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Comparative Analysis of 5-Year Clinical Outcomes and Patterns of Failure of Proton Beam Therapy Versus Intensity Modulated Radiation therapy for Prostate Cancer in the Postoperative Setting

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Abstract

Purpose: Although proton beam therapy (PBT) is a rapidly expanding modality to treat prostate cancer compared with intensity modulated radiation therapy (IMRT), data comparing disease control outcomes and patterns of failure in the postprostatectomy setting remain substantially limited.

Methods and Materials: All patients who underwent postoperative IMRT or PBT to the prostate bed only at a single institution were included (2009-2017). Endpoints included biochemical failure (BF; using institutional and recent cooperative group trial definitions), local failure (LF), regional failure (RF), distant failure (DF), and all-cause mortality. A case-matched cohort analysis was performed using 3-to-1 nearest-neighbor matching; multivariable Cox proportional hazards modeling (MVA) estimated hazard ratios for disease-related outcomes by treatment modality.

Results: Of 295 men, 260 were matched (n = 65 PBT, 195 IMRT); after matching, only age at diagnosis ($P < .01$) significantly differed between cohorts. At a median follow-up of 59 months, BF (institution-defined), LF, RF, DF, and mortality rates were 45% (n = 29), 2% (n = 1), 9% (n = 6), 9% (n = 6), and 2% (n = 1) for PBT, and 41% (n = 80), 3% (n = 5), 7% (n = 13), 9% (n = 18), and 5% (n = 9) for IMRT (all $P > .05$). RT modality was not significantly associated with BF on MVA using institutional or cooperative group definitions (all $P > .05$), nor with LF ($P = .82$), RF ($P = .11$), DF ($P = .36$), or all-cause mortality ($P = .69$). Patterns of failure were qualitatively similar between cohorts (DF: bone, retroperitoneal nodes, lung).

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Research data are stored in an institutional repository and may be shared upon reasonable request to the corresponding author.

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Conclusions: In this single institution, case-matched analysis, PBT yielded similar long-term disease-related outcomes and patterns of failure to IMRT in the postprostatectomy setting.

Introduction

Approximately one-third of patients with localized prostate cancer (PC) undergoing radical prostatectomy (RP) will experience a recurrence,[1] and pathologic findings from an additional proportion of cases will illustrate high-risk features such as pT3 disease or positive resection margins. Radiation therapy (RT) is the recommended treatment of choice for salvage management of biochemical or clinical recurrence, and adjuvant RT can be considered based on pathologic findings.[2,3]

Whereas the standard RT technique for these settings is intensity modulated RT (IMRT), proton beam therapy (PBT) is a widely expanding modality that exploits physical properties inherent to heavy particles.[4] This may be advantageous to reduce RT-related toxicities, but no randomized data exist to date. In the postoperative setting, there are even fewer modality comparison publications. To address this gap in the literature, we recently reported the results of a retrospective case-matched cohort analysis of the comparative toxicity outcomes of IMRT versus PBT in the postprostatectomy setting.[5]

However, comparisons of disease control outcomes and patterns of failure between both modalities remain understudied, which is an essential component of evaluating the utility of PBT in this setting.[6,7] Although the primary theoretical advantage of PBT relates to toxicity reduction, it is imperative to demonstrate that outcomes of PBT are similar to those of IMRT. This is particularly important because PBT is associated with numerous uncertainties in adequately delivering dose to the target, such as relating to on-board imaging, patient setup, beam delivery, and dose calculations (eg, range uncertainties); these could in turn influence clinical outcomes.[8] To address this knowledge gap amid the striking lack of literature on this topic, we performed a case-matched analysis of long-term disease control outcomes and patterns of failure between PBT and IMRT in the post-RP setting.

Methods

Patient selection

The patient cohort for this study has been previously described elsewhere.[5] Briefly, all patients who underwent postoperative PBT or IMRT to the prostate bed only at the Abramson Cancer Center at the University of Pennsylvaniathe were included in this analysis (2009-2017). At the time these patients were treated, data regarding the utility of pelvic nodal RT in the post-RP setting had not been elucidated,[9] and hence this was done on a case-by-case basis. Patients who received pelvic nodal RT were excluded from analysis given that very few patients received such treatment at our institution entirely with PBT, which would leave the potential for imbalances between the cohorts. Moreover, most patients were treated before randomized data supporting androgen deprivation therapy (ADT) in the salvage setting.[10,11] Patients who received ADT were included in the analysis because ADT use was common enough that it was balanced between the cohorts and its use would not affect PBT versus IMRT planning differentially.

