Scientific Article

Intensity Modulated Proton Therapy for Bilateral Breast or Chest Wall and Comprehensive Nodal Irradiation for Synchronous Bilateral Breast Cancer: Initial Clinical Experience and Dosimetric Comparison

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Abstract

Purpose: Synchronous bilateral breast cancer (SBBC) poses distinct challenges for radiation therapy planning. We report our proton therapy experience in treating patients with SBBC. We also provide a dosimetric comparison of intensity modulated proton therapy (IMPT) versus photon therapy.

Methods and Materials: Patients with SBBC who received IMPT at our institution were retrospectively analyzed. The clinical target volume (CTV) included the breast or chest wall and comprehensive regional lymph nodes, including axilla, supraclavicular fossa, and the internal mammary chain. Intensity modulated proton therapy and volumetric modulated arc therapy (VMAT) plans were generated with the goal that 90% of the CTV would recieve at least 90% of the prescription dose (D90>=90%). Comparisons between modalities were made using the Wilcoxon signed rank test. Physician-reported acute toxic effects and photography were collected at baseline, end of treatment, and each follow-up visit.

Results: Between 2015 and 2018, 11 patients with SBBC were treated with IMPT. The prescription was 50 Gy in 25 fractions. The median CTV D90 was 99.9% for IMPT and 97.6% for VMAT ($P = .001$). The mean heart dose was 0.7 Gy versus 7.2 Gy ($P = .001$), the total lung mean dose was 7.8 Gy versus 17.3 Gy ($P = .001$), and the total lung volume recieving 20 Gy was 13.0% versus 27.4% ($P = .001$). The most common acute toxic effects were dermatitis (mostly grade 1-2 with 1 case of grade 3) and grade 1 to 2 fatigue. The most common toxic effects at the last-follow up (median, 32 months) were grade 1 skin hyperpigmentation, superficial fibrosis, and extremity lymphedema. No nondermatologic or nonfatigue adverse events of grade >1 were recorded.

Conclusions: Bilateral breast and/or chest wall and comprehensive nodal IMPT is technically feasible and associated with low rates of severe acute toxic effects. Treatment with IMPT offered improved target coverage and normal-tissue sparing compared with photon therapy. Long-term follow-up is ongoing to assess efficacy and toxic effects.

Introduction

Synchronous bilateral breast cancer (SBBC), defined as contralateral breast cancer diagnosed within 12 months of primary breast cancer, occurs in 1% to 3% of all breast cancer cases.[1-3] Many of these patients have indications for adjuvant radiation therapy to the bilateral chest wall or breasts and regional lymph nodes. Bilateral irradiation poses a particular treatment challenge, especially if internal mammary lymph nodes (IMNs) are targeted, owing to competing goals of target coverage and normal-tissue sparing. There is relatively little research published regarding treatment of these complex cases, mostly limited to case reports and dosimetric studies.[4-15] Proton beam therapy (PBT) is emerging as a promising treatment modality in patients with indications for regional nodal irradiation, especially in those with unfavorable anatomy such as pectus excavatum or small lung volume, because PBT reduces the dose to adjacent normal tissues including the heart and lungs.[16-20] Increased doses to these critical structures are associated with increased risks for late cardiopulmonary toxic effects and secondary cancers.[21-24] Proton therapy may also allow for better clinical target volume (CTV) coverage, especially of the IMNs.[25,26] Multiple institutions have reported experiences with postlumpectomy and postmastectomy plus regional nodal PBT for unilateral breast cancer. These studies have suggested this technique is technically feasible and associated with acceptable patient outcomes.[27-35] A randomized phase 3 trial of photon versus proton therapy is ongoing.[36]

We hypothesized that the normal-tissue sparing of PBT would be pronounced in bilateral radiation therapy owing to the greater volume of irradiated tissue and more challenging treatment geometry. The ability of intensity modulated proton therapy (IMPT) to provide a smooth gradient that is robust to setup uncertainty between fields with multiple isocenters may also avoid hot or cold junctions, potentially decreasing the risk of adverse events or undercoverage of the CTV. The goal of this study was to demonstrate the feasibility of IMPT for SBBC by reporting our institutional experience, including technique, dosimetry, and acute toxicity, as well as comparison with volumetric modulated arc therapy (VMAT) plans.

