addition, patients in

the PBT group had a larger proportion of their femoral heads within the treatment field (184.4 ± 25.9 cc) compared with patients in the IMRT group (171.7 ± 38.6 cc; $P = .03$). Consequently, PBT maximum, mean, median, and low-range (V10-V40) femoral head doses were significantly higher (all $P < .01$) (Fig. 1H; see Supporting Fig. 1) .

Acute Toxicities
Patients in the IMRT and PBT groups reported acute grade ≥2 GU toxicities at rates of 21.8% and 17.1%, respectively (Table 1). There were no significant differences in the frequency of acute GU toxicities, including hematuria, urinary frequency, incontinence, urgency, retention, and urinary tract pain, between the groups (Table 1). One case of acute grade 3 dysuria was reported in the IMRT group by a patient who developed a urinary tract infection in the setting of known nephrolithiasis. Treatment group was not associated with grade ≥2 GU toxicity on UVA (OR, 0.74; 95% CI, 0.37-1.50;
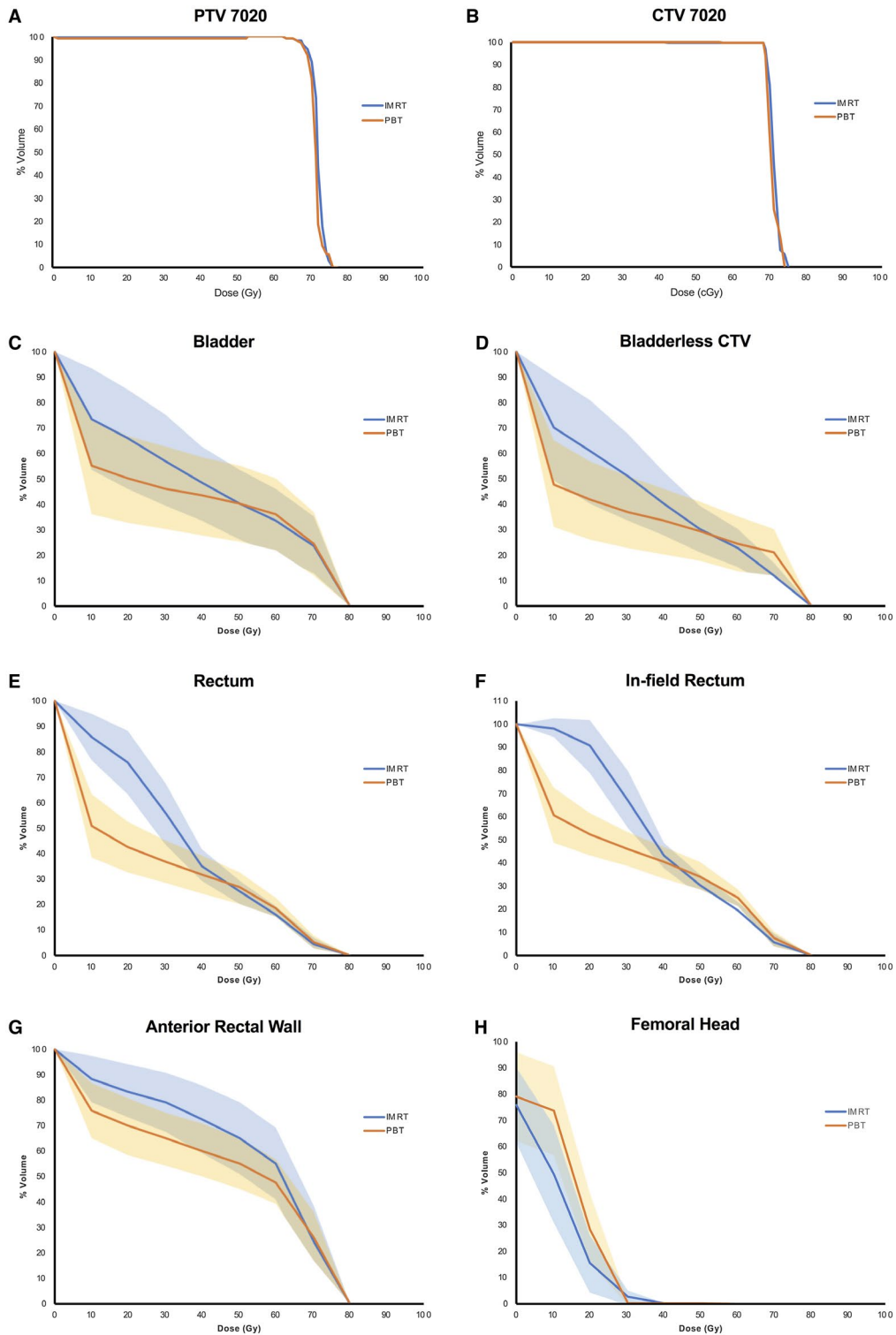
Figure 1. Comparative mean dose-volume histograms by treatment group are shown. Dosimetric parameters for (A) a planning target volume (PTV) of 7020 centigray (cGy) and (B) a clinical target volume (CTV) of 7020 cGy did not differ significantly between patients who received intensity-modulated radiotherapy (IMRT) (blue) and those who received proton-beam therapy (PBT) (yellow). PBT plans were superior at minimizing a low-range dose (volumes receiving 10% to 40% of the dose, respectively) to the (C) bladder, (D) bladderless CTV, (E) rectum, (F) in-field rectum, (G) anterior rectal wall, and (H) femoral head, as well as a high-range dose (V50-V65) to (G) the anterior rectal wall (all $P < .01$). In contrast, PBT (E) rectum and (F) in-field rectum V50 to V70 doses were significantly higher, albeit to a lower absolute degree (all $P < .01$). In addition, patients who received PBT had a higher low-range (V10-V40) dose to (H) the femoral heads (all $P < .01$).

