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Scientific Article

Comparative Evaluation of Proton Therapy and Volumetric Modulated Arc Therapy for Brachial Plexus Sparing in the Comprehensive Reirradiation of High-Risk Recurrent Breast Cancer

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Purpose: Recurrent or new primary breast cancer requiring comprehensive regional nodal irradiation after prior radiation therapy (RT) to the supraclavicular area and upper axilla is challenging due to cumulative brachial plexus (BP) dose tolerance. We assessed BP dose sparing achieved with pencil beam scanning proton therapy (PBS-PT) and photon volumetric modulated arc therapy (VMAT).

Methods and Materials: In an institutional review board–approved planning study, all patients with ipsilateral recurrent breast cancer treated with PBS-PT re-RT (PBT1) with at least partial BP overlap from prior photon RT were identified. Comparative VMAT plans (XRT1) using matched BP dose constraints were developed. A second pair of proton (PBT2) and VMAT (XRT2) plans using standardized target volumes were created, applying uniform prescription dose of 50.4 per 1.8 Gy and a maximum BP constraint <25 Gy. Incidence of brachial plexopathy was also assessed.

Results: Ten consecutive patients were identified. Median time between RT courses was 48 months (15-276). Median first, second, and cumulative RT doses were 50.4 Gy (range, 42.6-60.0), 50.4 Gy relative biologic effectiveness (RBE) (45.0-64.4), and 102.4 Gy (RBE) (95.0-120.0), respectively. Median follow-up was 15 months (5-33) and 18 months for living patients (11-33) Mean BP max was 37.5 Gy (RBE) for PBT1 and 36.9 Gy for XRT1. Target volume coverage of V85% (volume receiving 85% of prescription dose), V90%, and

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V95% were numerically lower for XRT1 versus PBT1. Similarly, axilla I-III and supraclavicular area coverage were significantly higher for PBT2 than XRT2 at dose levels of V55%, V65%, V75%, V85%, and V95%. Only axilla I V55% did not reach significance ($P = .06$) favoring PBS-PT. Two patients with high cumulative BPmax (95.2 Gy [RBE], 101.6 Gy [RBE]) developed brachial plexopathy symptoms with ulnar nerve distribution neuropathy without pain or weakness (1 of 2 had symptom resolution after 6 months without intervention).

Conclusions: PBS-PT improved BP sparing and target volume coverage versus VMAT. For patients requiring comprehensive re-RT for high-risk, nonmetastatic breast cancer recurrence with BP overlap and reasonable expectation for prolonged life expectancy, PBT may be the preferred treatment modality.

Introduction

Approximately 25% to 30% of patients with breast cancer present with regional nodal involvement or other high-risk features for which regional nodal irradiation (RNI) is indicated in the adjuvant setting for improvement in local-regional recurrence risk reduction, along with improvement in disease-free survival and overall survival.[1-7] Treatment volumes generally include the breast in the postlumpectomy setting or the chest wall in the postmastectomy setting, the axilla levels I-III, and the supraclavicular region. The internal mammary chain is also sometimes included depending on practice patterns and individual risk level.

Even after ideal multimodality treatment, these patients are at substantial risk of local-regional relapse in the years after radiation therapy (RT) completion. Ipsilateral recurrent or new primary breast cancer is a high-risk situation at baseline, requiring strong consideration for treatment escalation for adequate tumor control given treatment-refractory and aggressive biologic behavior, along with the presence of baseline unfavorable features in most cases, such as nodal involvement, lymphvascular invasion, and dermal lymphatic/skin involvement. In these situations, our standard approach is maximal surgical resection along with systemic therapy when indicated, along with salvage comprehensive reirradiation to the breast/chest wall and regional lymphatic basins, including the axilla levels I-III, supraclavicular fossa (SCV), and internal mammary lymph nodes (IMN) to a dose of 45 to 50.4 Gy in 1.8 Gy daily fractions. Proton therapy (PBT) is often recommended for these patients to achieve maximal sparing of previously irradiated tissues, in particular the lungs and heart, along with the surrounding nontarget soft tissue, in an attempt to mitigate lung fibrosis/pneumonitis, major cardiac sequelae, and soft tissue fibrosis, respectively.

Although PBT is a favorable option in the reirradiation setting for sparing of aforementioned normal tissue given the unique physical property of the Bragg peak and lack of exit dose of the proton beamlets,[8,9] the brachial plexus (BP) is an organ at risk (OAR) that remains at significant risk for radiation-related damage given its location, traversing multiple nodal regions at risk, most commonly with significant volumes of the plexus included in the axilla level II, axilla level III, and SCV regions. This is of major concern in the setting of prior RNI, but even with prior tangent field alone RT, the BP may be at least partially included with the use of a "high tangent" technique, as was delivered in half of all patients who received tangent-only irradiation based on the radiation field design analysis of the ACOSOG Z0011 trial.[10] Two definitive courses of breast RT to the BP, without any specific constraints placed on this OAR, would deliver at least 100 Gy, which substantially exceeds commonly used BP dose constraints (commonly 60-62 Gy based on volume of BP irradiated).[11] Brachial plexopathy, defined per Common Terminology Criteria for Adverse Events v5.0 as "A disorder characterized by regional paresthesia of the BP, marked discomfort and muscle weakness, and limited movement in the arm or hand," is a potential morbidity of RT that can severely affect patient quality of life. Thus, identifying the ideal radiation modality and treatment approach that can optimally reduce dose to the BP, while maintaining prescription dose coverage to the surrounding target volumes at risk, remains a challenge and a priority for these patients.