Methods and Materials

After institutional review board approval, we queried our prospectively collected outcomes database to identify all patients who received IMPT for bilateral breast cancer between 2015 and 2018. Since opening our proton center in 2015, we have routinely considered IMPT in patients requiring bilateral chest wall and/or breast and comprehensive nodal irradiation based on improvements in target coverage and normal-tissue sparing in studies of patients treated with unilateral proton therapy.[16-20,25,26] Patients were included in this study if they had a proton plan that was approved for clinical use.

Patient immobilization was performed with an angled breast board with both arms above the head or with arms down holding indexed hand grips, with the head and neck immobilized in a 3- or 5-point thermoplastic mask with custom neck rest.[31] The latter position is considered for comfort owing to prolonged treatment times. Planning computed tomography (CT) scans were routinely obtained with free breathing. Breath hold scans were occasionally obtained at initial simulation in anticipation of clinical photon planning owing to uncertain insurance coverage for proton therapy. The CTV included the breast or chest wall and regional lymph nodes, including levels 1, 2, and 3 of the axilla, supraclavicular lymph nodes (SCVs), and IMNs. The CTV resembled the Radiation Therapy Oncology Group Breast Cancer Atlas with some notable exceptions. The chest wall CTV did not routinely extend deeper than the anterior surface of the ribs and intercostal muscles. The CTV excluded the first 3 mm of tissue under the skin for the chest wall or 5 mm for intact breasts. The SCV volumes included the medial and lateral SCV, except the CTV was not routinely extended medial to the lateral border of the internal carotid artery to reduce the dose to midline organs, because nodal recurrences and presentations are rare in that location.[37,38] The IMN volume was a 4- to 5-mm medial and lateral expansion on the internal mammary vessels and extended from the most caudal extent of the SCV volume near the junction of the internal mammary and brachiocephalic veins to the cranial CT slice of the fourth rib.[39] The CTV coverage goal was for the minimum dose received by 90% of the volume (D90) to be >90%, and the second-priority goal was for the D95% to be >95%, with the exception of the IMN CTV, where the coverage goal was for the D90% to be >80%. The dose prescription for the CTV was 50 Gy (relative biological effectiveness [RBE] of 1.1) in 25 fractions. Lumpectomy cavity boosts were routinely administered, whereas chest wall boosts were administered at physician discretion for adverse clinical features. Nodal boosts were considered in patients with undissected nodal disease. To ensure adequate coverage of dermal lymphatics while minimizing dermatologic toxic effects, we attempted to constrain the skin by using target coverage planning objectives of D90 >90%. For patients with inflammatory

breast cancer, we attempted to treat the skin to prescription dose while limiting the skin 1 cc (D1cc) to <105%.

Proton planning was performed using the Eclipse treatment planning system (Varian Medical Systems, Palo Alto, CA) using multifield optimization. Two beams per side angled 45° to 60° apart were chosen to account for the metallic expander port as previously described,[31] with occasional use of a fifth posterior field to cover a limited scanning target volume. Plans were evaluated for robustness to ensure CTV coverage in 8 separate worst-case scenarios of ±5-mm isocenter shifts in the x, y, and z directions and an uncertainty range of ±3%. Plans were verified in a Monte Carlo physical dose simulation based in an in-house graphics processing unit and an in-house Monte Carlo biologic dose simulation that assumes a linear relationship between RBE and linear energy transfer.[40,41] Plans generated by Monte Carlo biologic dose simulation (RBE 1.1) were evaluated side by side for target coverage and increased RBE within organs at risk (OARs), such as the brachial plexus and chest wall, and were modified as necessary to limit hot spots in these structures.[42] Protons were delivered using pencil-beam scanning IMPT on a Hitachi PROBEAT-V system with a range shifter with 4.5-cm water-equivalent thickness. Daily image alignment included oblique pair kilovoltage x-rays with 6° of freedom matching to the chest wall and intrafraction body-surface monitoring using AlignRT (Vision RT Inc, London, United Kingdom). Verification CT scans were obtained at least once during the treatment course with additional verification scans per physician discretion. Replanning was done if target coverage or normal-tissue constraints on the verification scan did not meet original planning objectives.