TABLE 3. Univariate and Multivariate Models of Acute and Late Genitourinary and Gastrointestinal Toxicity

Variable	Acute Toxicity, No. (%)		UVA		MVA	
	No	Yes	OR [95% CI]	P	OR [95% CI]	P^a
Acute grade ≥2 GU toxicity						
Treatment group						
IMRT	154 (72.6)	43 (78.2)	0.74 [0.37-1.50]	.406	1.19 [0.45-3.12]	.724
PBT	58 (27.4)	12 (21.8)				
ADT, concurrent with RT						
No	177 (83.5)	45 (81.8)	1.12 [0.52-2.44]	.768	0.14 [0.02-0.97]	.047[b]
Yes	35 (16.5)	10 (18.2)				
Hypertension						
No	112 (52.8)	24 (43.6)	1.45 [0.80-2.63]	.226	1.57 [0.61-4.06]	.35
Yes	100 (47.2)	31 (56.4)				
Diabetes mellitus						
No	179 (84.4)	0.832	1.51 [0.72-3.17]	.272	0.89 [0.29-2.73]	.832
Yes	33 (15.6)					
GI PMH						
No	120 (56.6)	29 (52.7)	1.17 [0.65-2.12]	.606		
Yes	92 (43.4)	26 (47.3)				
GU PMH						
No	71 (33.5)	13 (23.6)	1.63 [0.82-3.23]	.163		
Yes	141 (66.5)	42 (76.4)				
Positive margins						
Unknown	9 (4.2)	1 (1.8)	1.28 [0.70-2.35]	.428	1.50 [0.58-3.84]	.4
No	95 (44.8)	22 (40.0)				
Yes	108 (50.9)	32 (58.2)				
Baseline IPSS						
No. of patients	190	50	1.09 [1.03-1.15]	.004[b]	1.19 [1.05-1.35]	.006[b]
Range/Minimum-Maximum	29.0 (0.0-29.0)	23.0 (2.0-25.0)				
Median	5.0	7.0				
Mean ± SD	6.3 ± 5.1	8.8 ± 5.4				
IQR/P25-P75	7.0 (2.0-9.0)	8.0 (4.0-12.0)				
Preoperative PSA, ng/mL						
No. of patients	175	46	0.99 [0.95-1.04]	.759	1.01 [0.95-1.08]	.782
Range/Minimum-Maximum	46.8 (0.5-47.3)	65.5 (0.5-66.0)				
Median	6.1	5.7				
Mean ± SD	8.7 ± 7.5	8.3 ± 9.7				
IQR/P25-P75	5.5 (4.5-10.0)	4.5 (4.3-8.8)				
Late grade ≥2 GU toxicity						
Treatment group						
IMRT	149 (71.6)	37 (82.2)	0.55 [0.24-1.24]	.149	0.96 [0.30-3.15]	.951
PBT	59 (28.4)	8 (17.8)				
ADT, concurrent with RT						
No	182 (87.5)	33 (73.3)	2.55 [1.17-5.54]	.019[b]	2.61 [0.57-11.97]	.216
Yes	26 (12.5)	12 (26.7)				
Hypertension						
No	112 (53.8)	17 (37.8)	1.92 [0.99-3.72]	.053	1.08 [0.35-3.35]	.892
Yes	96 (46.2)	28 (62.2)				
Diabetes mellitus						
No	179 (86.1)	32 (71.1)	2.51 [1.18-5.33]	.017[b]	1.66 [0.40-6.84]	.480
Yes	29 (13.9)	13 (28.9)				
GI PMH						
No	118 (56.7)	24 (53.3)	1.15 [0.60-2.19]	.677		
Yes	90 (43.3)	21 (46.7)				
GU PMH						
No	67 (32.2)	9 (20.0)	1.90 [0.87-4.17]	.109		
Yes	141 (67.8)	36 (80.0)				
Positive margins						
Unknown	8 (3.8)	1 (2.2)	0.98 [0.51-1.89]	.956	0.69 [0.23-2.13]	
No	90 (43.3)	20 (44.4)				.523
Yes	110 (52.9)	24 (53.3)				
Baseline IPSS						
No. of patients	187	43	1.06 [1.00-1.12]	.062	1.08 [0.94-1.23]	.279
Range/Minimum-Maximum	29.0 (0.0-29.0)	23.0 (2.0-25.0)				
Median	5.0	7.0				
Mean ± SD	6.6 ± 5.3	8.2 ± 5.0				
IQR/P25-P75	8.0 (2.0-10.0)	5.0 (5.0-10.0)				
Preoperative PSA, ng/mL						
No. of patients	171	38	1.00 [0.96-1.05]	.978	1.01 [0.95-1.06]	.842