RT details and disease control endpoints

Details of RT planning for both PBT and IMRT, along with RT delivery and follow-up have been described in the prior publication.[5] The primary objective for this investigation was to evaluate disease-related outcomes and patterns of failure. Prostate specific antigen (PSA) values were typically obtained every 3 to 6 months after completion of RT, and imaging, including a combination of computed tomography (CT), magnetic resonance imaging (MRI) ± endorectal coil, bone scintigraphy, ^{18}F-fluciclovine positron emission tomography/CT (PET/CT), ^{68}Ga-prostate specific membrane antigen PET/CT, or ^{18}F-DCFPyL PET/CT was obtained at the discretion of the treating physician based on symptoms or clinical suspicion. Biochemical failure (BF) was defined according to multiple metrics. The institutional definition of BF was 2 consecutive PSA rises above the post-RT nadir, a post-RT PSA greater than the pre-RT PSA, or clinical failure (eg, initiation of post-RT salvage therapy or imaging-defined progression). Given the lack of a single failure definition in the postsalvage RT setting, BF was also measured according to the definitions set forth by the Genitourinary Group and French Association of Urology (GETUG-AFU) 16 trial[11] and Radiation Therapy Oncology Group (RTOG) 0534 Short Term Androgen Deprivation with Pelvic Lymph Node or Prostate Bed Only Radiotherapy (SPPORT) trial.[9] Local failure (LF) was defined as imaging or examination-based evidence of failure in the prostate bed; biopsies of suspected local recurrences were not routinely performed. Regional failure (RF) referred to failure in a regional (pelvic) node. All other failures were categorized as distant (DF). Time to failures was

calculated from the start of RT to the date of failure. Time to death was calculated from the time of diagnosis to death.

Statistical analysis

Descriptive statistics, Student's t test, and Pearson χ^2 tests were used to examine differences in baseline characteristics. For our case-matched analysis, a 3:1 nearest neighbor algorithm was performed using the MatchIt package (R Foundation for Statistical Computing).[5] Matching was optimized on age at diagnosis, pT3 versus <pT3 disease, and pathologic Gleason score. Age and pT3 versus <pT3 disease were used due to their imbalances in the initial baseline characteristics assessment. Pathologic Gleason score was used because it previously has been shown to be associated with BF.[12] Cumulative incidence functions were used to calculate probabilities of events according to RT modality. Significant differences were evaluated using Gray's test P values. We then performed univariable (UVA) and multivariable (MVA) Cox proportional hazards analyses to estimate hazard ratios (HR) for disease control outcomes by treatment group. For MVAs, we tested the effects of potential confounders and retained final covariates if they met the P value threshold $\leq .05$, using backward elimination. As a sensitivity analysis, a matched MVA was repeated excluding patients who received ADT. All statistical analyses were performed within the R programming language (v3.5.1, www.r-project.org).

Results

Cohort characteristics

Before matching, 295 men were identified for this analysis (n = 230 IMRT, n = 65 PBT). Table 1 displays the baseline characteristics of this population. Before matching, there were statistical imbalances in age, preoperative PSA, surgical technique, and pT stage ($P < .05$ for all). There were no imbalances in Gleason score or pre-RT PSA ($P > .05$ for both). The median prescribed RT dose was 70.2 Gy for both groups and a minority (16%-17%) of patients in either group received concurrent ADT. Of the 295 cases, 260 were matched (Table 1). After matching, the only characteristic for which an imbalance persisted was age ($P < .05$). The median follow-up was 59 months for each group (PBT range, 16-87 months; IMRT range, 3-128 months).