Several patients had VMAT plans generated during treatment planning as a backup option in case of proton outage or in the event that IMPT was not approved by insurance. For patients who did not have a VMAT plan, an experienced breast dosimetrist generated a VMAT plan in Eclipse for comparison. To achieve comparable target coverage with acceptable homogeneity and dose to normal tissues, all photon comparison plans used VMAT rather than 3-dimensional techniques. The CTVs were the same as the ones used for proton planning plus a CTV to a planning target volume (PTV) expansion of 5 mm, excluding the lungs and cropped from the skin. A tissue equivalent bolus was used to achieve adequate skin dose when indicated. A single isocenter was placed at the level of the midsternum, and 4 to 5 partial arcs were used per side. Volumetric modulated arc therapy plans were generated using the same target coverage parameters used in proton planning. No plan normalization was used in either proton or photon planning.

Standard skin care included topical emollients, with the addition of topical steroidal creams or dilute vinegar soaks as indicated for more severe radiation dermatitis. Mepitel film, which has been shown to reduce the severity of radiation dermatitis,[43] was used at the discretion of the treating physician and patient as an out-of-pocket expense.

Adverse events were prospectively collected using the Common Terminology Criteria for Adverse Events, version 4.0. Baseline toxic effects were assessed by the treating radiation oncologist before the start of radiation. End-of-treatment toxic effects were assessed at the last on-treatment visit. Acute treatment toxic effects were assessed at the first clinical follow-up. Photography was obtained with patient consent at baseline, end-of-treatment, and follow-up visits to document skin toxic effects and cosmetic outcomes.

ProKnowDS (Elekta AB, Stockholm, Sweden) was used to aggregate CT images, structure sets, Digital Imaging and Communications in Medicine plans, and dose files and to generate comparative dose-volume histograms (DVHs) for target volumes and normal tissues. Plan comparisons were performed in terms of dosimetric parameters characterizing target coverage and OARs. Although dose was prescribed to the PTV for photon plans, comparison of target coverage was made for the CTV because this volume was the same for both modalities. Differences between modalities were tested using the Wilcoxon signed

Table 1   Patient, cancer, and treatment characteristics of 11 patients with 22 tumors treated with intensity modulated proton therapy

Characteristic	Number	%
Histology		
Invasive ductal carcinoma	21	95
Invasive lobular carcinoma	1	5
Hormone receptor at diagnosis		
ER and/or PR+/HER2−	16	73
ER and/or PR+/HER2+	2	9
ER−/PR−/HER2−	4	18
Clinical stage at diagnosis		
0	4	18
I	1	5
II*	10	45
III*	7	32
Pathologic stage at surgery		
0	3	14
I*	3	14
II*	8	36
III*	8	36
Axillary surgery		
Sentinel lymph node dissection	7	35
Axillary lymph node dissection	13	65
* Includes patients who had recurrence after breast-conserving therapy.		

rank test, with a *P* value <.05 considered statistically significant.