TABLE 3. *Continued*

Variable	Acute Toxicity, No. (%)		UVA		MVA	
	No	Yes	OR [95% CI]	*P*	OR [95% CI]	*P*ª
Range/Minimum-Maximum	46.1 (1.2-47.3)	65.5 (0.5-66.0)				
Median	5.8	5.8				
Mean ± SD	8.5 ± 7.2	8.6 ± 10.4				
IQR/P25-P75	5.7 (4.3-10.0)	3.7 (4.9-8.6)				
Acute grade ≥1 GI toxicity						
Treatment group						
IMRT	119 (60.4)	78 (39.6)	0.57 [0.31-1.03]	.065	0.90 [0.31-2.61]	.845
PBT	51 (72.9)	19 (27.1)				
ADT, concurrent with RT						
No	144 (64.9)	78 (35.1)	1.35 [0.70-2.59]	.368	1.93 [0.46-8.04]	.368
Yes	26 (57.8)	19 (42.2)				
Hypertension						
No	85 (62.5)	51 (37.5)	0.90 [0.55-1.49]	.685	0.50 [0.17-1.50]	.218
Yes	85 (64.9)	46 (35.1)				
Diabetes mellitus						
No	137 (61.7)	85 (38.3)	0.59 [0.29-1.20]	.142	0.56 [0.10-3.11]	.506
Yes	33 (73.3)	12 (26.7)				
GI PMH						
No	96 (64.4)	53 (35.6)	1.08 [0.65-1.78]	.772		
Yes	74 (62.7)	44 (37.3)				
GU PMH						
No	54 (64.3)	30 (35.7)	1.04 [0.61-1.78]	.887		
Yes	116 (63.4)	67 (36.6)				
Positive margins						
No	90 (43.3)	20 (44.4)	1.02 [0.61-1.71]	.930	0.63 [0.19-2.06]	.44
Yes	110 (52.9)	24 (53.3)				
Baseline EPIC-BASS						
No. of patients	113	68	0.99 [0.98-1.00]	.019ᵇ	0.99 [0.97-1.01]	.217
Range/Minimum-Maximum	0.57-100	0.42-100				
Median	92.8	89.3				
Mean ± SD	83.9 ± 28.8	74.3 ± 35.1				
IQR/P25-P75	10.7/89.3-100	25/71.4-96.4				
Preoperative PSA, ng/mL						
No. of patients	138	83	1.00 [0.97-1.04]	.947	0.97 [0.90-1.05]	.47
Range/Minimum-Maximum	0.46-47.3	2.5-66.0				
Median	6.2	5.7				
Mean ± SD	8.5 ± 7.1	8.8 ± 9.4				
IQR/P25-P75	5.4/4.6-10	4.5/4.3-8.8				
Late grade ≥1 GI toxicity						
Treatment group						
IMRT	130 (66.0)	67 (34.0)	0.72 [0.40-1.32]	.292		
PBT	51 (72.9)	19 (27.1)				
ADT, concurrent with RT						
No	155 (69.8)	67 (30.2)	1.69 [0.88-3.26]	.117		
Yes	26 (57.8)	19 (42.2)				
Hypertension						
No	97 (71.3)	39 (28.7)	1.39 [0.83-2.33]	.209		
Yes	84 (64.1)	47 (35.9)				
Diabetes mellitus						
No	153 (68.9)	69 (31.1)	1.35 [0.69-2.62]	.382		
Yes	28 (62.2)	17 (37.8)				
GI PMH						
No	108 (72.5)	41 (27.5)	1.62 [0.97-2.72]	.066		
Yes	73 (61.9)	45 (38.1)				
GU PMH						
No	59 (70.2)	25 (29.8)	1.18 [0.67-2.07]	.562		
Yes	122 (66.7)	86 (33.3)				
Positive margins						
No	78 (66.7)	39 (33.3)	0.92 [0.54-1.55]	.745		
Yes	96 (68.6)	44 (31.4)				
Baseline EPIC-BASS						
No. of patients	124	57	0.99 [0.98-1.00]	.251		
Range/Minimum-Maximum	99.6 (0.43-100.0)	99.5 (0.54-100.0)				
Median	96.4	89.3				
Mean ± SD	82.4 ± 31.2	76.7 ± 31.7				
IQR/P25-P75	14.3/85.7-100.0	21.4/71.4-92.9				