Patterns of failure

Patterns of failure analysis in the matched cohort is presented in Table 2. Rates of BF by institutional, GETUG, and SPPORT definitions, respectively, for PBT were 45% (n = 29), 31% (n = 20), and 32% (n = 21), and for IMRT were 41% (n = 80), 31% (n = 61), and 34% (n = 67) (all $P > .05$). There were 1 (2%) and 5 (3%) LFs, and 6 (9%) and 13 (7%) RFs in the PBT and IMRT cohorts, respectively (all $P > .05$). PBT RFs all occurred in the upper pelvis (n = 5, 83% common iliac lymph nodes [LN]; n = 1, 17% external iliac LN), outside of the irradiated fields. IMRT RFs occurred most commonly in common, internal, or external iliac LN (n = 10, 77%), as well as in perirectal (n = 1, 8%), obturator (n = 1, 8%), and presacral LN (n = 1, 8%). All LFs and RFs were detected by imaging (CT, MRI, ^{18}F-fluciclovine PET/CT, or ^{18}F-DCFPyL PET/CT) obtained in the setting of rising post-RT PSA, without biopsy. Most prompted initiation of ADT or other systemic therapies. The first sites of DF for the PBT cohort included bone (n = 4, 67%), lung (n = 1, 17%), and retroperitoneal (RP) LN (n = 1, 17%). For the IMRT cohort, these included bone (n = 9, 50%), RP LN (n = 4, 22%), mediastinal and RP LN (n = 2, 11%), bone and RP LN (n = 1, 6%), mediastinal LN (n = 1, 6%), and lung (n = 1, 6%). There were 1 (2%) and 9 (5%) deaths in the PBT and IMRT arms, respectively, of which 0 (0%) and 2 (22%) were due to PC. The most common cause of non-PC death was non-PC malignancy (n = 4, 50%).

Cumulative incidences of events

In the unmatched cohort, 5-year cumulative incidences of PSA failure according to institutional, GETUG, and SPPORT definitions for IMRT versus PBT were 40.4% (95% confidence interval [CI], 33.6%-47.1%) versus 48.9% (95% CI, 35.0%-62.9%, $P = .45$), 29.9% (95% CI, 23.2%-36.6%) versus 34.8% (95% CI, 21.8%-47.8%, $P = .57$), and 34.3% (95% CI, 27.6%-41.1%) versus 37.1% (95% CI, 23.6%-50.6%, $P = .92$), respectively (Fig E1). In the matched cohort, 5-year cumulative incidences of PSA failure according to institutional, GETUG, and SPPORT definitions for IMRT versus PBT were 41.4% (95% CI, 34.0%-48.8%) versus 48.9% (95% CI, 35.0%-62.9%, $P = .52$), 32.4% (95% CI, 24.9%-40.0%) versus 34.8% (95% CI, 21.8%-47.8%, $P = .79$), and 34.1% (95% CI, 26.8%-41.4%) versus 37.1% (95% CI, 23.6%-50.6%, $P = .94$), respectively (Fig 1). Figure E2 and Fig 2 depict the cumulative incidences of LF, RF, DF, and all-cause mortality according to treatment modality in the unmatched and matched cohorts, respectively.

UVA and MVA

Table E1 contains HRs from UVAs and MVAs for institutional BF by RT modality and potential confounders, for the unmatched and matched cohorts. Table 3 contains HRs from UVAs and MVAs for disease control outcomes