Results

A total of 11 patients, 10 female and 1 male, were identified who met study criteria. Patient and tumor characteristics are shown in Table 1. The median age of the patients at diagnosis was 51.5 years (range, 38-69 years). Two patients had inflammatory breast cancer (T4d). Three patients had recurrence after prior breast-conserving therapy including radiation therapy. All patients received chemotherapy with or without HER2 directed therapy and hormone therapy as indicated: neoadjuvant (n = 4), adjuvant (n = 5), and neoadjuvant plus adjuvant (n = 2). Five patients had reconstruction with immediate tissue expanders (n = 3) or autologous reconstruction (n = 2). The

Table 2   Comparison of target coverage and organs at risk between proton and VMAT photon plans*

Structure	Parameter	Proton, mean (range)	VMAT, mean (range)	Wilcox signed rank *P* value
Target volumes				
CTV	D90%	99.9% (94.9%-101.5%)	97.6% (92.7%-100.0%)	.001
	D95%	96.3% (92.2%-99.8%)	97.7% (91.8%-99.5%)	.520
Boost CTV	D90%	95.6% (78.5%-100.5%)	99.2% (81.9%-101.8%)	.016
	D95%	95.1% (77.1%-99.3%)	98.5% (80.0%-101.2%)	.016
IMN				
Right	D90%	95.9% (84.2%-99.3%)	91.8% (81.7%-103.1%)	.465
Left	D90%	96.2% (92.1%-99.7%)	92.9% (76.9%-100.8%)	.250
Organ at risk				
Heart	V5Gy	3.8% (0.7%-7.9%)	83.6% (46.8%-100%)	.001
	V15Gy	0.8% (0.0%-2.8%)	4.3% (0.1%-12.2%)	.002
	V25Gy	0.1% (0.0%-1.2%)	0.7% (0.0%-4.3%)	.009
	Mean (Gy)	0.7 Gy (0.3 Gy to 1.4 Gy)	7.2 Gy (5.3 Gy to 9.7 Gy)	.001
Coronary arteries				
Right	Max (Gy)	11.3 Gy (1.9 Gy to 27.9 Gy)	19.6 Gy (8.6 Gy to 35.0 Gy)	.003
	Mean (Gy)	1.0 Gy (0.02 Gy to 3.9 Gy)	10.4 Gy (5.4 Gy to 15.2 Gy)	.001
Left anterior descending	Max (Gy)	10.1 Gy (3.4 Gy to 30.3 Gy)	31.8 Gy (10.1 Gy to 42.5 Gy)	.001
	Mean (Gy)	1.3 Gy (0.3 Gy to 4.9 Gy)	13.3 Gy (6.5 Gy to 28.4 Gy)	.001
Lungs				
Total	V5Gy	42.8% (16.9%-48.4%)	99.6% (92.3%-100%)	.001
	V20Gy	13.0% (5.2%-15.4%)	27.4% (18.0%-45.8%)	.001
	Mean	7.8 Gy (3.3 Gy to 8.6 Gy)	17.3 Gy (13.7 Gy to 23.2 Gy)	.001
Right	V5Gy	43.3% (13.0%-50.2%)	99.4% (94.2%-100.0%)	.001
	V20Gy	13.5% (3.0%-18.7%)	27.9% (17.8%- 46.4%)	.001
Left	V5Gy	41.8% (6.6%-50.2%)	99.8% (90.1%-100%)	.001
	V20Gy	12.3% (0.1%-14.8%)	27.9% (17.6%-45.0%)	.001
Brachial plexus				
Left	Max (Gy)	50.7 Gy (49.4 Gy to 58.4 Gy)	54.9 Gy (53.3 Gy to 60.9 Gy)	.008
Right	Max (Gy)	50.9 Gy (48.5 Gy to 55.7 Gy)	54.2 Gy (51.7 Gy to 58.1 Gy)	.010
Esophagus	Max (Gy)	4.9 Gy (0.0 Gy to 16.4 Gy)	15.4 Gy (6.9 Gy to 34.9 Gy)	<.001

Abbreviations: CTV = clinical target volume; D90% = minimum dose received by 90% of the volume; IMN = internal mammary lymph node; RBE = relative biological effectiveness; V5Gy = volume recieving 5 Gy; V20Gy = volume recieving 20 Gy; VMAT = volumetric modulated arc therapy.

