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SHORT COMMUNICATION

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Acute toxicities after proton beam therapy following breast-conserving surgery for breast cancer: Multi-institutional prospective PCG registry analysis

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Abstract

We investigated adverse events (AEs) and clinical outcomes for proton beam therapy (PBT) after breast-conserving surgery (BCS) for breast cancer. From 2012 to 2016, 82 patients received PBT in the prospective multi-institutional Proton Collaborative Group registry. AEs were recorded prospectively at each institution. Median follow-up was 8.1 months. Median dose was 50.4 Gy in 28 fractions. Most patients received a lumpectomy bed boost (90%) and regional nodal irradiation (RNI)(83%). Six patients (7.3%) experienced grade 3 AEs (5 with dermatitis, 5 with breast pain). Body mass index (BMI) was associated with grade 3 dermatitis (P = .015). Fifty-eight patients (70.7%) experienced grade ≥2 dermatitis. PBT including RNI after BCS is well-tolerated. Elevated BMI is associated with grade 3 dermatitis.

KEYWORDS

breast cancer, breast-conserving therapy, proton beam therapy, radiation, radiation dermatitis

1 | INTRODUCTION

Radiotherapy (RT) after breast-conserving surgery (BCS) for breast cancer improves breast cancer mortality and decreases recurrence.[1] However, the benefit of adjuvant breast RT is partially offset by non-breast morbidity caused by dose to normal structures, including the heart.[2] Various techniques and technologies are used to minimize the dose to surrounding normal structures including deep inspiration breath-hold, intensity-modulated radiation therapy, and proton beam therapy (PBT).[3]

Adjuvant whole-breast RT can be delivered with photons or PBT. PBT offers unique dosimetric advantages, such as improved target and internal mammary nodal (IMN) coverage,[4,5] decreased lung dose,[6,7] and decreased heart dose.[6,7] However, PBT has some disadvantages including decreased patient access,[8] increased cost,[9] and higher rates of acute radiation dermatitis (RD).[10] We report a prospectively evaluated multi-institutional cohort of patients who received adjuvant whole-breast PBT after BCS for breast cancer.

Previous Presentations: Presented in part at ASTRO 2019.

2 | METHODS

The Proton Collaborative Group (PCG) REG001-09 trial is an IRB-approved, multi-institutional prospective registry of patients treated with PBT. Between 2012 and 2016, 82 patients underwent BCS followed by PBT to the whole breast at seven participating institutions.

TABLE 1 Patient and treatment characteristics

Age, median (y)		57 (30-75)
BMI, median (kg/m^2)		27.5 (18.4-47.9)[a]
Current/Former Smoking		
Yes		29 (35%)
No		38 (46%)
Not Reported		15 (18%)
ECOG Performance Status		
0		60 (73%)
1		22 (27%)
AJCC 7th Edition Stage		
0		2 (2%)
IA		20 (24%)
IIA		16 (20%)
IIB		25 (30%)
IIIA		6 (7%)
IIIB		2 (2%)
IIIC		10 (12%)
Not Reported		1 (1%)
Histology		
Invasive Ductal		70 (85%)
Invasive Lobular		6 (7%)
No otherwise specified		4 (5%)
Ductal carcinoma in-situ		2 (3%)
ER		
Positive		60 (73%)
Negative		21 (26%)
Not Reported		1 (1%)
PR		
Positive		58 (71%)
Negative		23 (28%)
Not Reported		1 (1%)
HER2		
Positive		21 (26%)
Negative		60 (73%)
Not Reported		1 (1%)
Treatment Side		
Left		61 (74%)
Right		21 (26%)
		50.4 (42.56-54)
Whole-breast Dose, median (Gy)		
Lumpectomy Boost		
Yes		74 (90%)
Dose, median (Gy)	10 (5.4-16)	
No		8 (10%)
Whole-breast Dose, median (Gy)		
Regional Nodal Irradiation		
Yes		68 (83%)
Axilla	58 (71%)	
Level IV (supraclavicular)	59 (72%)	
Internal Mammary	54 (66%)	
No		14 (17%)
Chemotherapy		
Yes		70 (85%)
Neoadjuvant	28 (34%)	
Adjuvant	31 (38%)	
Both	11 (13%)	
No		12 (15%)
HER2 Treatment		
Yes		20 (24%)
No		62 (76%)
Endocrine Treatment		
Yes		48 (59%)
No		20 (24%)
Not Reported		14 (17%)

Abbreviations: AJCC, American Joint Committee on Cancer; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; PR, progesterone receptor.