This study aims to compare 2 radiation techniques, PBT and photon volumetric modulated arc therapy (VMAT), which have the highest potential for conformality in the conventional (nonstereotactic body RT [SBRT]) dose setting to identify which modality provides optimal BP dose sparing while preserving target volume coverage. Early clinical outcomes of patients treated with BP dose-sparing techniques are also described.

Methods and Materials

Patient selection

Institutional review board approval was obtained for this retrospective planning study. All consecutive patients treated with definitive-intent PBT for recurrent or new nonmetastatic primary breast cancer with target volumes requiring at least partial BP overlap in the reirradiation

treatment plan who previously received ipsilateral RT for breast cancer at a single institution from June 2020 to October 2021 were identified.

PBT

All patients were treated on a ProBeam system (Varian Medical Systems, Palo Alto, California) with a dedicated nozzle and were immobilized with VacQfix Vacuum Cushions (Qfix, Avondale, Pennsylvania) on a Klarity WingSpan wingboard (Klarity Medical, Guangzhou, China). Bilateral arms were raised over the head for all patients.

Prior radiation treatment doses in Digital Communications in Medicine—RT format were obtained and deformable registrations were performed between the prior computed tomography (CT) simulation images and current CT simulation images to generate the deformable prior radiation treatment dose in Velocity Oncology Imaging Informatics System (Varian Medical Systems, Palo Alto, California). Cumulative doses were generated using Plan Sum function in Eclipse Treatment Planning System (TPS) (Varian Medical Systems, Palo Alto, California) across RT courses. Target volume delineation was performed according to the RadComp contouring atlas.[12] The BP was delineated using the Radiation Therapy Oncology Group—validated BP contouring atlas with a 5-mm diameter brush.[13] The BP was contoured to include its path distally through the axilla.

PBT was delivered with intensity modulated PT (IMPT) using pencil beam scanning PT. Patients were planned with Eclipse TPS (Varian Medical Systems) and were treated on a full gantry using 2 to 4 en face fields with a hinge angle of at least 20° and a 3.4- or 5.7-cm water-equivalent thickness range shifter. In patients treated with a third posterior beam, this beam was used to maximize target volume coverage posterior to the BP that can otherwise lose significant dose when constraining the BP to lower dose levels. A multi-field optimization (MFO) technique was used to allow for differential field design to account for arm position and for BP region isolation to improve target coverage posterior to the BP. A 2-cm safety margin from the edge of the treatment couch was incorporated for the posterior beam, and the inferior boundary of the wingboard was also avoided to mitigate interface setup uncertainties.

Pencil beam scanning—PBT plans were optimized with clinical target volume (CTV)—based robust optimization, and the plan robustness was evaluated to ensure V95 > 95% for all permutations of the CTV. The maximum MU per spot was manually edited to <200 MU per spot. Particular attention is given to any highly weighted spots within or immediately proximal to critical OARs, which are then redistributed to adjacent spots. A 0.5-cm setup uncertainty and 3.5% calibration curve error perturbation were applied to target volumes and to the BP and evaluated with the same metrics in plan uncertainty. The second to worst case scenario for coverage was evaluated.

Physician-specific OAR dose constraints were determined on an individual basis for each patient depending on the previously treated area and current clinical presentation. On all plans, the BP dose was minimized by cropping the target with a distance determined by the BP constraint. Overlapping dose with the BP was optimized until it was well below the constraint. The cropped area was then maintained at a minimum dose of 2 to 3 Gy below the BP dose constraint to maximize surrounding CTV coverage.

Patients were set up using image-guided RT employing daily cone beam CT (CBCT) scans (orthogonal kV radiographs followed by kV-CBCT). Verification simulations were performed every 2 weeks to verify reproducibility and assess for interval soft tissue swelling or other significant anatomic changes. If a change affecting dose distribution was noted, an adaptive plan was generated.

Comparative plan generation and proton versus photon comparative analysis

Four radiation plans were developed for each patient, with IMPT plans developed by proton dosimetrists at the New York Proton Center and VMAT plans developed by photon dosimetrists at Memorial Sloan Kettering Cancer Center, all specializing in breast cancer planning using Eclipse TPS. Each patient had the original proton plan used for treatment (PBT1); comparative VMAT plan using matched BP planning constraints, prescription dose, and target volumes used in the original proton plans for patient treatment (XRT1); control proton plan (PBT2); and control VMAT plan (XRT2), with PBT2 and XRT2 using uniform target volumes, including the unilateral breast/chest wall and regional lymph nodes (axilla I-III, SCV, IMN). For the control plans PBT2 and XRT2, the prescription dose was 50.4 Gy in 28 fractions, BP maximum dose constraint applied was 25 Gy, and clinical target volume goal coverage was V95% > 95%, Dose constraints for the heart, lungs, and esophagus were applied per institutional standard: PBT2 heart mean ≤1 Gy, ipsilateral lung V5 Gy ≤ 42%, ipsilateral lung V20 Gy ≤ 33%, contralateral lung V5 Gy ≤ 10%, esophagus max ≤4 Gy; XRT2 heart mean ≤4 Gy, ipsilateral lung V20 Gy ≤ 30%, ipsilateral lung V10 Gy ≤ 65%, contralateral lung V20 Gy ≤ 5%, esophagus max ≤35 Gy. Dose-volume histograms were generated and evaluated for individual target volume coverage as applicable (breast/chest wall, axilla I, axilla II, axilla III, IMN, SCV) and OAR doses (heart, ipsilateral lung, contralateral lung, BP) for each VMAT and IMPT plan. A comparative analysis of these metrics between proton and photon plans was performed.

