Evaluation of a mixed beam therapy for postmastectomy breast cancer patients: Bolus electron conformal therapy combined with intensity modulated photon radiotherapy and volumetric modulated photon arc therapy

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Purpose: The purpose of this study was to assess the potential benefits and limitations of a mixed beam therapy, which combined bolus electron conformal therapy (BECT) with intensity modulated photon radiotherapy (IMRT) and volumetric modulated photon arc therapy (VMAT), for left-sided postmastectomy breast cancer patients.

Methods: Mixed beam treatment plans were produced for nine postmastectomy radiotherapy (PMRT) patients previously treated at our clinic with VMAT alone. The mixed beam plans consisted of 40 Gy to the chest wall area using BECT, 40 Gy to the supraclavicular area using parallel opposed IMRT, and 10 Gy to the total planning target volume (PTV) by optimizing VMAT on top of the BECT + IMRT dose distribution. The treatment plans were created in a commercial treatment planning system (TPS), and all plans were evaluated based on PTV coverage, dose homogeneity index (DHI), conformity index (CI), dose to organs at risk (OARs), normal tissue complication probability (NTCP), and secondary cancer complication probability (SCCP). The standard VMAT alone planning technique was used as the reference for comparison.

Results: Both techniques produced clinically acceptable PMRT plans but with a few significant differences: VMAT showed significantly better CI (0.70 vs 0.53, $P < 0.001$) and DHI (0.12 vs 0.20, $P < 0.001$) over mixed beam therapy. For normal tissues, mixed beam therapy showed better OAR sparing and significantly reduced NTCP for cardiac mortality (0.23% vs 0.80%, $P = 0.01$) and SCCP for contralateral breast (1.7% vs 3.1% based on linear model, and 1.2% vs 1.9% based on linear-exponential model, $P < 0.001$ in both cases), but showed significantly higher mean (50.8 Gy vs 49.3 Gy, $P < 0.001$) and maximum skin doses (59.7 Gy vs 53.3 Gy, $P < 0.001$) compared with VMAT. Patients with more tissue (minimum distance between the distal PTV surface and lung approximately > 0.5 cm and volume of tissue between the distal PTV surface and heart or lung approximately > 250 cm³) between distal PTV surface and lung may benefit the most from mixed beam therapy.

Conclusion: This work has demonstrated that mixed beam therapy (BECT + IMRT:VMAT = 4:1) produces clinically acceptable plans having reduced OAR doses and risks of side effects compared with VMAT. Even though VMAT alone produces more homogenous and conformal dose distributions, mixed beam therapy remains as a viable option for treating postmastectomy patients, possibly leading to reduced normal tissue complications. © 2018 American Association of Physicists in Medicine [https://doi.org/10.1002/mp.12958]

Key words: bolus electron conformal therapy, intensity modulated photon radiotherapy, mixed beam therapy, postmastectomy radiotherapy, volumetric modulated photon arc therapy

1. INTRODUCTION

A mastectomy is highly recommended for patients with locally advanced primary breast cancer and extensive lymph node involvement. Due to prevalence of microscopic disease after mastectomy, postmastectomy radiotherapy (PMRT) is commonly performed to sterilize residual tumor cells; it has been shown to improve the overall survival for invasive breast cancer patients by reducing the risk of tumor recurrence and cancer mortality.¹ At our institution, the standard of care for PMRT has been Helical Tomotherapy^{2,3} or Volumetric Modulated photon Arc Therapy (VMAT).⁴ Both modalities provide good target coverage and dose homogeneity, but the large volume of stray radiation dose to normal tissues like lung, heart, and contralateral breast is a concern because that can potentially cause radiogenic side effects like radiation pneumonitis, cardiac toxicity, and secondary cancers.^{5–8}

The inherent rapid distal dose fall-off of therapeutic electron beams makes them suitable for treatment of the chest wall where the target volume is superficial and organs at risk (OARs) like the lungs and heart underlie the target.^{9,10} Advanced electron therapy technique uses energy (range) modulation without and with intensity modulation to further control the distal dose fall-off.¹¹ One method of achieving energy (range) modulation for electron beams is bolus electron conformal therapy (BECT).¹² It uses a variable thickness wax bolus on the patient surface, where the distal surface is machined to achieve an excellent fit to the patient's chest wall, and the proximal surface is machined to conform the 90% dose surface to the planning target volume (PTV) while sparing distal OARs.^{11,13} BECT has been shown to be very effective at treating postmastectomy patients,^{13–15} but dose homogeneity can sometimes be a problem.^{13,16} The feasibility of optimizing intensity modulated photon radiotherapy (IMRT) over a BECT dose plan to improve PTV dose homogeneity has been experimentally demonstrated using a phantom for simulated chest wall and parotid cases,¹⁷ but has not been evaluated for real patients' treatment planning.

The purpose of this planning study was to investigate the potential benefits and limitations of BECT mixed with IMRT and VMAT beams for left-sided postmastectomy breast cancer patients by comparing this mixed beam therapy with the standard VMAT planning technique used in our clinic.⁴

2. METHODS AND MATERIALS

2.A. Patient selection

This study retrospectively included nine left-sided post-mastectomy patients. All patients received a modified radical mastectomy and were treated by a single radiation oncologist at our institution. Computed tomography (CT) scans had been acquired on a large bore GE LightSpeed 16 CT scanner (General Electric Medical Systems, Little Chalfont, UK), and all patients had been scanned in the supine position with the free breathing CT data sets including anatomy from the top of head to lower abdomen with a slice thickness of 0.25 cm.