TABLE 3. *Continued*

Variable	Acute Toxicity, No. (%)		UVA		MVA	
	No	Yes	OR [95% CI]	P	OR [95% CI]	Pa
Preoperative PSA, ng/mL						
No. of patients	148	73	0.99 [0.96-1.03]	.657		
Range/Minimum-Maximum	65.5 (0.5-66.0)	22.6 (1.3-23.9)				
Median	5.9	5.8				
Mean ± SD	8.8 ± 8.8	8.3 ± 6.0				
IQR/P25-P75	5.4/4.4-9.8	5.6/4.6-10.2				

Abbreviations: ADT, androgen-deprivation therapy; EPIC-BASS, Expanded Prostate Cancer Index Composite-derived Bowel Symptom Score; GI, gastrointestinal; GU, genitourinary; IMRT, intensity-modulated radiotherapy; IPSS, International Prostate Symptom Score; IQR, interquartile range; MVA, multivariate analysis; P25-P75, 25th to 75th percentile; PBT, proton-beam therapy; PMH, past medical history; PSA, prostate-specific antigen; RT, radiotherapy; UVA, univariate analysis.
aFor all variables, the P values compare the 2 treatment groups (IMRT vs and PBT). The chi-square test was used for categorical variables, and the t test was used for continuous variables.
bThis P value indicates a significant difference.

P = .41) (Table 3). On MVA, baseline IPSS (OR, 1.19; 95% CI, 1.05-1.35; P = .006) and concurrent ADT (OR, 0.14; 95% CI, 0.02-0.97; P = .047) were associated with acute grade ≥2 GU toxicity (Table 3).

Most of the matched patients who received IMRT (39.6%) and PBT (27.1%) reported maximum acute grade 1 GI toxicities (Table 3). With the exception of a marginally significant difference in acute grade ≥1 rectal pain (IMRT, 10.7%; PBT, 2.9%; P = .049), there were no significant differences in the frequency of acute GI toxicities, including abdominal pain, bloating, diarrhea, and fecal incontinence, between groups. No patients reported grade ≥3 acute GI toxicity. Treatment group was not associated with acute grade ≥1 GI toxicity on UVA (OR, 0.57; 95% CI, 0.31-1.03; P = .07) (Table 3). Lower baseline EPIC-BASS scores were associated with acute grade ≥1 GI toxicity on UVA (OR, 0.99; 95% CI, 0.98-1.00; P = .02), but not on MVA (OR, 0.99; 95% CI, 0.97-1.01; P = .22) (Table 3).