BP sparing for the PBT2 plans involved the addition of an additional posterior field to the standard breast beam arrangement of 3 anterior oblique fields. The posterior field covered only the region of the BP, allowing for dose reduction to the BP while still maintaining coverage of the target volume occurring posterior to the BP. For the XRT2 plans, 5 partial arcs were used in general, with the addition of more arcs as needed. For the typical 5-arc plan, 2 arcs were limited to avoid direct entry into the arm or chin and to cover the whole planned target volume (PTV). The next 2 arcs covered the PTV inferior to the arm, including the lateral PTV. The fifth arc was limited to target the SCV PTV. A 90° collimator was used for the fifth arc, and a 0° collimator was used for the remaining arcs. This approach has been demonstrated to provide increased conformality, improved cardiac dose sparing, and reduced positioning uncertainty, compared with a treatment approach using fewer (2-3) partial arcs.[14,15]

Clinical outcomes analysis

Patient and tumor characteristics, treatment planning parameters, disease status, and incidence of radiation-induced brachial plexopathy (RIBP) were collected. RIBP was scored using Common Terminology Criteria for Adverse v5.0 (grade 1: asymptomatic; clinical or diagnostic observations only; intervention not indicated. Grade 2: moderate symptoms; limiting instrumental activities of daily life [ADLs]. Grade 3: severe symptoms; limiting self-care ADL; mechanical assistance indicated).

Statistical methods

Descriptive statistics were used to characterize the patients included in the study with respect to treatment details. To assess differences in percent dose received across the 2 treatment modalities in each region, unadjusted linear mixed effects models with treatment modality as the predictor of interest and subject included as a random intercept were performed separately for each region and each target dose metric. Finally, for each region, the average target dose across all patients was plotted as a function of the dose metric. Statistical significance was taken at the $P < .05$ level and was not adjusted for multiplicity due to the pilot nature of the study. All analyses were performed using R statistical software, version 4.0.4.

Results

Ten consecutive patients were identified who met criteria for inclusion in this analysis. Treatment details are outlined in Table 1. Median first, second, and cumulative RT doses were 50.4 Gy (42.6-60.0), 50.4 Gy (relative biological effectiveness [RBE]) (45.0-64.4), and 102.4 Gy (RBE) (95.0-120.0), respectively. IMPT and VMAT plans matched BP max doses, with the mean maximum BP doses 37.5 Gy (RBE) for IMPT and 36.9 Gy for VMAT (Table 2). Target volume coverage of V85% (volume receiving 85% of prescription dose), V90%, and V95% were generally lower for VMAT versus IMPT plans: axilla level II were 83.3% versus 86.5% ($P = .17$), 78.1% versus 83.4% ($P = .04$), and 71.7% versus 79.4% ($P < .01$) respectively; axilla level III were 75.7% versus 82.0% ($P = .39$), 66.7% versus 78.8% ($P = .12$), and 50.9% versus 58.3% ($P = .32$), respectively; and SCV were 76.9% versus 78.5% ($P = .69$), 67.3% versus 73.1% ($P = .15$), and 55.1% versus 56.3% ($P = .78$), respectively (Fig. 1).

Table 1 Radiation treatment details (N = 10)

Characteristic	n (%)/Median (range)
Laterality (recurrence)	
Left	3 (30%)
Right	7 (70%)
Time between RT courses (mo)	48 (15-276)
First RT dose (Gy RBE)	50.4 (42.6-60.0)
Re-RT dose (Gy RBE)	50.4 (45.0-64.4)
Cumulative RT dose (Gy RBE)	102.4 (95.0-120.0)

Abbreviations: RBE = relative biologic effectiveness; RT = radiation therapy.

Among comparison plans with standard treatment volumes, uniform prescription dose of 50.4 Gy and maximum BP dose constraint of <25 Gy (XRT2 and PBT2), coverage of the 3 levels of the axilla and supraclavicular region differed significantly at dose levels of V55%, V65%, V75%, V85%, and V95% between the VMAT and IMPT plans, with increased dose coverage in the IMPT plans (Table 3). Only V55% of axilla level I coverage did not differ significantly between the 2 plans ($P = .06$). The most significant difference in coverage between IMPT and VMAT was apparent in the SCV and axilla level III target volumes (Fig. 2). For the SCV, V95% was 70.2% with IMPT versus 22.6% with VMAT; V85% was 76.9% versus 29.1%, V75% was 81.6% versus 39%, and V65% was 85.7% versus 55.3% (all $P < .001$). For axilla level 3, V95% was 76.2% IMPT versus 50.4% VMAT, V85% was 82.4% versus 59.0%, V75% was 86.4% versus 66.5%, and V65% was 89.8% versus 75.0% (all $P < .001$). Coverage of regions through which the BP does not typically traverse, including the chest wall/breast and IMN chain, was not significantly different between VMAT and IMPT.