All CT data sets were anonymized and assigned a unique research identifier, CW1 to CW9 (Table I). Treatment planning for all modalities was performed in a commercially available TPS (Pinnacle³ v9.8, Philips Medical Systems, Fitchburg, WI, USA).

2.B. Contours

The PTV for each patient, which had been previously contoured by the same radiation oncologist at our institution based on consensus definitions from RTOG breast cancer Atlas, included the chest wall, supraclavicular area, and internal mammary chain (IMC) area. Contouring the chest wall targets on CT was aided by placing radiopaque marker at the time of CT simulation for identification of the mastectomy scar and the area of the chest wall, which in the radiation oncologist's judgment was at risk for recurrence and should be included in the prescription dose. As for the supraclavicular area, the upper border was below the level of the cricoid, the medial border was at the vertebral pedicles and lateral border consisted of the portion of the axilla that remained undissected, and the inferior border extended to the caudal aspect of the clavicular head. The IMC area included the internal mammary vessels in the first three intercostal spaces. The patients had a 1-cm thick Superflab bolus (Superflab Bolus, Radiation Products Design, Inc., Albertville, MN, USA) placed on the surface of their ipsilateral chest wall for the purpose of dose buildup.^{3,4,18}

Figure 1 illustrates the contours used in the treatment planning for patient CW1. The green plus red is the original PTV contour created by the radiation oncologist. The red contour is the modified "PTV evaluation" that does not include the 1-cm tissue-equivalent bolus because the dose within the thermoplastic bolus was unnecessary for this study. This contour was used in planning and optimizing all VMAT techniques and for evaluating the PTV dose metrics for all techniques; its volume is shown in Table I for each patient. The yellow contour is a 5-mm shell that is used to estimate skin dose within the PTV. The red double arrow

TABLE I. The PTV volume, minimum (min) distance between the distal PTV surface and lung ($d_{\text{PTV-Lung}}$), volume of tissue between the distal PTV surface and heart or lung ($V_{\text{PTV-heart/lung}}$), the electron energy used in mixed beam therapy for each patient.

Patient	PTV volume (cm ³)	Min $d_{\text{PTV-Lung}}$ (cm)	$V_{\text{PTV-heart/Lung}}$ (cm ³)	Electron energy (MeV)
CW1	991.0	0.5	292.4	13
CW2	749.4	0.7	293.7	11
CW3	700.0	0.4	255.5	11
CW4	1321.3	1.0	585.8	16
CW5	1137.6	0.2	323.2	11
CW6	724.4	0.2	169.9	11
CW7	894.1	0.5	210.3	13
CW8	572.6	0.4	188.9	11
CW9	999.8	0.5	287.8	13

FIG. 1. Planning target volume (red) of a typical PMRT patient for mixed beam therapy and VMAT, 1 cm tissue-equivalent bolus (green), and 5 mm skin contour (yellow). The white dashed line represents the central axis of electron beam, and the red double arrow represents the PTV-lung distance along the central axis ($d_{\text{PTV-Lung}}$). [Color figure can be viewed at wileyonlinelibrary.com]

along the central axis of electron beam represents the distance between the distal PTV surface and lung ($d_{\text{PTV-Lung}}$), which is shown in Table I for each patient. The volume of tissue between the distal PTV surface and heart or lung ($V_{\text{PTV-heart/Lung}}$) is also shown in Table I for each patient.

Figure 2 shows a three-dimensional (3D) rendering of the three defined PTVs used in planning and evaluating all techniques in this study together with their dose prescriptions. The image on the left shows the supraclavicular PTV and BECT PTV for mixed beam therapy. The border separating

the two PTVs was chosen where the lowest available electron energy that covered most of the BECT PTV but was insufficiently energetic to cover the thick, superior part of it. The border was always selected above the patient's heart and as superior as possible to reduce the radiation to the heart. The image on the right shows the composite PTV used for the standard VMAT plan and the VMAT component of the composite mixed beam plan; it was also used as the evaluation PTV for all techniques.

Organs at risk (OARs), contoured by the radiation oncologist for all the patients, included lungs, whole heart, contralateral breast, esophagus, trachea, and spinal cord. Additional contours that were added included: (a) a 0.8-cm thick ring around the PTV used to control hot or cold spots around the PTV, (b) an external skin contour used in the mixed beam planning, (c) a 0.5-cm thick shell for evaluating the skin dose inside the PTV, and (d) unspecified tissue which included everything inside the external skin contour excluding the above mentioned OARs.