Table 1 Cohort characteristics

Characteristic	Unmatched			Matched		
	IMRT, n = 230	PBT, n = 65	*P* value*	IMRT, n = 195	PBT, n = 65	*P* value
Age at diagnosis (y)			<.01			<.01
Mean (SD)	59.1 (6.2)	63.1 (7.3)		60.1 (6.1)	63.1 (7.3)	
Median (range)	59.0 (45.0-80.0)	65.0 (44.0-77.0)		60 (45-80)	65 (44-77)	
Race, n (%)			.42			.35
Non-white	67 (29.1)	23 (35.4)		55 (28.2)	23 (35.4)	
White	163 (70.9)	42 (64.6)		140 (71.8)	42 (64.6)	
Distance from center (miles)			.23			.49
Mean (SD)	63.3 (270.4)	39.3 (71.8)		51.8 (221.8)	39.3 (71.8)	
Median (range)	21.0 (1.1-2585.5)	24.1 (1.5-538.0)		20.8 (1.1-2585.5)	24.1 (1.5-538.0)	
Diabetes mellitus			.53			.39
No	192 (83.5)	57 (87.7)		160 (82.1)	57 (87.7)	
Yes	38 (16.5)	8 (12.3)		35 (17.9)	8 (12.3)	
Hypercholesterolemia			.95			1.00
No	187 (81.3)	52 (80.0)		154 (79.0)	52 (80.0)	
Yes	43 (18.7)	13 (20.0)		41 (21.0)	13 (20.0)	
Hypertension			.55			.35
No	119 (51.7)	37 (56.9)		96 (49.2)	37 (56.9)	
Yes	111 (48.3)	28 (43.1)		99 (50.8)	28 (43.1)	
GU past medical history			1.00			.76
No	80 (34.8)	23 (35.4)		63 (32.3)	23 (35.4)	
Yes	150 (65.2)	42 (64.6)		132 (67.7)	42 (64.6)	
Preoperative PSA (ng/mL)			.02			.09
Mean (SD)	9.0 (7.4)	7.2 (5.0)		8.5 (6.1)	7.2 (5.0)	
Median (range)	7.9 (0.5-66.0)	5.7 (0.5-29.8)		7.4 (0.5-47.3)	5.7 (0.5-29.8)	
Surgical technique			.04			.05
Nonrobotic	124 (53.9)	25 (38.5)		104 (53.3)	25 (38.5)	
Robotic	106 (46.1)	40 (61.5)		91 (46.7)	40 (61.5)	
Surgical margin status			.71			.57
Negative	118 (51.3)	31 (47.7)		103 (52.8)	31 (47.7)	
Positive	112 (48.7)	34 (52.3)		92 (47.2)	34 (52.3)	
Pathologic T stage			.01			.19
<T3	106 (46.1)	42 (64.6)		106 (54.4)	42 (64.6)	
T3	124 (53.9)	23 (35.4)		89 (45.6)	23 (35.4)	
Surgical Gleason grade			.79			.93
5-6	26 (11.3)	9 (13.8)		25 (12.8)	9 (13.8)	
7	165 (71.7)	44 (67.7)		137 (70.3)	44 (67.7)	
8-10	39 (17.0)	12 (18.5)		33 (16.9)	12 (18.5)	
Pre-RT PSA (ng/mL)			.50			.74
Mean (SD)	0.6 (1.8)	0.5 (0.9)		0.5 (1.5)	0.5 (0.9)	
Median (range)	0.2 (0.0-18.3)	0.3 (0.0-5.2)		0.2 (0.0-14.1)	0.3 (0.0-5.2)	
Months from surgery to RT			.11			.08
Mean (SD)	36.1 (41.7)	46.5 (47.5)		34.9 (40.7)	46.5 (47.5)	
Median (range)	19 (2-221)	30 (5-216)		18 (2-221)	30 (5-216)	
RT dose (Gy)			.58			.51
Mean (SD)	70.4 (1.0)	70.5 (1.6)		70.4 (1.0)	70.5 (1.6)	
Median (range)	70.2 (70.2-75.6)	70.2 (66.6-75.6)		70.2 (70.2-75.6)	70.2 (66.6-75.6)	
Concurrent ADT			1.00			.76
No	193 (83.9)	54 (83.1)		167 (85.6)	54 (83.1)	
Yes	37 (16.1)	11 (16.9)		28 (14.4)	11 (16.9)	
ADT duration (mo)			.84			.85
Mean (SD)	7.6 (6.6)	8.1 (6.0)		7.6 (7.1)	8.1 (6.0)	
Median (range)	6 (3-37)	7 (4-25)		6 (3-37)	7 (4-25)	

Abbreviations: ADT = androgen-deprivation therapy; GU = genitourinary; IMRT = intensity modulated radiation therapy; PBT = proton-beam therapy; PSA = prostate-specific antigen; RT = radiation therapy; SD = standard deviation.

* Student's *t* test and χ^2 tests were used for continuous and categorical variables, respectively. All tests were 2-tailed, and statistical significance was set at a threshold of $P \leq .05$.