The heart mean dose was significantly reduced with IMPT versus VMAT (0.7 Gy IMPT vs 6.4 Gy VMAT; $P < .01$) (Table 3). Ipsilateral and contralateral lung V5 Gy, V10 Gy, and V20 Gy were also significantly less in the

Table 2 Means and standard deviations (SDs) for regions receiving 85%, 90%, or 95% of the target dose by region and modality for patient plans XRT1 and PBT1

			VMAT (Plan XRT1)		IMPT (Plan PBT1)		Modality difference
Region	Dose metric	N	Mean	SD	Mean	SD	*P* value
Axilla level I*	V85% (%)	2	82.8	6.7	76.8	11.5	–
	V90% (%)	2	65.1	27.0	67.1	20.3	–
	V95% (%)	2	56.5	31.6	58.4	25.5	–
Axilla level II	V85% (%)	6	83.3	13.3	86.5	13.9	.17
	V90% (%)	6	78.1	15.8	83.4	15.4	.04†
	V95% (%)	6	71.7	15.6	79.4	16.4	<.01†
Axilla level III	V85% (%)	5	75.7	32.1	82.0	31.4	.39
	V90% (%)	5	66.7	29.5	78.8	34.0	.12
	V95% (%)	5	50.9	27.8	58.3	46.7	.32
SCV	V85% (%)	8	76.9	25.5	78.5	31.0	.69
	V90% (%)	8	67.3	28.8	73.1	30.4	.15
	V95% (%)	8	55.1	29.5	56.3	35.8	.78
Brachial plexus	Max (Gy)	10	36.9	10.3	37.5	10.6	.39
	Mean (Gy)	10	36.9	10.3	20.1	11.6	<.01†

Abbreviations: IMPT = intensity modulated proton therapy; N = number of patients with available data; PBT = proton therapy; SCV = supraclavicular region; VMAT = volumetric modulated arc therapy; XRT = VMAT plan.

* No *P* values were generated for target dose comparisons due to the very small sample size (N = 2).

† $P < .05$.

IMPT plans. Notably, ipsilateral lung V5 Gy and V20 Gy for the IMPT plans were 32.3% and 12.5%, and for the VMAT plans were 85.7% ($P < .001$) and 21.1% ($P < .01$), respectively.

Of the 10 patients included, none received concurrent chemotherapy; 4 patients (40%) received chemotherapy before reirradiation for their breast cancer recurrence. All patients were assessed for baseline lymphedema and neuropathy. Two patients had pre-existing ipsilateral arm lymphedema, and 1 patient with gross tumor involving the BP had baseline ipsilateral arm/shoulder neuropathy. Clinical outcomes of treated patients are outlined in Table 4. Patients were treated to a maximum cumulative BP maximum dose ranging from 56.2 Gy to 106.1 Gy. All patients included in this study received prior comprehensive RT to the breast or chest wall with inclusion of the

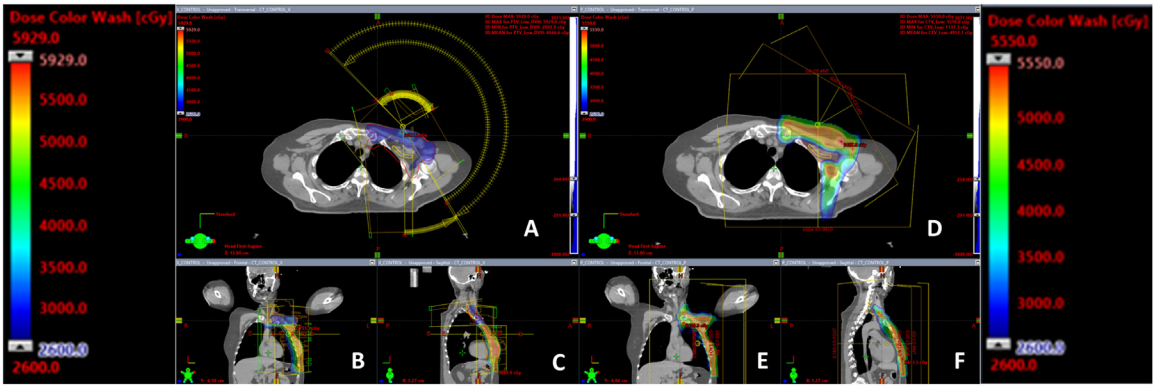

Figure 1 Representative treatment plan of a patient receiving comprehensive reirradiation to the left chest wall and regional lymph nodes in the setting of recurrent disease and a history of prior ipsilateral comprehensive nodal irradiation. (A) Axial, (B) coronal, and (C) sagittal slices using volumetric modulated arc therapy technique. (D) Axial, (E) coronal, (F) sagittal slices using intensity modulated proton therapy technique. Yellow contour outline = left brachial plexus.

Table 3 Means and standard deviations (SDs) for regions receiving standard treatment volumes of the target dose by region and modality for control plans XRT2 and PBT2