2.C. VMAT treatment planning

VMAT plans were created for an Elekta Versa HDTM radiotherapy system (Elekta, Crawley, UK) using 6 MV photons, 0° couch angle, and 45° collimator angle. The dose prescription was 50 Gy administered in 25 fractions, and the dose calculations were conducted using a dose grid resolution of 0.4 cm³. Each plan utilized two partial arcs due to the complexity of the cases and close proximity to lungs, heart, and contralateral breast. Each arc covered approximately 220° with about 56 control points (4° gantry spacing). The first arc was planned to be delivered counterclockwise with starting angles between 170° and 180° (floor to ceiling) and stopping angles between 304° and 320°. The second arc was

FIG. 2. Planning target volumes (PTV) with prescriptions for mixed beam therapy and VMAT. (Left) BECT PTV (red) and supraclavicular PTV (yellow) for mixed beam therapy; (Right) the same green area used as VMAT PTV, VMAT component of mixed beam therapy PTV and evaluation PTV. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE II. Starting VMAT optimization objectives and constraints.

ROI	Type	Target dose [cGy]	Volume [%]	Weight
PTV evaluation	Min DVH	5000	98	100
PTV evaluation	Max Dose	5200	—	100
Total lung	Max DVH	1500	15	1
Total lung	Max DVH	1000	35	1
Total lung	Max DVH	500	60	1
Total lung	Max Dose	4500	—	1
Heart	Max DVH	1500	15	1
Heart	Max DVH	1000	30	1
Heart	Max Dose	4000	—	1
Esophagus	Max Dose	2000	—	1
Airway	Max Dose	2000	—	1
Spinal cord	Max Dose	1000	—	1
Contralateral breast	Max Dose	1500	—	1
Unspecified tissue	Max Dose	2800	—	1

Min, minimum; Max, maximum; DVH, dose volume histogram. Dashed table entry indicates the value does not apply to that type of objective.

planned to be delivered clockwise over the same arc. Inverse planning for all VMAT techniques was done using the SmartArc optimization algorithm utilized by Pinnacle TPS.

The VMAT plans were optimized using a four-run technique. The first run consisted of 75 iterations of the SmartArc algorithm in addition to 25 iterations of the convolution dose algorithm with the primary focus on PTV coverage. All PTV optimization objectives were set to a weight of 100. The starting optimization objectives and constraints for all VMAT plans are shown in Table II. All subsequent runs consisted of 35 iterations each of the SmartArc algorithm. For the second run the hotspots from the first run were contoured, and an objective was added with maximum dose constraint set to 52 Gy with a weight of 100. The hot spots were contoured by creating a contour from the 53.5 Gy isodose line. For the third run the “PTV evaluation” region of interest (ROI) was uniformly contracted by 0.2 cm and labeled PTV min dose. This ROI was added to the optimizer and given a minimum dose objective of 50 Gy with a weight of 100. In addition, hotspots from the second run were contoured, and an objective was added with maximum dose constraint set to 52 Gy with a weight of 100. The fourth run focused on reducing the dose to the heart, total lung (both left and right lungs), and contralateral breast. At the beginning of the run the target doses were reduced by an amount that resulted in the objective value for that ROI to be around 0.005. The objectives can be adjusted in real time as the optimizer is running. While the last run was being optimized the target doses of the aforementioned ROIs were adjusted to keep their objective value around 0.005.

2.D. Mixed beam treatment planning

The mixed beam treatment planning was a multiple modality technique utilizing electrons, IMRT photon beams, and a dual-arc VMAT. It used a 4:1 ratio where 20 of the 25 total fractions consisted of an electron field to the chest wall

(including internal mammary chain and axillary lymph nodes) and parallel opposed IMRT photon beams to the superior chest wall and supraclavicular volume. Generalizations of these two PTVs are shown in the left image of Fig. 2. The final 5 of the 25 total fractions utilized a dual-arc VMAT technique, which was optimized on top of the dose distribution from the first 20 fractions. The VMAT PTV for this technique, as well as the PTV used for final plan evaluation, is shown in the right image of Fig. 2. The prescription doses of the electron and IMRT photon fields were 40 Gy in 20 fractions, and the dual-arc VMAT was prescribed to a composite 50 Gy in 5 additional fractions.

For BECT planning, the 1-cm Superflab bolus that was in place in the original CT images was removed by contouring it and overriding its density to that for air (0.001 g cm^{-3}), because it was replaced with a 3D conformal electron bolus for the electron portion of this technique. Electron isocenter was placed on the central slice of the BECT PTV, 5 cm anterior to the patient surface, resulting in a prebolus SSD of 105 cm, which allowed for adequate electron applicator clearance. The electron isocenter was also located laterally from the BECT PTV patient midline edge to approximately place the point in the center of the BECT PTV. The gantry angle (approximately 45°) was chosen so the beam direction was approximately perpendicular to the patient surface on central axis (cf Fig. 1). For each patient the lowest available electron energy that gave adequate coverage of the BECT PTV using a single electron beam was selected. The goal of having the 90% dose surface circumscribe the distal surface of the BECT PTV required energies of 11, 13 and 16 MeV with R_{90} values of 3.5, 4.0 and 5.0 cm respectively (cf Table I).

The electron field shape was created to conform its perimeter to the beams-eye-view (BEV) of the BECT PTV plus a 1-cm margin, which ensured the PTV was inside the penumbra and should receive 90% of the given dose. The couch was rotated so the beam at the superior border had a straight edge. The superior field edge matched the superior border of the “BECT PTV” to reduce the penumbra from spilling into the supraclavicular PTV. The collimator was adjusted so the medial jaw was parallel to the BECT PTV medial edge. This adjustment maximized the distance between the BECT PTV outer edge and the electron field’s (cutout) outer edge. The smallest electron applicator that contained the field shape was selected, being either $20 \times 20 \text{ cm}^2$ or $25 \times 25 \text{ cm}^2$.