Table 2 Patterns of failure analysis by radiation modality in matched cohort

Clinical outcome	Radiation modality	No. of patients (%)	Sites of failure (no., %)
PSA failure (institutional*)	PBT	29 (45)	N/A
	IMRT	80 (41)	N/A
PSA failure (GETUG†)	PBT	20 (31)	N/A
	IMRT	61 (31)	N/A
PSA failure (SPPORT‡)	PBT	21 (32)	N/A
	IMRT	67 (34)	N/A
Local failure	PBT	1 (2)	PB (1, 100%)
	IMRT	5 (3)	PB (5, 100%)
Regional failure	PBT	6 (9)	Common iliac LN (5, 83%)
			External iliac LN (1, 17%)
	IMRT	13 (7)	Common iliac LN (3, 23%)
			Internal iliac LN (3, 23%)
			External iliac LN (2, 15%)
			Common + external iliac LN (1, 8%)
			Internal + external iliac LN (1, 8%)
			Perirectal LN (1, 8%)
			Obturator LN (1, 8%)
			Presacral (1, 8%)
Distant failure	PBT	6 (9)	Bone (4, 67%)
			Lung (1, 17%)
			RP LN (1, 17%)
	IMRT	18 (9)	Bone (9, 50%)
			RP LN (4, 22%)
			Mediastinal + RP LN (2, 11%)
			Bone + RP LN (1, 6%)
			Lung (1, 6%)
			Mediastinal LN (1, 6%)
PC-specific mortality	PBT	0 (0)	N/A
	IMRT	2 (1)	N/A
All-cause mortality	PBT	1 (2)	N/A
	IMRT	9 (5)	N/A

Abbreviations: ADT = androgen-deprivation therapy; GETUG = Genitourinary Group; IMRT = intensity modulated radiation therapy; LN = lymph node; PB = prostate bed; PBT = proton-beam therapy; PC = prostate cancer; PSA = prostate-specific antigen; RP = retroperitoneal; RT = radiation therapy; SPPORT = Radiation Therapy Oncology Group (RTOG) 0534 Short Term Androgen Deprivation with Pelvic Lymph Node or Prostate Bed Only Radiotherapy (SPPORT) Trial.

* Institutional PSA failure: 2 consecutive PSA rises above post-RT nadir, or post-RT PSA greater than pre-RT PSA, or clinical failure (eg, initiation of post-RT salvage therapy, or radiographic evidence of progressive disease).

† GETUG-AFU 16 trial PSA failure: Post-RT PSA ≥ post-RT PSA nadir + 0.5 ng/mL, or clinical progression.

‡ SPPORT trial PSA failure: Post-RT PSA ≥ post-RT PSA nadir + 2.0 ng/mL, or clinical progression, or post-RT PSA ≥0.4 ng/mL and rising, or 3 consecutive rises in PSA on ADT