* Doses are given as Gy (VMAT) or Gy RBE (proton) received by volume (%) of targets.
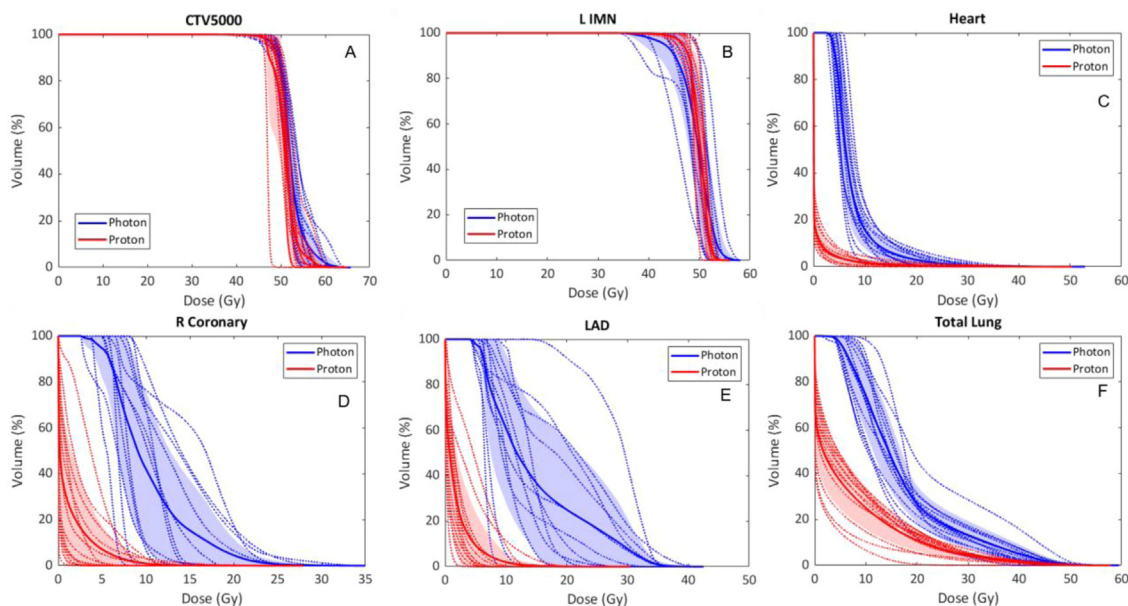
Fig. 1 Dose-volume histograms for photon (blue) and proton (red) plans for 11 patients.
Target volumes: **(A)** clinical target volume (CTV) and **(B)** left internal mammary lymph nodes. Coverage goals for the CTV were for the minimum dose received by 90% of the volume (D90) to be greater than 90%, with a second priority for D95% to be greater than 95%. Coverage goals for internal mammary lymph nodes were a D90% greater than 80%. Organs at risk: **(C)** heart; **(D)** right coronary artery; **(E)** left anterior descending artery; and **(F)** total lung.

CTVs included bilateral postmastectomy with regional nodal irradiation (n = 9) and bilateral whole breast with regional nodal irradiation (n = 2). The prescription was 50 Gy (RBE 1.1) in 25 fractions. Seven patients received boosts: 4 to the chest wall, 1 to the lumpectomy cavity, and 2 to one or more nodal regions. Boosts were typically delivered with a simultaneous integrated technique to 54.05-58.75 Gy in 25 fractions (n = 6). A sequential boost was administered in 1 patient (12.5 Gy in 5 fractions). Six patients were treated with arms up and 5 patients were treated with arms down. Four patients had arms-down immobilization chosen at initial simulation, and 1 patient required resimulation owing to intolerance of arms-up positioning. All patients had at least 1 CT verification scan. Replanning occurred for 4 patients: 3 owing to unacceptable target coverage and 1 after new immobilization was made for better patient tolerance. All 11 patients received all planned fractions with protons, and backup photon plans were not used.