The dose for the electron beam without bolus was calculated in Pinnacle using the pencil beam algorithm (PBA)^{19,20} with a dose grid resolution of 0.2 cm^3 . The plan’s finalized ROI structures and electron beam characteristics were exported from the TPS and transferred to the decimal p.d BolusECT[®] software (v5.1.9) (.decimal LLC, Sanford, FL, USA) for bolus design.

Bolus design began by entering the beam energy for the BECT PTV and external skin ROI structures. The bolus was designed using a series of bolus operators, typically including creation operator, isodose shift operator, smoothing operator, truncation operator, and specified shift operator, based on

FIG. 3. Axial view of dose distribution for mixed beam plans in the BECT area (a, d), in the supraclavicular area (b, e), and sagittal view of dose distribution (c, f) for patient CW2 (the best case). The left column (a, b, c) and right column (d, e, f) show the doses for plans without and with VMAT component respectively. The orange color wash contour represents the PTV, the dark blue color wash represents the electron bolus. [Color figure can be viewed at wileyonlinelibrary.com]

those of Low *et al.*¹² that resulted in the most conformal coverage of the distal surface of the BECT PTV by the 90% dose surface. The decimal p.d BolusECT[®] software calculated dose using the pencil beam redefinition algorithm (PBRA).^{21–24}

Once the bolus design was finalized, the digital bolus contour was transferred as a structure back into a copy of the original treatment plan in the Pinnacle TPS. The density of the bolus structure was set to 0.92 g cm^{-3} according to Low and Hogstrom.²⁵ The dose distributions relative to given dose were calculated using the PBA in the Pinnacle TPS. Monitor Units (MUs) were calculated to deliver the prescribed dose (40 Gy) to 95% of the given dose. Dose per monitor unit for

the beam, which depended on beam energy, applicator size, field size, and SSD to the bolus surface along central axis, was calculated according to Hogstrom *et al.*²⁶

Continuing the planning process, the parallel opposed 6 MV IMRT photon fields based on the Elekta Versa HD[™] radiotherapy system were delivered to the supraclavicular PTV. The isocenter was placed on the inferior, medial border of the supraclavicular PTV. The gantry beam angles, chosen to reduce dose to the esophagus and trachea, were approximately 345° and 165° . The couch angle and collimator angle were 0° . The IMRT beams were optimized to deliver 40 Gy to supraclavicular PTV and limit dose to OARs using the direct machine parameter optimization (DMPO) optimization

FIG. 4. Axial view of dose distribution for mixed beam plans in the BECT area (a, d), in the supraclavicular area (b, e), and sagittal view of dose distribution (c, f) for patient CW6 (the worst case). The left column (a, b, c) and right column (d, e, f) show the doses for plans without and with VMAT component respectively. The orange color wash contour represents the PTV, the dark blue color wash represents the electron bolus. [Color figure can be viewed at wileyonlinelibrary.com]

algorithm and a dose grid resolution of 0.4 cm^3 in Pinnacle TPS.

After the BECT PTV and supraclavicular PTV were covered by their 40 Gy prescription, the VMAT component of the plan was determined using the VMAT planning technique identical to that described previously with the exception it was optimized on top of the initial mixed beam dose distributions. The purpose of the 10 Gy VMAT component was to reduce dose heterogeneities in the mixed beam plan due to the irregular bolus surface,^{16,17} the abutting electron and photon beams, and the parallel opposed photon beams in the supraclavicular region.

2.E. Plan evaluation

For each treatment plan, the following three criteria were required to be met to be considered clinically acceptable and representative of those plans administered to our patients: (a) the fraction of the PTV receiving at least 95% of the prescribed dose is greater than or equal to 95% ($V_{95} \geq 95\%$); (b) the volume of total lung receiving greater than 20 Gy is less than 20% ($V_{20} < 20\%$), as this has been shown to be the clinical threshold for pneumonitis^{27,28}; and (c) the volume of heart receiving greater than 22.5 Gy is less than 20% ($V_{22.5} < 20\%$), as a dose of 22.5 Gy to the heart has been

correlated with increased rates of reduced myocardial perfusion.²⁹

In addition, the volume of lung receiving at least 5 Gy should be less than or equal to 42% ($V_5 \leq 42\%$), as any more is related to an increase in lung toxicity.³⁰ The mean heart dose should be less than 5 Gy ($D_{\text{mean}} < 5$ Gy), and doses to the heart above 30 Gy have also been shown to increase cardiac mortality and should be minimized.³¹

Among the dosimetric evaluation metrics, the dose homogeneity index (DHI) is defined as:

$$DHI = \frac{D_{\text{max}} - D_{\text{min}}}{D_{\text{Rx}}},$$

where D_{max} is the dose to 2% of the PTV, D_{min} is the dose to 98% of the PTV, and D_{Rx} is the prescription dose.³² A DHI value of zero is ideal and represents a homogenous dose to the entire PTV. The conformity index (CI) is defined as

$$CI = \frac{TV_{RI}}{TV} \times \frac{TV_{RI}}{V_{RI}},$$

where TV_{RI} is the target volume receiving the reference dose (47.5 Gy), TV is the PTV, and V_{RI} is the volume receiving reference isodose of 47.5 Gy.³³ A CI value of unity means the reference dose volume conformed exactly to the target volume.