		VMAT (Plan XRT2)		IMPT (Plan PBT2)		Modality difference
Region	Dose metric	Mean	SD	Mean	SD	*P* value
Chest wall/Breast	V95% (%)	96.8	3.3	95.1	3.4	.26
	V85% (%)	99.2	1.6	99.6	0.8	.43
	V75% (%)	99.5	1.5	99.8	0.5	.44
	V65% (%)	99.6	1.2	99.9	0.3	.46
	V55% (%)	99.9	0.3	100.0	0.2	.63
Axilla level I	V95% (%)	82.4	8.5	91.5	7.0	<.01*
	V85% (%)	88.4	6.4	94.3	4.8	<.01*
	V75% (%)	91.8	5.9	95.9	3.5	<.01*
	V65% (%)	94.6	5.4	97.2	2.5	.02*
	V55% (%)	97.2	3.1	98.3	1.5	.06
Axilla level II	V95% (%)	52.9	17.5	75.0	11.1	<.01*
	V85% (%)	61.5	17.6	81.7	9.2	<.01*
	V75% (%)	70.8	17.2	85.9	7.5	<.01*
	V65% (%)	78.8	16.5	89.4	6.1	<.01*
	V55% (%)	87.1	12.4	92.8	4.6	.046*
Axilla level III	V95% (%)	50.4	20.2	76.2	21.3	<.01*
	V85% (%)	59.0	22.7	82.4	20.0	<.01*
	V75% (%)	66.5	24.1	86.4	18.0	<.01*
	V65% (%)	75.0	25.9	89.8	15.7	<.01*
	V55% (%)	82.1	24.2	93.0	12.6	.01*
IMN	V95% (%)	92.3	7.9	97.8	3.9	.03*
	V85% (%)	96.5	7.2	99.1	2.1	.12
	V75% (%)	97.8	5.8	99.6	1.1	.25
	V65% (%)	98.2	5.6	99.9	0.3	.32
	V55% (%)	98.5	4.7	100.0	0.02	.32
SCV	V95% (%)	22.6	23.2	70.2	6.9	<.01*
	V85% (%)	29.1	28.0	76.9	5.7	<.01*
	V75% (%)	39.0	27.7	81.6	4.8	<.01*
	V65% (%)	55.3	25.2	85.7	4.0	<.01*
	V55% (%)	75.0	21.7	89.9	3.2	.02*
Heart	Mean (Gy)	6.4	5.9	0.7	0.2	<.01*
	Max (Gy)	28.4	13.1	34.6	7.6	.13
Ipsilateral lung	V5 Gy (%)	85.7	20.8	32.3	21.5	<.01*
	V10 Gy (%)	51.3	15.7	23.6	16.1	<.01*
	V20 Gy (%)	21.1	12.7	12.5	8.6	<.01*
Contralateral lung	V5 Gy (%)	56.7	25.3	14.7	21.5	<.01*
	V10 Gy (%)	29.7	24.8	9.9	15.5	<.01*
	V20 Gy (%)	8.7	12.9	4.3	7.1	.03*
Brachial plexus	Max (Gy)	20.1	9.0	23.1	3.7	.27

(*continued on next page*)

Table 3 (*Continued*)

		VMAT (Plan XRT2)		IMPT (Plan PBT2)		Modality difference
Region	**Dose metric**	**Mean**	**SD**	**Mean**	**SD**	***P* value**
	D2 cc (Gy)	16.5	8.9	19.2	5.3	.37
	Mean (Gy)	18.6	2.9	16.6	2.4	<.01*

Abbreviations: IMN = internal mammary lymph nodes; IMPT = intensity modulated proton therapy; max = maximum; N = number of patients with available data; PBT = proton therapy; SCV = supraclavicular region; VMAT = volumetric modulated arc therapy; XRT = VMAT plan.
* $P < .05$.

regional lymph nodes. Target volumes were heterogeneous among patients but, in general, most patients were treated to the chest wall/breast along with at least 2 or more regional nodal volumes that placed the BP at risk of overlap with the prior radiation field. At a median follow-up of 15 months,[5–32] 7 patients (70%) were alive at the time of data censoring. Among patients alive at last follow-up, median follow-up was 18 months.[11–32] The 3 patients who died developed distant progression of disease. Five of the 7 patients still living have no evidence of disease; the remaining 2 had local recurrence, one of whom had gross disease at the time of treatment and progressed at 13 months after re-RT, and the second who recurred at 11 months after re-RT.

Two patients have developed symptoms of grade 1 brachial plexopathy, both with neuropathy ("pins and needles" sensation) in the ulnar nerve distribution, both beginning approximately 8 months after completion of reirradiation; symptoms were transient in 1 patient and resolved without intervention after 6 months. Neither of these patients developed pain or weakness to the affected upper extremity. The cumulative BP maximum doses for each of these patients were among the highest of the cohort after shared decision-making and patient preference, with a reirradiation course maximum BP dose of 101.6 Gy and estimated 94.7 Gy, respectively. These patients were at particularly high risk for recurrence due to positive margins after recurrent tumor resection in the