[a]Data missing from 6 patients.

Patients were selected for PBT at the discretion of the treating physician.

Endocrine therapy consisted of tamoxifen or an aromatase inhibitor. Adverse events (AEs) were recorded prospectively at each institution according to Common Terminology Criteria for Adverse Events v4.0. AEs were recorded by the treating physician during weekly on-treatment visits and in follow-up at the discretion of the treating physician. Acute AEs occurred within 180 days from the start of PBT.

Statistical analysis included Fisher's exact and Wilcoxon's test were performed to assess the association of clinical and treatment characteristics with AEs. *P*-values <.05 were considered significant. Statistical analysis was performed using SAS v 9.4 (SAS Institute Inc).

3 | RESULTS

Eighty-two patients were included in this analysis. Median follow-up was 8.1 months (range, 0-39.9 months). Patient and tumor characteristics are listed in Table 1. Most patients were ER+ (73%), PR+ (71%), and HER2− (73%). Left-sided cancers (74%) were more common than right-sided cancers (26%). Median dose was 50.4 Gy relative biologic effectiveness (RBE) in 28 fractions (range, 42.5-54 Gy RBE in 16-30

TABLE 2 Radiation dermatitis by grade

	Grade 1-2 (N = 73)	Grade 3 (N = 5)	Total (N = 78)	*P* value
Lumpectomy boost				
Yes	67	5	72	1.00
No	6	–	6	
Regional Nodal Irradiation				
Yes	63	4	67	.54
No	10	1	11	
Proton Technology				
Uniform Scanning	51	3	54	.75
Pencil Beam Scanning	15	1	16	
Not Reported	7	1	7	
Systemic Treatment				
Yes	64	5	69	1.00
No	9	–	9	
Smoking History				
Yes	28	1	29	.62
No	32	3	35	
Not Reported	13	1	14	
BMI, median (kg/m^2)	27.4	38.2	27.8	.02

Abbreviation: BMI, body mass index.

fractions), and the majority of patients (90%) received a boost to the lumpectomy bed (median, 10 Gy RBE; range, 5.4-16). Uniform scanning PBT (67%) was more common than pencil beam scanning (22%). Most patients received regional nodal irradiation (RNI) (83%), which included a combination of supraclavicular nodes (72%), axillary nodes (71%), and internal mammary nodes (66%). There was no patient or treatment characteristic that was statistically significant for the development of grade 3 AE, including RNI or receiving a boost (*P* = 1.0 for both).

During follow-up, there were 2 local recurrences (2%) within the tumor bed. The first local recurrence was at 4.2 months in a 55-year-old woman with triple-positive disease. The second local recurrence was at 14.1 months in a 75-year-old woman with ER−/PR−/HER2+ grade 3 disease. Four patients (5%) developed metastatic disease at a median of 7.7 months (range, 3.5-14.3). Two of these patients (2%) died from their disease at 19.5 months and 21.4 months.

Six patients (7%) experienced a grade 3 AE. Grade 3 AEs included RD in 1 patient (1%), breast pain in 1 patient (1%), and both RD and breast pain in 4 patients (5%). All of these were acute except the 1 patient with breast pain alone. Grade 2 AE was the highest recorded AE for 60 patients (73%) with most experiencing only acute AEs (56/60 patients). One patient experienced late grade 2 pericardial effusion from trastuzumab. The most common grade 2 AE was