The Lyman-Kutcher-Burman (LKB) probit model^{34–36} was used to calculate the normal tissue complication probability (NTCP) for the lungs with radiation pneumonitis grade two or higher as an endpoint:

$$NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^t e^{-t^2/2} dt$$

$$t = (D - D_{50}(V)) / (m \cdot D_{50}(V))$$

$$D_{50}(V) = D_{50} / V^n$$

where $D_{50}(V)$ is the tolerance dose that would result in a 50% complication probability for the partial volume V , D_{50} is the tolerance dose that would result in a 50% complication probability for the full organ, n indicates the volume effect, and m is inversely proportional to the slope of the dose–response curve. $D_{50} = 30.8$ Gy, $n = 0.99$, and $m = 0.37$ ³⁶ were used in this study.

NTCP for radiation-induced cardiac mortality was computed for the heart using the relative seriality model:³⁷

$$NTCP = \left\{ 1 - \prod_{i=1}^n [1 - P(D_i)^s]^{V_i/V} \right\}^{1/s}$$

$$P(D) = 2^{-\exp\{\gamma(1-D/D_{50})\}}$$

where γ is the maximum relative slope of the dose–response curve and D_{50} is the dose that will result in a 50% probability of a complication, s is the relative seriality that describes the hybrid serial/parallel architecture of the organ, n is the number of voxels in the dose-calculation volume, D_i is the dose in each subvolume, V_i is the volume of each subvolume in the differential dose–volume histogram, and V is the total volume

of the organ. $D_{50} = 52.3$ Gy, $s = 1.0$, and $\gamma = 1.28$ ³⁸ were used in this study.

Secondary cancer complication probabilities (SCCP) were calculated using the product of the linear organ equivalent dose (OED_{org}) and the organ specific absolute cancer incidence rate in percent per gray (In_{org}).³⁹ OED_{org} was calculated using the linear nonthreshold (LNT) and linear exponential (LEXP) models, i.e.,

$$OED_{\text{org}} = \frac{1}{V_{\text{org}}} \sum_i (v_i \cdot D_i),$$

$$OED_{\text{org,linear-exp}} = \frac{1}{V_{\text{org}}} \sum_i (v_i \cdot D_i \cdot e^{-\alpha D_i}),$$

where v_i is the volume receiving dose D_i and is summed over all voxels of the organ of volume V_{org} , α is the organ specific cell sterilization parameter. SCCP was calculated for the lungs where $In_{\text{org}} = 1.68\% \text{ Gy}^{-1}$ and $\alpha = 0.085 \text{ Gy}^{-1}$, and for the contralateral breast where $In_{\text{org}} = 0.78\% \text{ Gy}^{-1}$ and $\alpha = 0.085 \text{ Gy}^{-1}$.⁴⁰

2.F. Statistical Analysis

The paired two-sided t test was used to determine the statistical significance of the differences. The analyses were conducted with R software (version 3.2.3, R Foundation), and the differences were considered significant when $P < 0.05$.

TABLE III. PTV and OAR evaluation metrics for each PMRT patient.

Patient	SCCP (%)							
	PTV		NTCP (%)		LNT		LEXP	
	CI	DHI	Lung	Heart	Lung	CL breast	Lung	CL breast
VMAT								
CW1	0.7	0.2	2.7	0.7	14.9	3.0	4.6	2.0
CW2	0.7	0.1	2.7	1.0	14.7	2.1	4.3	1.5
CW3	0.6	0.1	2.8	0.3	15.1	4.6	4.6	2.4
CW4	0.7	0.1	3.0	0.3	15.7	3.2	4.7	2.0
CW5	0.7	0.2	2.6	1.7	14.4	1.9	4.2	1.4
CW6	0.7	0.1	3.4	1.6	16.8	3.7	4.8	2.2
CW7	0.8	0.1	2.7	0.5	14.6	2.5	5.0	1.6
CW8	0.7	0.1	2.4	0.6	13.8	3.2	4.4	1.9
CW9	0.7	0.1	2.4	0.5	13.7	3.9	4.4	2.2
Mixed beam								
CW1	0.6	0.2	2.4	0.1	13.9	1.3	3.9	1.0
CW2	0.5	0.2	1.7	0.1	11.2	1.1	3.6	0.9
CW3	0.5	0.2	2.6	0.1	14.3	1.9	4.0	1.4
CW4	0.4	0.2	2.3	0.02	13.4	2.4	4.5	1.5
CW5	0.6	0.2	2.6	0.1	14.4	1.3	4.0	1.1
CW6	0.5	0.2	3.2	0.7	16.1	2.2	3.9	1.3
CW7	0.6	0.2	3.0	0.7	15.8	1.5	3.9	1.1
CW8	0.5	0.2	3.2	0.1	16.2	1.2	3.2	1.0
CW9	0.6	0.2	2.8	0.1	15.0	2.3	3.7	1.4

LNT, linear non-threshold; LEXP, linear-exponential; CL breast, contralateral breast.