Late Toxicities
From the day-90 landmark, 1-year, 2-year, and 5-year late grade ≥2 GU TFS was 72.5%, 66.8%, and 61.1%, respectively, after IMRT and 72.5%, 70.7%, and 70.7%, respectively, after PBT (P = .20) (Fig. 2A). Five-year late grade ≥3 GU TFS was >95% for both groups (P ≥ .05). Compared with no patients who received PBT, 5 patients who received IMRT experienced late grade 3 GU toxicities, including urinary frequency (n = 1), urinary incontinence secondary to bladder neck contracture (n = 2), and urinary retention secondary to bulbar urethral stricture (n = 2). One patient developed late grade 4 urinary retention in the setting of bladder mucosa changes consistent with catheter-induced edema and radiation cystitis; he underwent suprapubic

tube placement after multiple failed attempts at surgical dilation, ultimately requiring augmentation cystoplasty with an ileocecal conduit for stoma catheterization. On UVA, concurrent ADT (OR, 2.55; 95% CI, 1.17-5.54; P = .019) and diabetes mellitus (OR, 2.51; 95% CI, 1.18-5.33; P = .017) were associated with late grade ≥2 GU toxicity, whereas treatment modality was not (OR, 0.55; 95% CI, 0.24-1.24; P = .15) (Table 3). No patient covariates were associated with late grade ≥2 GU toxicity on MVA (all P ≥ .05) (Table 3).