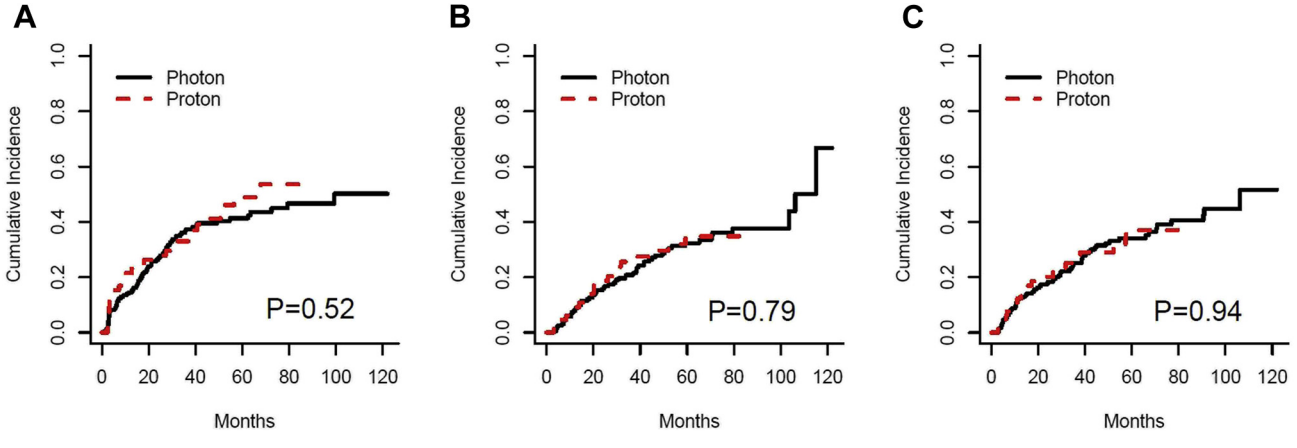

Figure 1 Cumulative incidences of biochemical failure according to (A) institutional, (B) GETUG, and (C) SPPORT definitions in the matched cohort. Gray's test was used to calculate *P* values.

by RT modality in the unmatched and matched cohorts. On MVA in the unmatched and matched cohorts, BF was not significantly different between modalities. On matched MVA, there was no difference between RT modalities according to the institutional definition (hazard ratio [HR] 1.15; 95% CI, 0.74%-1.82%; $P = .52$), GETUG definition (HR 1.16; 95% CI, 0.68%-1.97%; $P = .58$), or SPPORT definition (HR 1.03; 95% CI, 0.62%-1.73%; $P = .90$). We also did not find significant differences in LF ($P = .82$), RF ($P = .11$), DF ($P = .36$), and all-cause mortality ($P = .69$) according to RT modality, although there were few such events (Tables 2-3). These results remained consistent on a sensitivity analysis in which a matched MVA was performed excluding patients who received ADT (institutional BF HR 1.40; 95% CI, 0.84%-2.37%; $P = .20$; GETUG BF HR 1.35; 95% CI, 0.73%-2.52%; $P = .34$; SPPORT BF HR 1.24; 95% CI, 0.68%-2.27%, $P = .48$; LF, $P = .06$; RF, $P = .60$; DF, $P = .57$; and all-cause mortality, $P = .92$).

Discussion

Despite the rapidly expanding use of PBT for many cancers such as PC, comparative outcomes in the postoperative setting are substantially limited. Characterization of long-term disease control outcomes of new technologies, such as PBT, in the postprostatectomy setting is an essential step to further characterize its utility going forward. Our novel analysis was aimed to address this knowledge gap, along with providing the only known patterns of failure comparison between both modalities. Regardless of the definition of BF, in this matched comparison, disease control outcomes are similar between both modalities, along with the patterns of failure.

It may be largely expected that postoperative RT using PBT or IMRT would deliver similar disease-related outcomes because PBT is primarily touted to be associated with a potentially toxicity-reducing effect due to its physical properties and lack of exit dose. However, technical uncertainties unique to PBT cannot be discounted, as these could potentially result in underdosing the target, thereby leading to poorer disease control outcomes.[13,14] The main results of this analysis are hence reassuring, especially based on the notable strength of having long-term follow-up data. It is also reassuring that each of the regional failures in the PBT cohort occurred in the upper pelvis, well outside of the targeted field. Both our PBT and IMRT results compare favorably with those of other postprostatectomy photon RT reports. The initial GETUG analysis reported 5-year progression-free survival rates ranging from 62% with salvage RT alone to 80% with salvage RT and ADT, with only 7% to 16% of patients experiencing clinical progression without biochemical progression.[15] SPPORT preliminary results found similar progression-free survival rates at 5.4 years of median follow-up, ranging from 71% to 89%, depending on salvage RT field and use of ADT.[9] Although the PBT versus IMRT randomized study of intact prostate cancer (PARTIQoL, NCT01617161) has nearly completed accrual, no randomized studies have been completed that compare PBT versus IMRT in the postprostatectomy setting. In the absence of such studies, retrospective experiences such as this study are important to consider.

The vast majority of these patients were treated before the publication of GETUG 16 and RTOG 9601, both of which illustrated lower BF with the addition to ADT in the salvage setting (with RTOG 9601 also showing a survival advantage), along with interim results of RTOG 0534, which shows additional benefits to elective pelvic nodal RT in addition to ADT.[9-11] Although the comparative efficacy of PBT versus IMRT in the setting of more uniform ADT and pelvic nodal RT cannot be addressed by this analysis, ADT use was balanced between cohorts herein, and furthermore on our matched MVA sensitivity analysis excluding patients who received ADT, we still did not find significant differences in clinical outcomes between PBT and IMRT. Hence, it could be relatively unlikely that the results of this study meaningfully change in a population that has received uniform ADT.