3. RESULTS

Table III shows CI, DHI for PTV and NTCP, SCCP values for OARs for each PMRT patient. Figures 3 and 4 show the dose distributions for two (CW2 and CW6) PMRT patients' mixed beam plans with and without VMAT component. These two patients were chosen as patients who, based on normal tissue sparing, benefited the most (CW2) and the least (CW6) from mixed beam therapy. For plans without VMAT component, the prescription dose was changed from 40 to 50 Gy for the BECT and supraclavicular IMRT fields to make them clinically comparable. Consistent with previous study,¹⁷ the mixed beam reduced the hot spots within and outside the target at the expense of increased low dose outside PTV.

Figures 5–7 show the dose distributions and dose volume histograms (DVHs) for patients CW2 and CW6 from mixed beam therapy. Compared to VMAT plans, the mixed beam plans shrink the medium and low dose volumes within the normal tissues especially for CW2, while showing greater dose spread (e.g., hotspots) within the PTV. This is most apparent in the lateral portion of the PTV at the beam abutment region of the electron field and the supraclavicular IMRT fields. In addition, any region of the machineable wax bolus that has a steep or sharp edge causes underlying dose heterogeneities in the patient. Smoothing the machineable

wax bolus reduced some of the dose heterogeneities, but not all could be removed because of bolus surface following the curvature of chest wall. Mixing VMAT with BECT + IMRT (1:4) reduced, but did not eliminate dose heterogeneities, as was the case reported previously.¹⁷

The mean PTV evaluation metrics are summarized in Table IV. All of the mixed beam and VMAT treatment plans were deemed clinically acceptable by the radiation oncologist. As a result of the hotspots in the mixed beam plans, the maximum dose to the PTV and the PTV volume receiving 107% of the prescription dose were significantly higher than VMAT plans. The VMAT plans also showed better conformity and homogeneity than the mixed beam plans.

The mean OAR evaluation metrics are also summarized in Table IV. All plans met the acceptance criteria that $V_{20} < 20\%$ for the lungs and $V_{22.5} < 20\%$ for the heart. Mixed beam therapy showed an average reduction in volume of lungs receiving at least 5 Gy of nearly 10% compared to VMAT; however, the high dose region of lungs was slightly greater for mixed beam therapy compared to VMAT, but still under the 20% requirement of the plan acceptance criteria. Mixed beam therapy did not significantly change NTCP for radiogenic pneumonitis or SCCP for secondary lung cancer based on LNT model from those using VMAT, but it significantly reduced SCCP based on LEXP model. The volume of

FIG. 5. Axial and sagittal views of isodose distribution for VMAT (upper) and mixed beam plans (lower) for patient CW2 (the best case). The orange color wash contour represents the PTV, the dark blue color wash represents the electron bolus. [Color figure can be viewed at wileyonlinelibrary.com]

FIG. 6. Axial and sagittal views of isodose distribution for VMAT (upper) and mixed beam plans (lower) for patient CW6 (the worst case). The orange color wash contour represents the PTV, the dark blue color wash represents the electron bolus. [Color figure can be viewed at wileyonlinelibrary.com]

FIG. 7. DVHs for two PMRT patients comparing PTV (red), lungs (blue), heart (magenta), and contralateral breast (green) for mixed beam therapy (dashed line) and VMAT (solid line). [Color figure can be viewed at wileyonlinelibrary.com]

heart receiving at least 5 Gy was significantly lower, over 20%, for mixed beam therapy compared to VMAT. Also the volume of heart receiving at least 22.5 Gy or 30 Gy was significantly decreased for mixed beam therapy. These great differences in dose metrics were reflected in statistically

significant reduction in NTCP for cardiac mortality over VMAT. The mean contralateral breast dose, the volume of contralateral breast receiving at least 5 Gy, and SCCP were statistically significantly reduced for mixed beam therapy. Mean dose to the skin (5 mm shell) was statistically

TABLE IV. PTV and OAR evaluation metrics (mean $\pm$ SD) for a set of 9 PMRT patients and *P* value for statistical significance tests.