From the day-90 landmark, 1-year, 2-year and 5-year late grade ≥1 GI TFS was 79.1%, 76.3%, and 73.7%, respectively, in the IMRT group and 78.5%, 75.3%, and 75.3%, respectively, in the PBT group (P = .74) (Fig. 2B). Five-year late grade ≥3 GI TFS was >95% for both groups (P ≥ .05). There were no significant differences in late grade ≥1 abdominal pain, bloating, diarrhea, or fecal incontinence (Table 1). Four patients in the IMRT group (1.7%) reported late grade ≥2 GI toxicities, including abdominal pain (n = 1), hematochezia (n = 3), and rectal pain (n = 1). Of these patients, 1 experienced late grade 3 hematochezia requiring sigmoidoscopy and argon plasma coagulation, which resolved 6 months after conservative management. Only 1 patient in the PBT group (0.9%) reported late grade 2 GI toxicities, specifically hematochezia and rectal mucositis. Notably, this patient was on anticoagulation with prasugrel. No other patients with late grade ≥2 GI bleeding complications were on anticoagulation. There were no late grade 3 GI toxicities in the PBT cohort. On UVA, treatment group was not associated with late grade ≥1 GI toxicity (OR, 0.57; 95% CI, 0.31-1.03; P = .07) (Table 3). No other factors were significant on UVA, thus multivariate models were not pursued.
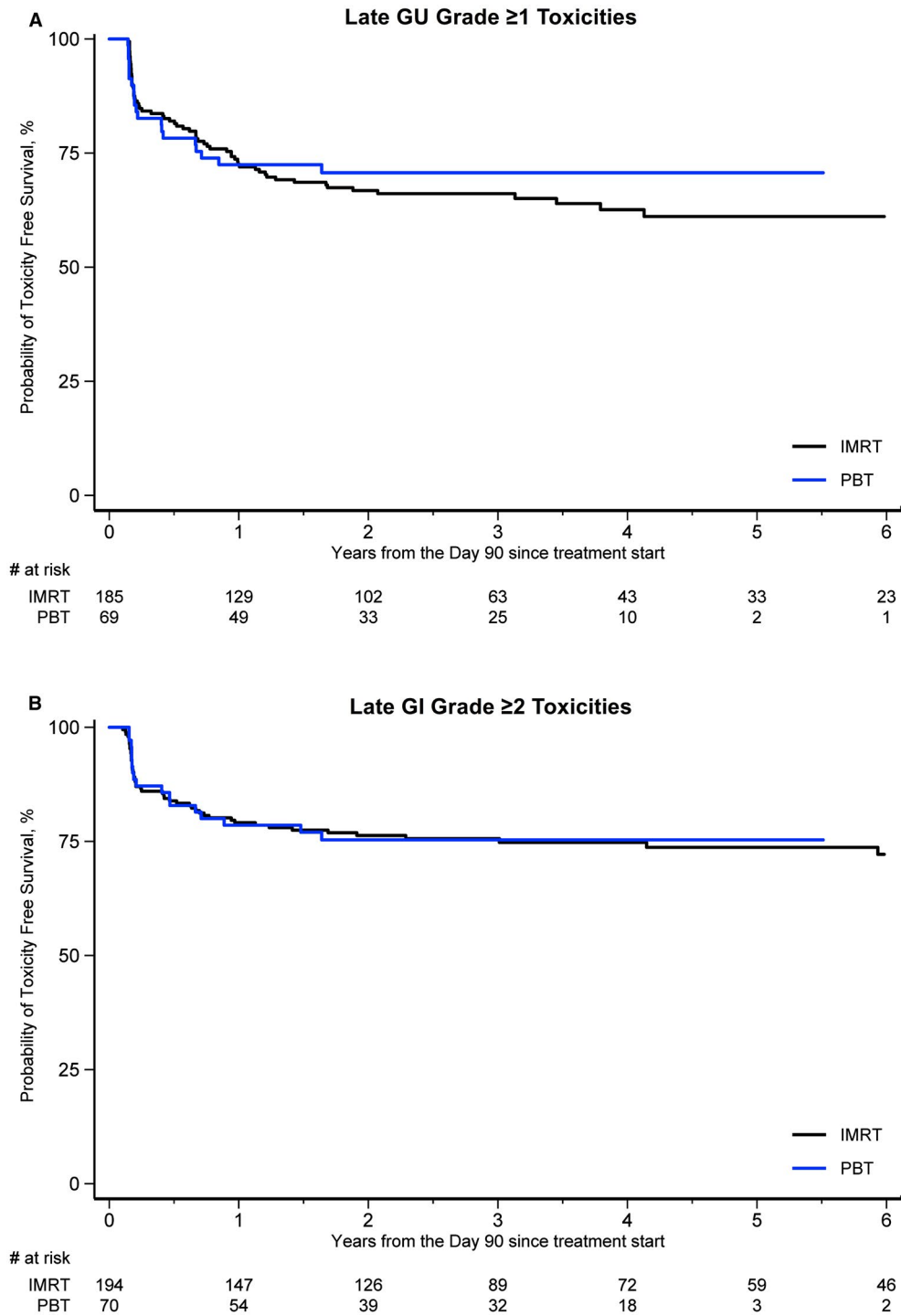
Figure 2. Kaplan-Meier estimates of toxicity-free survival (TFS) are shown by treatment group. From 90 days after the start of radiation (day-90 landmark), the time to (A) late grade ≥1 genitourinary (GU) and (B) late grade ≥2 gastrointestinal (GI) toxicities were estimated in patients who received intensity-modulated radiotherapy (IMRT) (black line) and proton-beam therapy (PBT) (blue line). One-year, 2-year, and 5-year Kaplan-Meier estimates of late grade ≥2 GU TFS were 72.5%, 66.8%, and 61.1%, respectively, after IMRT and 72.5%, 70.7%, and 70.7%, respectively, after PBT (log-rank test; *P* = .20). One-year, 2-year, and 5-year Kaplan-Meier estimates of late grade ≥1 GI TFS were 79.1%, 76.3%, and 73.7%, respectively, in the IMRT group and 78.5%, 75.3%, and 75.3%, respectively, in the PBT group (log-rank test; *P* = .74).

DOSIMETRIC ASSOCIATIONS

On UVA, no bladder or bladderless CTV parameters were associated with overall acute/late grade ≥2 GU toxicity (see Supporting Table 4). Similarly, no rectum, in-field rectum, or anterior rectal wall parameters were associated with overall acute or late grade ≥1 GI toxicity (see Supporting Table 5). However, on MVA, bladder and bladderless CTV V40 to V50 were associated with acute grade ≥2 urinary incontinence/retention, whereas bladder CTV V50 to V70 and bladderless CTV V40 to V60 were associated with late grade ≥2 urinary incontinence/retention (all $P < .05$) (see Supporting Figure 1 and Table 6). Mean and median rectum as well as low-range rectum (V10-V20), in-field rectum (V10), and anterior rectal wall (V20-V30) bladder CTV and bladderless CTV were associated with acute grade ≥1 rectal pain on UVA (all $P < .05$) (see Supporting Figure 1 and Table 7), but not on MVA (data not shown).