Although this study illustrates similar clinical outcomes between PBT and IMRT in the postprostatectomy setting, and other data have shown similar toxicity results between both modalities,[5] both of these investigations are not meant to address a major roadblock to the implementation of PBT: cost-effectiveness. It has been shown that the cost-effectiveness of PBT for intact PC may be suboptimal[16]; however, it is acknowledged that the aforementioned toxicity results cannot exclude finer differences in quality of life, which could in turn effect cost-effectiveness.[17] Nevertheless, when considering our data with conclusions from other economic analyses,[18] there is no current evidence to suggest that PBT is the most cost-effective modality for routine implementation in the postprostatectomy setting. As with all technology, increasing access and availability of PBT as a result of refinement over time may render it less expensive, and thereby reduce the current gap in cost between PBT and IMRT. Future analyses in this setting should consider this question given the increased costs relative to IMRT.

Despite the novelty of this work, there are a few limitations to note. Despite the long-term follow-up, the analysis is inherently limited by its retrospective nature and relatively small sample size. Given the sample size and that all HR's for BF were greater than 1 (albeit all with P values $> .05$), a difference in HR for BF cannot be entirely excluded. Age was unable to be matched adequately using case matching to maintain robust sample size, likely due to the higher proportion of Medicare recipients in the PBT cohort. Nonetheless differences in follow-up times were equal between

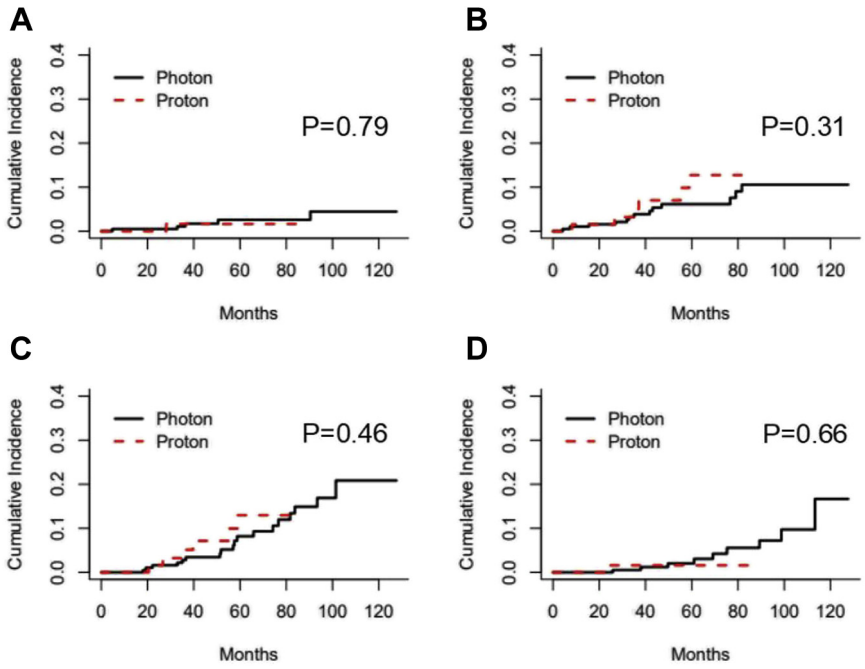

Figure 2 There were no significant differences in the cumulative incidences of (A) local failure, (B) regional failure, (C) distant failure, or (D) all-cause mortality in the matched cohort.