Volumetric modulated art therapy comparison plans were generated for 7 patients who did not have photon plans as part of the treatment workflow. The CTV coverage goals of D90 >90% and D95 >95% were achieved in both proton and photon plans for all patients. Intensity modulated proton therapy achieved better D90% coverage of the CTV (P = .001). Volumetric modulated art therapy achieved better D90% and D95% coverage of the boost CTV (P = .016 for both). Otherwise, there was no statistical difference in

coverage of the CTV or IMNs between modalities (Table 2). The DVHs for the CTV and IMNs are depicted in Figure 1, A-B. Figure 2 shows plan comparisons for 2 representative patients.

Intensity modulated proton therapy was associated with a significant improvement in normal-tissue sparing for all evaluated OARs (Table 2) and was also associated with significant reduction in the mean heart dose (0.7 Gy vs 7.2 Gy; P = .001), total lung mean dose (7.8 Gy vs 17.3 Gy; P = .001), and total lung volume recieving 20 Gy (13.0% vs 27.4%; P = .001). The DVHs for the heart, coronary arteries, and lungs are depicted in Figure 1, C-F. Comparison of VMAT plans for patients simulated in deep inspiratory breath hold (DIBH) (n = 3) versus free-breathing (n = 8) showed no statistically significant differences in target coverage or dose to all evaluated OARs. There were no differences in IMPT or VMAT treatment planning or dosimetry for patients positioned with arms down.

Baseline and end-of-treatment toxicity data are shown in Table 3. The most common end-of-treatment toxic effect was radiation dermatitis, which occurred in all patients: grade 1 in 5 patients, grade 2 in 5 patients, and grade 3 in 1 patient. Five patients in the study had Mepitel film applied to the treatment area, of whom 4 had grade 1 dermatitis and 1 had grade 3 dermatitis. Of those who did not use Mepitel, 1 patient had grade 1 dermatitis and 5 patients had grade 2 dermatitis. Fatigue was reported by 8 patients at the end of treatment, mostly grade 1 (7
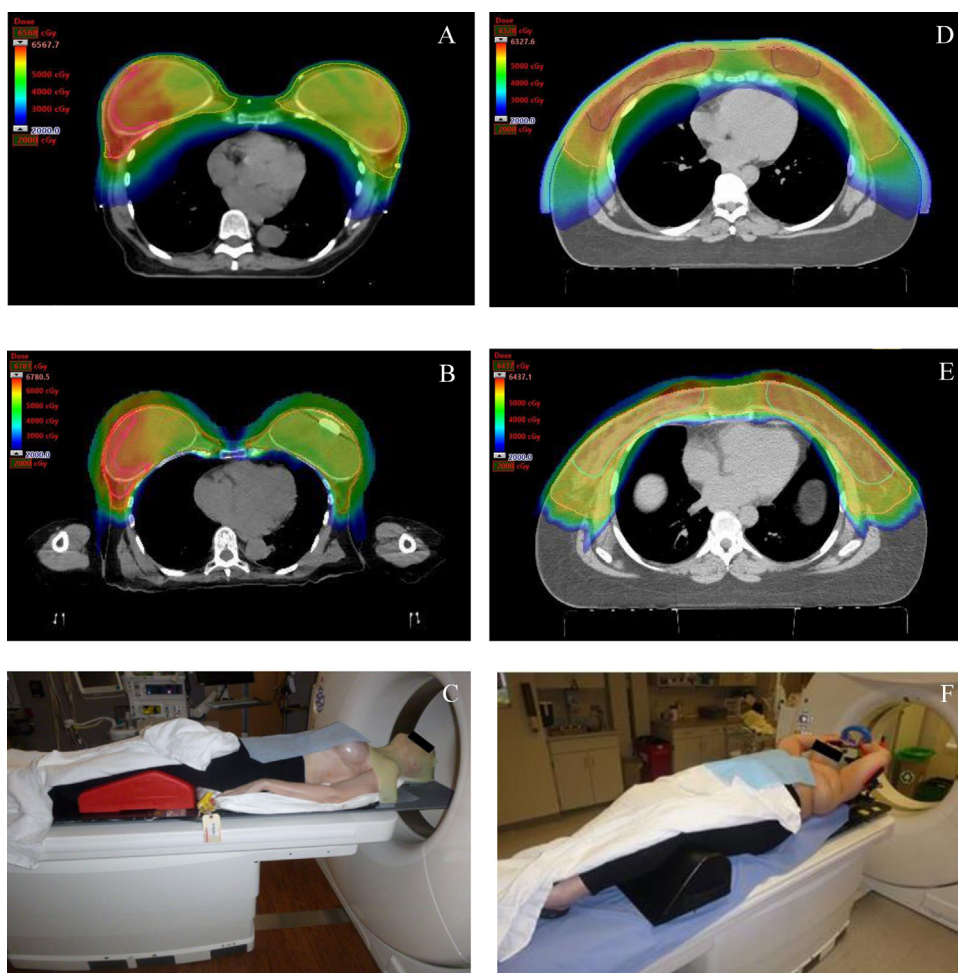
Fig. 2   Axial slices through the level of the heart comparing volumetric modulated arc therapy photon (**A** and **D**) and pencil-beam scanning intensity modulated proton therapy (**B** and **E**) plans for 2 patients in the study. Both patients were simulated in deep inspiratory breath hold for photon planning and free breathing for proton planning. One patient was immobilized with arms down (**A-C**) and 1 patient with arms above the head (**D-F**). The clinical target volume for both patients included the bilateral chest wall and regional lymph nodes plus chest wall boosts. The color wash displays 2000 to 6000 cGy isodose levels.