DISCUSSION

To our knowledge, the current study—in which we used a case-matched cohort approach to assess toxicity outcomes of patients with PC who received IMRT versus PBT—is the first such report in the postprostatectomy setting. Rates of acute and late GU and GI toxicities did not differ significantly between groups and were largely consistent with previously published single-institution and multi-institution series.[6,13-20] Also consistent with prior reports was the association between higher baseline IPSS scores and acute GU toxicities.[8] Similarly, lower baseline EPIC-BASS scores were associated with acute GI toxicity on UVA but not MVA, likely attributable to low event rates within our cohort.

Our analysis showed that, relative to IMRT, PBT was superior at reducing 1) low-range dose (V10-V40) to most bladder and rectal structures and 2) high-range dose (V50-V65) to the anterior rectal wall. PBT carried some dosimetric disadvantages relative to IMRT, namely, significantly increased high-range dose (V50-V70) to the rectum and in-field rectum; however, absolute differences in dose were small compared with the low-dose range (Fig. 1E,F). Despite these dosimetric distinctions, our results demonstrate that treatment modality was not associated with changes in overall GU/GI toxicity. These findings held true despite lower pre-RT EPIC-BASS scores (suggesting worse baseline GI function) among patients who received IMRT. Rates of clinician-reported GU/GI toxicity were low overall, with grade ≥3 GU and GI TFS estimates >95% at 5 years for both groups. Collectively,

these results support findings in the intact setting, which, altogether demonstrate that both IMRT and PBT confer small, largely equivalent risks of GU/GI toxicities.[6,13-20]

Although no dosimetric parameters were associated with differences in overall GU toxicities, multivariate models identified associations between late grade ≥2 urinary incontinence/retention and high-range bladder dose (V60-V70). Patients treated with either modality received conventionally fractionated RT (maximum dose, 70.2 Gy [RBE]); however, these dosimetric associations may carry greater importance in the context of growing interest in hypofractionation based on data extrapolated from the intact setting.[21-25] Although official recommendations regarding postoperative hypofractionation are pending, small retrospective studies have reported low rates of acute and late GU and GI toxicities with early follow-up.[26-29] In the largest of these studies (n = 1176), Cozzarini et al reported a significantly higher 5-year risk of late grade ≥3 GU toxicity with postoperative hypofractionation (18.1% vs 6.9%) after a median follow-up of 98 months.[30] Therefore, continuing trends toward a higher dose per fraction necessitate ongoing investigation to determine whether dosimetric differences between postoperative IMRT and PBT confer meaningful clinical differences in the hypofractionated setting.

Radiobiological Insights and Long-Term Outcomes

Classically described as a disease of the elderly, PC is steadily rising in incidence among younger men: approximately 43.6% of new cases are expected to occur in men aged <65 years in 2018 alone.[31] Rates of radical prostatectomy have also increased, particularly for men with high-risk disease.[32,33] Consequently, more patients will likely require postprostatectomy RT given biochemical/local control and possibly survival benefits in the adjuvant[34-39] and salvage settings.[40-42] Emerging technological developments in PBT, such as smaller footprint beam-delivery systems, will result in significant cost reduction and broader financial accessibility in the future.[43] As PBT becomes more readily available across demographic and socioeconomic groups, ongoing evaluation of the long-term effects of higher femoral head and lower integral dose (ie, global radiation dose delivered to the body) will become increasingly important as the younger patient population, with longer life expectancy post-RT, begins to age.

Our results demonstrate higher mean and low-range dose (V10-V40) to the femoral heads with PBT—an expected consequence of its opposed-lateral beam arrangement compared with multiple-field IMRT.