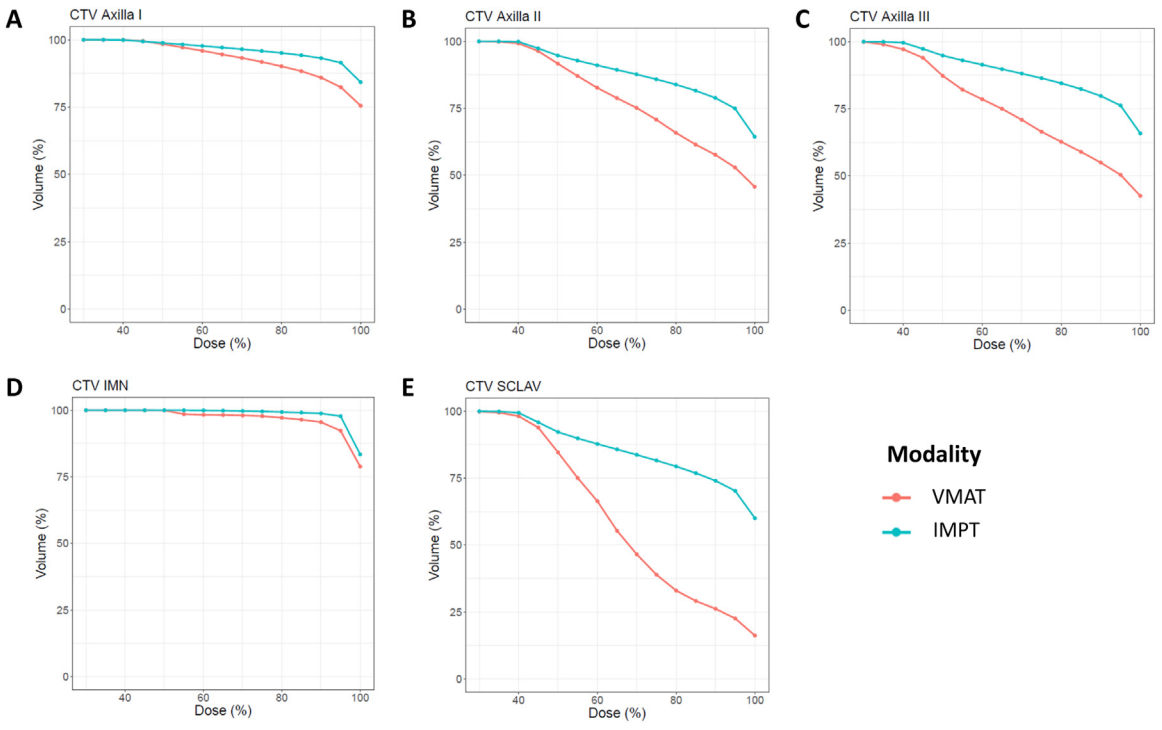

Figure 2 Graphs of proton versus photon dose for target regions for XRT2 and PBT2 plans. (A) Axilla level 1 CTV, (B) axilla level 2 CTV, (C) axilla level 3 CTV, (D) IMN CTV, and (E) SCLAV CTV. Red line = VMAT dose-volume curve. Blue line = IMPT dose-volume curve. *Abbreviations:* CTV = clinical target volume; IMN = internal mammary lymph nodes; IMPT = intensity modulated proton therapy; PBT = proton therapy; SCLAV = supraclavicular region; SCV = supraclavicular region; VMAT = volumetric-modulated arc therapy; XRT = VMAT plan.

Table 4 Patient treatment details and clinical outcomes (N = 10)

Pt	Age (y)	TV included	Months between courses	BP max dose (Gy)	BP cumulative max dose (Gy)	F/u (mo)	Brachial plexus toxicity	Disease status
1	63	CW axilla I-3 SCV	91	48.0	101.6	28	Grade 1 RIBP (ipsilateral ulnar nerve neuropathy)	NED
2	51	CW axilla 2-3 SCV	119	44.7	95.2	29	No RIBP (transient ipsilateral ulnar nerve neuropathy)	NED
3	82	CW axilla 2-3 SCV	18	35.0	78.2	18	No RIBP	NED
4	61	SCV	36	42.7	93.8	6	No RIBP	Deceased (DP)
5	53	CW axilla 2-3 SCV	60	45.9	89.9	11	No RIBP	NED
6	65	IMN SCV	109	30.9	91.3	18	No RIBP	Deceased (DP)
7	42	CW axilla 1-2	15	15.4	56.2	11	–	AWD
8	55	CW, SCV	276	36.8	NR	33	No RIBP	NED
9	62	Breast axilla 3 SCV	27	43.3	83.2	12	No RIBP	AWD
10	41	CW axilla 2 SCV	18	26.1	80.3	5	No RIBP	Deceased (FTT)

Abbreviations: AWD = alive with disease; BP = brachial plexus; CW = chest wall; DP = distant disease progression; F/u = follow-up; FTT = failure to thrive; IMN = internal mammary lymph nodes; max = maximum; NED = no evidence of disease; NR = no record; Pt = patient; RIBP = radiation-induced brachial plexopathy; SCV = supraclavicular region; TV = target volume.

upper axilla/SCV abutting the BP and inflammatory, multicentric, node-positive disease recurrence, respectively.

Discussion

Ipsilateral locoregional breast cancer recurrence after definitive therapy that included RT presents a treatment challenge, particularly in the setting of recurrent disease requiring repeat comprehensive nodal irradiation for high-risk features such as nodal involvement, skin or dermal lymphatic invasion, lymphovascular invasion, high-grade disease, and triple negative disease. Practice patterns remain heterogeneous due to concerns for excess morbidity of a second definitive course of RT and given limited data to guide treatment recommendations, ranging from radiation omission to treatment of selective partial target volumes to repeat comprehensive nodal irradiation, with reirradiation doses ranging widely.