	Mixed beam	VMAT	<i>P</i>
PTV			
D _{mean} (Gy)	51.6 $\pm$ 0.4	49.7 $\pm$ 0.3	<0.001
D _{max} (Gy)	59.9 $\pm$ 3.6	53.5 $\pm$ 0.7	<0.001
V ₁₀₇ (%)	15.0 $\pm$ 8.6	0.03 $\pm$ 0.05	<0.001
CI	0.53 $\pm$ 0.06	0.70 $\pm$ 0.04	<0.001
DHI	0.20 $\pm$ 0.02	0.12 $\pm$ 0.02	<0.001
Lung			
D _{mean} (Gy)	8.4 $\pm$ 0.9	8.7 $\pm$ 0.6	NS
D _{max} (Gy)	52.0 $\pm$ 2.2	51.1 $\pm$ 1.6	0.006
V ₅	33.5 $\pm$ 2.6	43.5 $\pm$ 5.8	<0.001
V ₁₀	23.4 $\pm$ 2.9	24.3 $\pm$ 2.4	NS
V ₂₀	15.5 $\pm$ 2.6	13.0 $\pm$ 1.0	0.02
NTCP (%)	2.7 $\pm$ 0.5	2.7 $\pm$ 0.3	NS
SCCP (LNT) (%)	14.5 $\pm$ 1.6	14.9 $\pm$ 1.0	NS
SCCP (LEXP) (%)	3.9 $\pm$ 0.4	4.6 $\pm$ 0.3	<0.001
Heart			
D _{mean} (Gy)	7.1 $\pm$ 1.3	9.3 $\pm$ 1.1	0.001
D _{max} (Gy)	38.9 $\pm$ 4.6	42.8 $\pm$ 3.6	NS
V ₅	44.3 $\pm$ 7.6	66.9 $\pm$ 13.0	<0.001
V ₁₀	21.0 $\pm$ 5.7	25.3 $\pm$ 4.1	NS
V _{22.5}	4.5 $\pm$ 3.4	9.8 $\pm$ 1.9	0.001
V ₃₀	1.3 $\pm$ 1.8	5.0 $\pm$ 2.6	0.003
NTCP (%)	0.23 $\pm$ 0.27	0.80 $\pm$ 0.53	0.01
CL breast			
D _{mean} (Gy)	1.8 $\pm$ 0.6	4.0 $\pm$ 1.1	<0.001
D _{max} (Gy)	26.6 $\pm$ 7.7	27.1 $\pm$ 8.4	NS
V ₅	4.6 $\pm$ 3.2	24.2 $\pm$ 12.1	<0.001
SCCP (LNT) (%)	1.7 $\pm$ 0.5	3.1 $\pm$ 0.9	<0.001
SCCP (LEXP) (%)	1.2 $\pm$ 0.2	1.9 $\pm$ 0.3	<0.001
Skin			
D _{mean} (Gy)	50.8 $\pm$ 0.5	49.3 $\pm$ 0.4	<0.001
D _{max} (Gy)	59.7 $\pm$ 1.6	53.3 $\pm$ 0.7	<0.001

LNT, linear nonthreshold; LEXP, linear-exponential; CL breast, contralateral breast; NS, not significant.

significantly higher (50.8 Gy) and just over prescription dose (50 Gy) for mixed beam therapy and was slightly lower (49.3 Gy) than the prescription dose for VMAT. Mixed beam therapy also showed 12% higher maximum skin dose (59.7 Gy vs 53.3 Gy).

4. DISCUSSION

This study compared a mixed beam therapy with a well-defined VMAT used at our institute for postmastectomy breast cancer patients. Both techniques provided good coverage of the target, while mixed beam therapy showed, with statistical significance, less conformity and less dose homogeneity compared to standard VMAT. The mixed beam's inclusion of 25% VMAT significantly reduced the dose heterogeneities within the target. Our technique significantly reduced the portion of the target volume receiving

greater than 110% of the prescription dose (PTV₁₁₀), being $3.9 \pm 2.7\%$, as compared to $15.1 \pm 5.8\%$ from a study by Opp *et al.*¹⁴ that evaluated BECT alone for 21 left-sided PMRT patients. Although their PTV did not include regional nodal area, this significant reduction still indicated the improvement of dose homogeneity and the benefit of adding VMAT component to BECT.

Our mixed beam technique reduced low doses but increased high doses to the lungs as compared to VMAT. This is apparently due to dose spilling of the electron beam to the ipsilateral lung. However, since the electron beam dose falls off quickly in the low dose area, the contralateral lung has reduced dose. D_{mean}, $\bar{V}_5$ and $\bar{V}_{20}$ for the lungs in our mixed beam study are lower than those in one study by van der Laan *et al.*⁹ that evaluated a combined conformal electron and photon IMRT planning technique for 10 left-sided PMRT patients. D_{mean} for the lungs from our mixed beam therapy is comparable to that in Opp *et al.*¹⁴

D_{mean} for the heart from our mixed beam therapy is comparable to that in Opp *et al.*,¹⁴ while D_{mean}, $\bar{V}_5$ and $\bar{V}_{30}$ for the heart in our mixed beam study are lower than those in van der Laan *et al.*⁹ Cardiac toxicity is a serious concern for women undergoing PMRT and has been indicated as a primary reason for mortality among breast cancer survivors.^{41–44} This work has shown with statistical significance that our mixed beam therapy applied to left-sided PMRT patients can reduce NTCP for cardiac mortality from 0.8% with VMAT to 0.2%. Hence, patients with prior or current cardiopulmonary complications or those at an increased risk of cardiovascular disease⁴⁵ might benefit from our mixed beam therapy technique.

D_{mean} for the contralateral breast in our mixed beam study is comparable to that in Opp *et al.*,¹⁴ while D_{mean} and $\bar{V}_5$ for the contralateral breast in our study are higher than those in van der Laan *et al.*⁹ It was also determined that our mixed beam therapy can significantly reduce SCCP for the contralateral breast from 3.1% with VMAT to 1.7% based on LNT model, and from 1.9% with VMAT to 1.2% based on LEXP model. This is especially important for younger patients. Studies have determined that premenopausal women under the age of 40–45 years old are at the highest risk for second cancers of the contralateral breast after radiation exposure and women over that age shown little or no risk of radiation-induced breast cancer.^{46,47} It is possible that younger patients requiring PMRT may further benefit from mixed beam therapy.