Along with treatment-related and disease-related factors (eg, concurrent ADT, metastasis), RT may compromise bone integrity in patients with PC secondary to subsequent inflammatory and fibrotic response.[44-47] Moreover, some researchers hypothesize that a higher femoral head dose with PBT may increase hip-joint symptoms and fracture risk,[48] although Kil et al demonstrated that, after 36 months of follow-up, patient-reported hip-joint symptoms after PBT did not exceed the scores of men aged ≥50 years in the general population.[49]

In addition, multiple models accounting for lower integral dose to normal tissues with PBT predict a lower risk of secondary malignancy relative to photon-based RT.[50,51] Although long-term clinical data are limited, several single-institution and multi-institution series comparing PBT with photon-based RT have demonstrated decreased incidence of secondary malignancy after early follow-up. One case-matched cohort analysis of 1176 patients treated with either PBT at the Harvard cyclotron or photon-based RT from the Surveillance, Epidemiology, and End Results database showed that PBT was associated with a nearly 2-fold decreased risk of secondary malignancy (adjusted hazard ratio, 0.52; 95% CI, 0.32-0.85; $P = .009$).[52] In the pediatric setting, significantly lower rates of secondary malignancy were observed in patients with medulloblastoma and retinoblastoma after a median follow-up of 7 years and 6.9 years, respectively.[53,54]

As such, critical to interpreting our findings is the recognition that they represent an evaluation not only of treatment modalities but also of the radiobiology underlying treatment-related toxicities. In 2010, the Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) Group first estimated dose/volume OAR tolerances using 3-dimensional conformal RT data.[55] Since then, there have been numerous efforts to build upon QUANTEC findings. However, those studies were predominantly photon-photon comparisons (3-dimensional conformal RT vs IMRT), were limited by substantial dosimetric differences in both the low-dose and high-dose range,[56-59] and thus were not equipped to evaluate the impact of low-range dose on treatment-related events. Our study, which offers the first head-to-head proton-photon comparison in the postprostatectomy setting, largely controls for differences in high-range dose to the bladder and rectum, thereby allowing us to better isolate and assess the clinical effects of the low-dose "bath." Future prospective investigations to further characterize the toxicity profiles of IMRT and PBT in the postprostatectomy setting, including the collection of patient-reported quality-of-life data, are ongoing. As we accumulate long-term follow-up, rates of clinician-reported hip fractures and secondary malignancy will ultimately offer critical insight into the pathophysiology and radiobiology of these adverse treatment-related events.

Limitations

Our study has several important limitations. First, our findings are limited by the nonrandomized, retrospective nature of our cohort. Case-matching based on prior GU/GI disorder history and age at diagnosis (±5 years) was used to help minimize the potential impact of confounders. Second, because of modest patient and event numbers, we sought parsimonious, multivariable models to avoid over-fitting; however, other patient factors, including medication use (eg, anticoagulation) as well as postoperative complications (eg, bladder neck contracture and urethral stricture), were not controlled for in this study and thus may present as theoretical sources of confounding. Third, although we found no significant difference with respect to the incidence of late grade 3 GU and GI toxicities (with 5-year TFS estimates >95% for both groups), the low event rates suggest that our analyses still may have been underpowered to detect clinically important differences. We posit that our low event rates may have been because of limited follow-up (maximum, 5 years) and the clinician-reported nature of our outcomes, which may be more susceptible to underreporting relative to patient-reported outcomes.[60-62] Finally, our study does not include patients who were initially planned for PBT but were re-planned for IMRT after failing to meet rectal dose constraints.

Conclusion

Our study represents the first rigorous comparative analysis of toxicity outcomes after postprostatectomy IMRT versus PBT. Although PBT minimizes low-range dose to the bladder and rectum, treatment modality was not associated with significant differences in clinician-reported acute and late GU/GI toxicities. As PBT achieves broader patient accessibility, trends toward earlier diagnosis and more aggressive surgical management necessitate ongoing prospective evaluation to determine whether dosimetric differences between postoperative IMRT and PBT confer clinically meaningful differences in long-term outcomes.

CONFLICT OF INTEREST DISCLOSURES

AUTHOR CONTRIBUTIONS

Patricia Mae G. Santos: Conceptualization, data curation, formal analysis, project administration, funding acquisition, writing–original draft, and writing–review and editing. **Andrew R. Barsky:** Conceptualization, data curation, and writing–review and editing. **Wei-Ting Hwang:** Methodology, formal analysis, funding acquisition, and writing–review and editing. **Curtiland Deville:** Conceptualization, methodology, data curation, and writing–review and editing. **Xingmei Wang:** Methodology and formal analysis. **Stefan Both:** Writing–review and editing. **Justin E. Bekelman:** Writing–review and editing. **John P. Christodouleas:** Writing–review and editing. **Neha Vapiwala:** Conceptualization, methodology, project administration, funding acquisition, and writing–review and editing.

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