The risk of brachial plexopathy after breast irradiation has been cited in the literature, with reported rates ranging widely from 0% to 46%,[16] and with an well-accepted dose relationship for higher risk of BP injury with increasing total doses and higher doses per fraction.[17–20] In other disease site settings in which BP injury is also of concern, such as in the treatment of apical lung tumors and head and neck cancer, there has also been established risk of radiation-induced BP injury, again with a clear dose relationship.[21–23]

Guidance for BP radiation constraints are provided in the primary RT setting by Emami et al, citing a tolerance dose (TD) 5 of 5 (probability of 5% complications within 5 years of treatment) for the whole BP of 60 Gy, 2 of 3 BP of 61 Gy, 1 of 3 BP of 62 Gy, and a TD 50 of 5 of 75 Gy, 76 Gy, and 77 Gy, respectively, suggesting a volume and dose effect of BP radiation exposure and toxicity risk.[11] The Quantitative Analysis of Normal Tissue Effects in the Clinic summary did not include the BP among its organ normal tissue complication probability (NTCP) data.[24]

In an study from investigators at MD Anderson Cancer Center, 90 patients with non-small cell lung cancer (NSCLC) treated with definitive chemoradiation with >55 Gy delivered to the BP and median BP dose of 70 Gy,

16% developed brachial plexopathy at a median follow-up of 14 months. Multivariate analysis demonstrated a median BP dose of >69 Gy and maximum BP dose of 75 Gy to 2 cm^3 for the BP were predictive of brachial plexopathy.[25]

A volume relationship for increased risk of brachial plexopathy was also noted in an analysis from MD Anderson Cancer Center, in which patients with NSCLC with superior tumor/nodal disease location received ≥50 Gy definitive RT were found to have an estimated 3-year brachial plexopathy rate of 12%, with higher hazard ratio for development of radiation-induced brachial plexopathy in patients who received dose of 76 Gy to ≥1 cc of the BP.[21] An increased incidence of brachial plexopathy has also been reported in patients with head and neck cancer, with a precipitous increase in risk of complications with maximum point doses of >70 Gy.[23]

There is as yet limited guidance across disease sites on BP constraints in the reirradiation setting. In a recent executive summary from the American Radium Society on guidelines for reirradiation for NSCLC, the suggested cumulative BP maximum dose recommended across radiation courses was <85 Gy (2 Gy equivalents), which was applied in the standardized treatment comparison analysis in this study.[26]

Eastern Cooperative Oncology Group EA3191 (NCT04671667) is a recently activated 3-arm trial of patients with locoregionally recurrent or second primary head and neck squamous cell carcinoma receiving reirradiation alone or with pembrolizumb or platinum chemotherapy. In the protocol treatment planning parameters, the suggested BP dose constraint for the reirradiation treatment course is 60 Gy with hotspot avoidance.

Several reports of reirradiation using proton therapy or PBT are now available, with a portion of included patients in these series receiving reirradiation to the nodal regions including the upper axilla and SCV. A retrospective series from the Mayo Clinic included 72 women treated with a repeat course of RT to the breast/chest wall/regional lymph nodes, of whom 61% were treated with curative intent.[27] The regional lymph nodes were included in the treatment volume for the majority of patients, and patients received a median reirradiation dose of 50 Gy. Median cumulative dose was 103.54 Gy_2, including boosts. Grade 1 brachial plexopathy developed in 1 patient and grade 2 brachial plexopathy in 2 patients; both patients who developed grade 2 brachial plexopathy were treated with photons in both initial and reirradiation courses and had minimal BP overlap between the treatment courses (first patient initial course was to the whole breast alone; second patient reirradiation course was to the chest wall alone with palliative intent), with plexopathy potentially attributed to subsequent tumor recurrence with plexus involvement.

In the Memorial Sloan Kettering Cancer Center institutional experience of 46 patients treated for ipsilateral recurrent or new primary nonmetastatic breast cancer with reirradiation using PBT, patients were treated with curative intent to a median initial course dose of 60 Gy, median PBT re-RT course dose of 50.4 Gy and cumulative median dose of 110 Gy (RBE).[9] In the first course, the SCV was included in 11% of patients, whereas in the re-RT course, the comprehensive regional lymph nodes were included in 67%, and an additional 2% were treated to the SCV. Four patients had significant overlap of the BP; of the 2 with prior Digital Communications in Medicine RT treatment plans available, cumulative BP maximum doses were 99.0 Gy (RBE) and 94.5 Gy (RBE). One of these patients developed decreased arm range of motion and mild axillary pain.

There are limited data on the degree of tissue recovery that occurs between radiation courses and the implications that partial recovery has on individualization of dose constraints to any tissue, including the BP. Extrapolating from literature focusing on spinal cord tolerance of reirradiation, experiments involving 56 adult rhesus monkeys reirradiated to the spinal cord at MD Anderson Cancer Center suggest that after initial radiation of 44 Gy, delivery of reirradiation to 57.2 to 66.0 Gy in 2.2 Gy per fraction after 1, 2, or 3 years results in recovery of 76%, 85%, and 101% at the 5% myelopathy incidence level.[28] In an analysis of 5 patients with Hodgkin disease treated twice with chemoradiotherapy with overlapping spinal cord radiation fields and 1 to 3 years between treatment courses, there was no incidence of myelopathy with a cumulative radiation cord dose of 50 to 70 Gy after a follow-up of more than 10 years.[29] Two published series of 78 total patients treated with spinal reirradiation demonstrated that cumulative dose, along with interval of <6 months between RT courses and dose of >50 Gy in 2 Gy fractions in 1 of the 2 courses, increased the risk of myelopathy.[30,31] These studies generally have limited follow-up, use heterogeneous dose-fractionation regimens, report on small patient numbers, and focus specifically on spinal cord injury. It is unclear how the findings from these spinal cord reports can extrapolate this to the risk of BP injury. One report suggested that an interval between radiation courses to the BP in the setting of head and neck cancer of >2 years may result in a reduced risk of brachial plexopathy,[32] whereas a more recent and comprehensive study reported that the interval between treatment courses may not be a significant predictor of BP injury.[33]

Although daily fractionation is used at our institution in the setting of breast reirradiation, we recognize that the use of twice-daily fractionation has also commonly been used, especially in the treatment of radiation-induced breast angiosarcoma, in an attempt to decreased toxicities of reirradiation.[34–36] Based on our institutional experience using a once-daily treatment approach for reirradiation for recurrent breast cancer[9], and also drawing on similar favorable reported toxicity and efficacy outcomes from other published institutional experience,[27] this

remains our standard approach and that used in the treatment of the patients included in this study.