Table 3 UVA and MVA for disease control outcomes by radiation modality in unmatched and matched cohorts

		Unmatched				Matched*			
		UVA		MVA†		UVA		MVA	
Clinical outcome	RT modality	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
PSA failure (institutional‡)	PBT	1.18 (0.77-1.79)	.44	1.33 (0.87-2.04)	.19	1.14 (0.75-1.76)	.52	1.15 (0.74-1.82)	.52
	IMRT	REF		REF		REF		REF	
PSA failure (GETUG§)	PBT	1.16 (0.70-1.91)	.57	1.09 (0.65-1.83)	.75	1.07 (0.64-1.79)	.79	1.16 (0.68-1.97)	.58
	IMRT	REF		REF		REF		REF	
PSA failure (SPPORT‖)	PBT	1.02 (0.63-1.66)	.92	1.21 (0.74-1.98)	.44	1.02 (0.62-1.67)	.94	1.03 (0.62-1.73)	.90
	IMRT	REF		REF		REF		REF	
Local failure	PBT	0.70 (0.08-6.00)	.75	0.77 (0.09-6.66)	.81	0.74 (0.08-6.65)	.80	0.77 (0.08-7.53)	.82
	IMRT	REF		REF		REF		REF	
Regional failure	PBT	1.98 (0.73-5.32)	.18	1.74 (0.63-4.83)	.29	1.67 (0.62-4.50)	.31	2.32 (0.82-6.57)	.11
	IMRT	REF		REF		REF		REF	
Distant failure	PBT	1.48 (0.58-3.80)	.41	1.50 (0.59-3.87)	.39	1.43 (0.55-3.74)	.46	1.60 (0.59-4.33)	.36
	IMRT	REF		REF		REF		REF	
All-cause mortality	PBT	0.74 (0.09-6.26)	.78	0.57 (0.06-5.18)	.62	0.62 (0.07-5.31)	.67	0.64 (0.07-5.91)	.69
	IMRT	REF		REF		REF		REF	

Abbreviations: 95% CI = 95% confidence interval; ADT = androgen-deprivation therapy; GETUG = Genitourinary Group; HR = hazard ratio; IMRT = intensity modulated radiation therapy; MVA = multivariable analysis; PBT = proton-beam therapy; PSA = prostate-specific antigen; REF = reference; RT = radiation therapy; SPPORT = Radiation Therapy Oncology Group (RTOG) 0534 Short Term Androgen Deprivation with Pelvic Lymph Node or Prostate Bed Only Radiotherapy (SPPORT) Trial; UVA = univariable analysis.

* Analyses are matched according to age at diagnosis, pT3 versus <pT3 disease, and pathologic Gleason score. In addition to matching, we adjusted for significant confounders on MVA at the *P* value threshold ≤ .05.

† We adjusted for significant confounders on MVA at the *P* value threshold ≤ .05.

‡ Institutional PSA failure: 2 consecutive PSA rises above post-RT nadir, or post-RT PSA greater than pre-RT PSA, or clinical failure (eg, initiation of post-RT salvage therapy, or radiographic evidence of progressive disease).

§ GETUG PSA failure: Post-RT PSA ≥ post-RT PSA nadir + 0.5 ng/mL, or clinical progression.

‖ SPPORT PSA failure: Post-RT PSA ≥ post-RT PSA nadir + 2.0 ng/mL, or clinical progression, or post-RT PSA ≥0.4 ng/mL and rising, or 3 consecutive rises in PSA on ADT.

cohorts and significant differences were not noted in any disease-specific outcomes. Because age has been associated with clinical outcomes in some series,[19,20] it is unclear if disparate outcomes would be noted with adequate matching. Additionally, event rates for LF, RF, DF, and all-cause mortality were relatively low, thus reducing the ability to discriminate small differences between groups. Suspected LFs and RFs were not routinely biopsied to confirm recurrence, and therefore such measures were dependent on clinical correlation of radiographic findings. In the setting of rising PSA, clinicians typically opted to initiate ADT or systemic therapy. Although the advised follow-up protocol for the 2 cohorts did not differ, it is possible the nonuniform use of imaging after RT could bias results. Lastly, we did not explicitly assess adjuvant versus salvage therapy intent, as the definitions for these entities are heterogeneous and potentially overlapping; we did assess time from surgery to RT and pre-RT PSA as related surrogates.

Conclusions

This study represents the first comparative analysis of oncologic outcomes of postoperative PBT versus IMRT for PC. In this relatively small analysis, PBT yielded similar rates of biochemical failure, long-term disease-related outcomes, and patterns of failure as IMRT in the postprostatectomy setting.

Supplementary Materials

Supplementary material for this article can be found at https://doi.org/10.1016/j.prro.2020.11.005.

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