TABLE 3 Proton Beam Therapy Studies after Breast-conserving Surgery

Author	n	Surgery (# of pts)	Radiation	PBT technology	Median Follow-up (mo)	Dose (Gy RBE)	Adverse events
Bradley et al 2016[5]	18	BCS (7) Mast (11)	PBT for 10 pts (9 PMRT, 1 BCS) PBT + photon for 8 pts (6 BCS, 2 PMRT)	Passive	20	50.4	≥G2 RD 100% G3 RD 22%
Cuaron et al 2015[11]	30	BCS (4) Mast (24) WLE (2)	PBT	US	9.3	50.4	G2 RD 71.4% G3 RD 0%
DeCesaris et al 2019[10]	86	BCS (34) Mast (50) Other (2)	PBT for 39 pts (16 BCS, 21 Mast, 2 other) Photon for 47 pts (18 BCS, 29 Mast)	PBS	NR	45-54	PBT pts: G2 RD 69.2% G3 RD 5.1%
Liang et al 2018[13]	23	BCS (12) Mast (11)	PBT	Passive	NR	50-50.4	G3 RD 43%
Verma et al 2017[12]	91 (93 cancers)	BCS (27) Mast (66)	PBT	PBS + US	15.5	50.4	G2 RD 72% G3 RD 5%
Present Study	82	BCS	PBT	PBS + US	8.1	50.4	≥G2 RD 70.7% Any G3 7.3% G3 RD 6.1%

Abbreviations: BCS, breast-conserving surgery; G, grade; Mast, mastectomy; NR, not reported; PBS, pencil beam scanning; PBT, proton beam therapy; PMRT, postmastectomy radiation therapy; pts, patients; RBE, relative biologic effectiveness; RD, radiation dermatitis; US, uniform scanning; WLE, wide local excision.