It has been well described in the literature across disease sites that IMPT allows for improved normal tissue sparing through improved dose conformality compared with the most sophisticated photon planning tools currently available, including VMAT.[37−40] The ability to provide improved dose coverage of the target volume with maximal avoidance of surrounding OARs has significant implication on the potential for optimal disease control to areas at risk for disease recurrence or progression. This OAR sparing affording by PT can be particularly important in the reirradiation setting to reduce the risk of toxicities.[41,42] Additionally, with the increasing availability of advanced pretreatment setup imaging on IMPT gantries such as on-board cone beam CT,[43] there is improved ability to align to areas of concern such as around the BP in the setting of reirradiation, thus allowing for a reduction of set-up uncertainty margin to clinical target volumes and increasing reliability of OAR sparing compared with what has been historically achievable with photon treatment. The potential to incorporate biologic dose constraints taking into consideration the differential RBE of the proton beam may further optimize delivery of PBT to the BP and reduce risk of RIBP.[44] RBE-based planning and increased incorporation of spot weighting in the treatment planning process may also be of particular value for the delivery of RNI for breast cancer as proton beam angles are selected to be in the direction that is least affected by respiratory motion. Due to the limited number of beams interacting with one another, a higher maximum dose could result than may be seen using arcs with photon VMAT techniques. As such, other methods to minimize hotspots and ensure an optimally homogeneous dose distribution will be of value.

This comparative analysis demonstrates that with the application of uniform dose parameters of BP maximum dose, prescription dose, and target volume inclusion, IMPT is able to provide dose sparing of the BP to meet goal dose constraints while maintaining excellent coverage of the target tissue immediately surrounding the BP at risk of harboring microscopic residual disease, include the axilla and supraclavicular regions. Moreover, the ability of IMPT to provide this level of dose conformality is superior to that achievable with VMAT. Of the patients included in this analysis, 2 developed possible evidence of at least transient BP injury, both of whom had cumulative maximum BP doses in excess of 85 Gy. This suggests adherence to reirradiation cumulative dose constraints to the BP is of importance, and further study to understand the optimal dose limits in this setting is needed, also taking into consideration time interval between courses, volume of BP overlap, and clinical risk.

Limitations of this comparative analysis include heterogeneous target volumes, BP dose constraints, and accepted target volume coverage used in patient treatment plans PBT1, making interpretation of clinical outcome information challenging. We attempted to address these and provide more clarity on the true relative benefits of PBT in comparison with VMAT to provide optimal target volume and BP sparing by creating control plans XRT2 and PBT2, providing a standardized approach to planning and plan analysis. In addition, a maximum dose constraint of 25 Gy was placed on the BP for the control plans; however, identifying the ideal dose constraint requires further study, and extrapolating from recent lung cancer guidelines, a maximum cumulative dose of 85 Gy could be considered. CT-based planning was used for BP delineation using BP contouring atlases, including the Radiation Therapy Oncology Group−validated atlas by Hall et al.[13,45] This approach, while widely used in radiation oncology treatment planning, has some limitations due to the resolution of a CT simulation scan. Magnetic resonance imaging of the BP in the treatment position that can be fused with the CT simulation could allow for more accurate BP delineation and dose analyses in high-risk settings such as repeat comprehensive RNI. Follow-up duration of included patients is limited in our series, which may be of particular significance as RIBP is a toxicity that may not present until years after treatment, although with escalated cumulative doses as were used in this cohort, this timeline may be substantially shortened.[17−20] Finally, receipt of surgery and other baseline risk factors for brachial plexopathy may exist in these patients who have undergone multimodality treatment for their primary and recurrent breast cancer, which may affect the individual's risk of development of brachial plexopathy beyond reirradiation.

Strengths of this analysis include that the PBT and VMAT plans were intentionally developed by specialized proton and breast photon dosimetrists, respectively, to ensure quality plans were generation for this study, particularly important given the level of complexity of these reirradiation plans. While several physicians treated the patients included in this series, all patients were treated at a single institution, ensuring similar treatment planning and toxicity assessment approaches were applied. In the control plans, PBT2 and XRT2, a single radiation oncologist (JIC) contoured standardized volumes for all patients, reducing variability in BP and target volume delineation and subsequent treatment planning and analysis.

Conclusion

This is the first study to the authors' knowledge comparing VMAT and PBT in their ability to provide conformal dose sparing around the BP. We found that although both modalities provide conformal RT plans that can dose reduce in and around the BP, the resultant dose lost to the surrounding target volume at risk is substantially greater with VMAT compared with PBT.

Additional clinical experience and longer follow-up are needed to understand better cumulative BP dose constraints, the effect of time interval between courses, and reirradiation treatment parameters, including optimal prescription dose and target volumes. Based on our study, for patients requiring comprehensive reirradiation for high-risk, nonmetastatic breast cancer recurrence with concern for BP overlap and who have a reasonable expectation for prolonged life expectancy, PBT may be the preferred treatment modality.

Disclosures

J. Isabelle Choi reports personal fees from Varian Medical Systems outside of the scope of this work.

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