patients) and grade 2 (1 patient). Toxic effects were assessed in 11 patients at the first follow-up visit, which occurred at a median of 98 days (range, 84-134 days) posttreatment. Toxic effects were assessed in 8 patients at last follow-up at a median of 32 months (range, 8-48 months) posttreatment. The most common toxic effects at the last follow-up were superficial fibrosis, skin hyperpigmentation, and extremity lymphedema, all grade 1. No nondermatologic or nonfatigue adverse events greater than grade 1 were recorded. There were no differences in toxic effects between patients treated with arms up or arms down. There were no numerical differences in acute (<90 days) or longer-term (median, 27.5 months) toxic effects in the 3 patients receiving reirradiation. Figure 3 shows photographs taken at baseline, end of treatment, and the 3-month follow-up. At a median follow-up of 22 months (range, 2-48 months), 3 patients had developed

recurrence (1 local, 1 distant, and 1 local and distant), and 2 of those patients died of their disease.

Discussion

Radiation therapy for bilateral breast cancer is challenging to deliver with photon and/or electron techniques without compromises to target coverage or increased doses to OARs. This study demonstrated promising initial outcomes of a cohort of patients with SBBC treated with IMPT, which resulted in excellent target coverage with superior normal-tissue sparing compared with VMAT.

Attention to immobilization, beam arrangements, planning parameters, and daily image guidance is crucial for the safe delivery of IMPT. We occasionally position patients supine with arms down along their sides holding

Table 3   Physician-assessed toxic effects at baseline, end of treatment, first follow-up visit, and most recent clinical follow-up visit