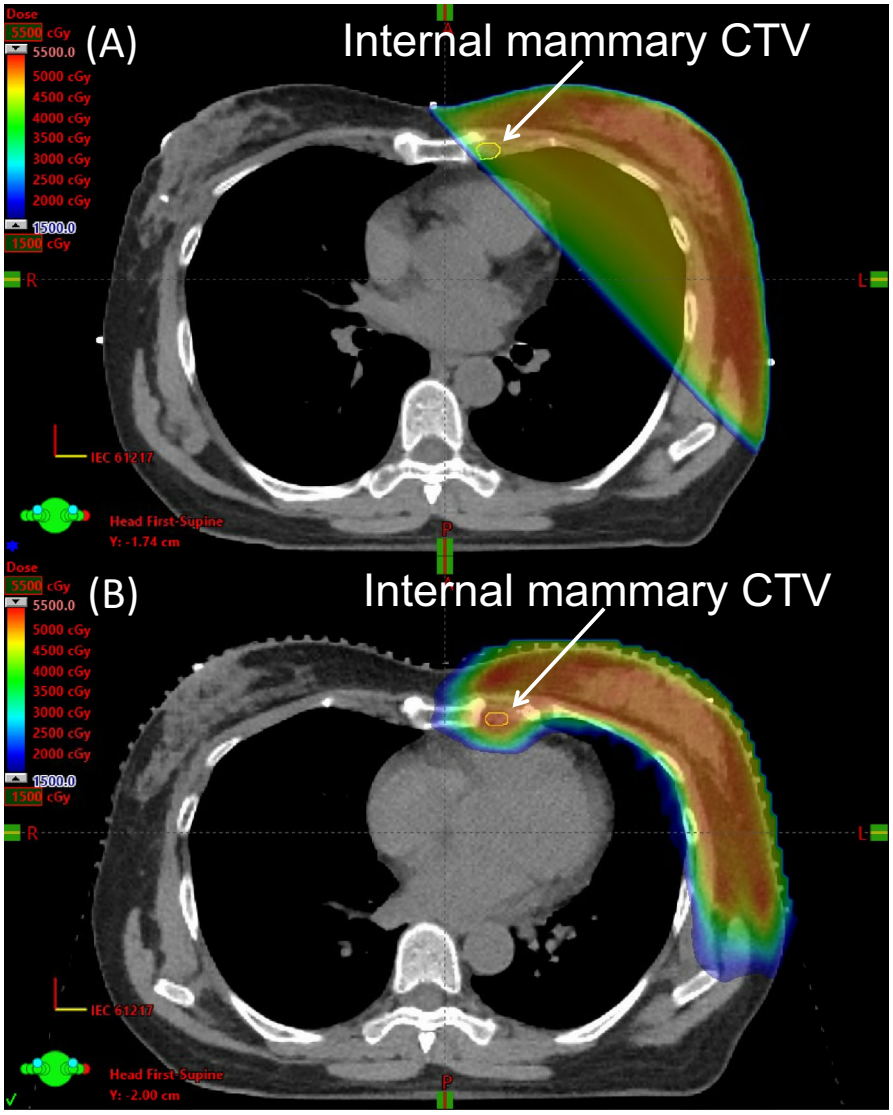

FIGURE 1 Comparison of typical internal mammary node clinical target volume (CTV) coverage with dose color wash with photons (A) and protons (B)

RD (52 patients) and pain (25 patients). Grade 1 AE was the highest recorded AE for 16 patients (20%) with most of experiencing only acute AEs (13/16 patients) and RD being the most common (15/16 patients).

Fifty-eight patients (70.7%) experienced ≥2 RD, and 5 patients (6.1%) experienced ≥3 RD. Two patients experienced grade 1 brachial plexopathy. There were no cases of pneumonitis of any grade.

Table 2 shows treatment characteristics by grade 1-2 RD vs grade 3. In total, 5 patients (6.2%) experienced grade 3 RD. Body mass index (BMI) was higher in patients who experienced grade 3 RD, with a median of 27.4 kg/m^2 in patients with grade 1-2 RD vs 38.2 kg/m^2 in patients with grade 3 RD (P = .02). No other treatment characteristic was found to be statistically significant for the development of grade 3 RD.

4 | DISCUSSION

As the use of PBT for breast cancer increases, prospective clinical trials and registries are necessary to establish possible clinical advantages of PBT. Adjuvant PBT after BCS has been reported in the literature in mostly small retrospective cohorts (Table 3).[5,10-13] Our reported rates of AEs compare favorably to the literature.

Although PBT offers several dosimetric advantages compared to photons,[4,6-8,14] higher rates of RD have been observed with PBT for breast cancer. DeCesaris et al reported higher rates of grade ≥2 RD with PBT compared to photons (69.2% vs 29.8%; P = .002).[10] There was no significant difference in grade 3 RD (5.1% PBT vs 4.3% photons; P = .848). These rates are consistent with our study. The only factor associated with grade 3 RD in our study was BMI (P = .02), which is consistent with other studies.[15,16] However, it is unclear if this is due to increased skin folds, larger amount of skin irradiated, or other factors. Furthermore, most patients in our study were treated with conventional fractionation. Hypofractionation may improve toxicity with PBT as it has been reported with photons.[17]

The clinical significance of grade ≥2 RD is uncertain, but is likely an acceptable trade-off in many situations given the improved coverage and decreased dose to normal tissues that PBT offers (Figure 1). The patient population of our study implies which patients who may

benefit from this trade-off—74% had left-sided cancers and 83% received RNI, including 66% with internal mammary nodes.

Our study has several limitations. Although the data were collected prospectively, this analysis is retrospective and relied on toxicity assessments of the treating physicians during weekly on-treatment visits and in follow-up at their discretion. This could lead to underreporting AEs. Additionally, the population is heterogeneous, treated across multiple institutions, and is subjected to selection bias. The short follow-up limits the evaluation of late toxicities like cardiac.

PBT including RNI after BCS is well-tolerated with only 7.3% of patients experiencing grade 3 adverse events. RD was the most common grade 3 adverse event (6.1% of patients). Elevated BMI may increase the risk of developing grade 3 RD. Further studies are needed to clarify which patients benefit from PBT for breast cancer.

CONFLICT OF INTEREST

We confirm that there are no known conflicts of interest associated with this publication.

AUTHOR CONTRIBUTIONS

We confirm that the manuscript has been read and approved by all named authors.

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