Skin erythema is expected for postmastectomy chest wall patients since the skin is included in the PTV. Dose to the skin should be as close to prescription dose (50 Gy) as possible to sterilize any microscopic disease still present. The mean skin dose from our mixed beam therapy was only slightly higher than VMAT (50.8 vs 49.3 Gy), although the maximum dose was much higher (59.7 vs 53.3 Gy). However, for all the mixed beam plans in this study, the volume of skin that has dose greater than 55 Gy does not exceed 8 cm³ (~16 cm² in terms of area) and the average volume is 3.7 cm³ (~7.4 cm² in terms of area), which is not clinically

significant. According to Hall and Giaccia,⁴⁸ the combination of total dose (50 Gy) and time (35 days) of our treatment may cause moist or dry desquamation of skin, and those usually can be managed. Patients who were treated with electron bolus were able to complete treatment without interruption: Perkins et al.¹³ studied two PMRTs patient who underwent BECT technique and found the patients had brisk erythema and moist desquamation but were able to complete treatment without interruption. Patient discomfort caused by skin reaction was not severe and was managed with healing occurring within 2 weeks of treatment completion; Kim et al.¹⁵ used BECT to treat a PMRT patient with recurrent inflammatory breast cancer and reported the patient developed grade 2 erythema and hyperpigmentation in the treatment area that did not cause desquamation. The patient developed erythematous and maculopapular rash 6 months after the treatment, which was consistent with the inflammatory effects of radiation treatment. Those patients were treated with electron bolus alone without IMRT or VMAT mixture, which means the skin doses were even higher than those in our study.

Based on Tables I and III, this work has suggested that patients like CW4 or CW2 with thicker minimum $d_{\text{PTV-Lung}}$ and/or larger volume of tissue between the distal PTV surface and heart or lung ($V_{\text{PTV-heart/Lung}}$) might benefit the most from mixed beam therapy, while patients like CW6 with a thin layer of intervening tissue could not receive the same dose sparing. Some tissue distal to the PTV (approximately, minimum $d_{\text{PTV-Lung}} > 0.5$ cm and $V_{\text{PTV-heart/Lung}} > 250$ cm³) is needed to attenuate the electrons before entering the lung tissue even with the use of the wax bolus, and the thicker tissue has increased ability to stop more of the electron beam leading to decreased dose to the heart and lungs. In addition it would be advantageous to pay closer attention to the BECT PTV thickness in the lateral and posterior areas. When this region of the PTV is very thick the required electron energy may need to be increased to achieve adequate target coverage, but the final choice of electron energy is still limited by the minimum $d_{\text{PTV-Lung}}$ because the high energy electrons will easily penetrate the chest wall and enter the lung tissue if the chest wall is very thin.

As VMAT was the standard of care for PMRT in our institute at the time of this study, we opted to compare our mixed beam therapy with VMAT instead of conventional tangential therapy which is current standard of care for PMRT in the US. However, according to literature⁵⁰ and our previous experience, tangential PMRT could introduce large dose heterogeneities in the PTV and can induce suboptimal cosmesis after treatment. In addition, tangential PMRT would introduce higher heart dose and slightly lower lung dose than bolus electron conformal therapy without mixing with IMRT,¹⁴ and would introduce higher lung, heart, and coronary artery doses than VMAT.⁵¹

Potential future work for this study could be adding intensity modulated electron therapy (IMET)¹⁶ for the chest wall into the study. This technique could potentially reduce dose spread and the magnitude of hot spots and reduce skin complications, which could remove the need for the VMAT

component of our mixed beam. IMET could therefore potentially lead to more conformal and homogenous dose distributions to the PTV than the current mixed beam technique, reducing the low dose bath to OARs. In addition, it would be interesting to study breath control for our mixed beam technique. Deep inspiration breath hold has been shown to significantly reduce mean heart and left anterior descending artery (LAD) dose in patients receiving breast-conserving radiotherapy or PMRT using photon techniques,^{53–60} which translates to further reduction in risk of heart disease. However, this may not be the case for the single electron field (approximately perpendicular to the chest wall) used in our study and the low-density lung tissue may not be able to attenuate the electron beam sufficiently although the distance between PTV and heart has been increased. Further study is required to confirm the benefit of breath hold for our mixed beam therapy.

5. CONCLUSION

The results of this study have effectively shown that our mixed beam therapy technique might be advantageous to VMAT particularly for specific patients. Even though VMAT produces more homogenous and conformal dose distribution to the PTV, the dose coverage of mixed beam therapy was sufficient for it to be a viable option for treating postmastectomy patients. Contrastingly, mixed beam therapy can significantly lower the dose to the heart and contralateral breast. The former makes it potentially beneficial for the patients with prior or current cardiopulmonary complications or those at an increased risk of cardiovascular disease, the latter makes it potentially beneficial for young women with an increased risk of radiation-induced cancer of the contralateral breast. In line with the benefits of personalized medicine, patients with more tissue between the distal PTV surface and lung might benefit the most from our mixed beam therapy technique.

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CONFLICTS OF INTEREST

The authors does not have any conflict of interest.

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