Toxic effect	Patients, n			
	Baseline (n = 11)	End of treatment (n = 11)	First follow-up (n = 11)	Last follow-up (n = 8)
Fatigue	6	8*	7	1
Esophagitis	0	1	0	0
Limb edema	1	0	1	3
Noncardiac chest pain	2	1	0	0
Breast infection	0	0	0	0
Radiation dermatitis	0	11†	0	0
Fracture	0	0	0	0
Seroma	1	0	0	0
Superficial connective tissue fibrosis	0	0	2	3
Deep connective tissue fibrosis	0	0	1	1
Decreased joint range of motion	1	1‡	5‡	2‡
Brachial plexopathy	0	0	0	1§
Pneumonitis	0	0	0	0
Skin hyperpigmentation	0	0	8	2
Skin hypopigmentation	0	0	3	0
Lymphedema	0	2	1	1

* Grade 1 (n = 7) and grade 2 (n = 1).
† Grade 1 (n = 5), grade 2 (n = 5), and grade 3 (n = 1).
‡ Present in 1 patient at baseline.
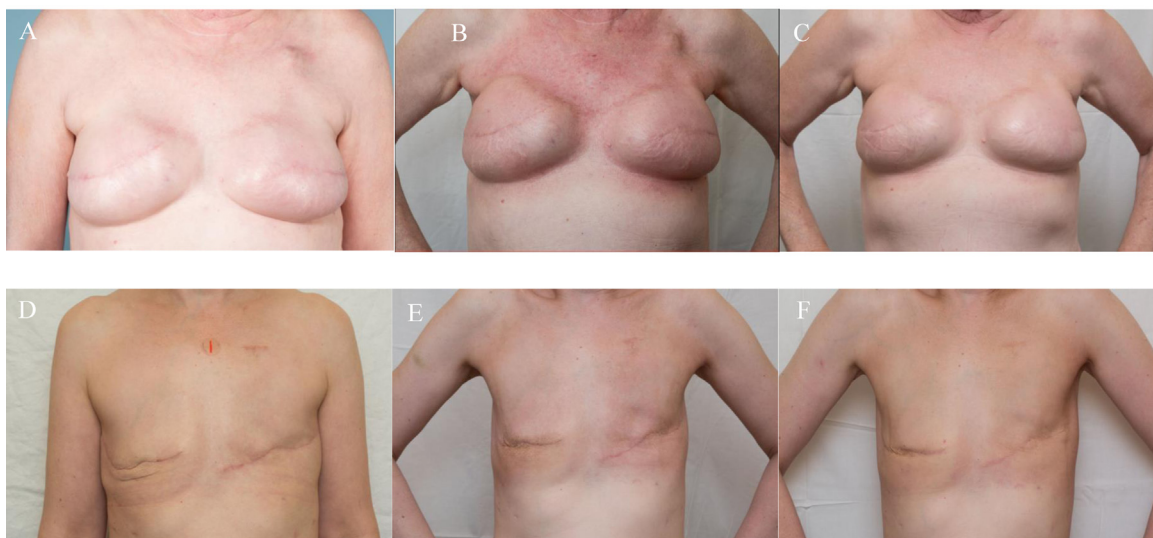§ Owing to recurrent inflammatory breast cancer.

Fig. 3   **(A-C)** A patient who underwent reconstruction with immediate tissue expanders. She received 50 Gy (relative biological effectiveness [RBE] of 1.1) to the bilateral chest wall and axilla. **(D-F)** A patient who received 50 Gy (RBE 1.1) to the bilateral chest wall and axilla with simultaneous integrated boost of 56.25 Gy (RBE 1.1) to the right chest wall. Photos were taken at postsurgical baseline (**A** and **D**), at the end of treatment (**B** and **E**), and at the 3-month follow-up (**C** and **F**).

indexed handgrips or immobilized in a Vac-Lok (Fig 2C).[31] Pain and reduced mobility are common after surgery, which may be further exacerbated by long treatment times, on the order of 45 minutes, required for bilateral IMPT. Arms-up positioning may necessitate a break between fields, leading to longer daily treatment times and increased room use. In cases requiring a supraclavicular or high axillary boost, the arms-down position allows for use of additional posterior beam angles to avoid end-of-range elevated biologic dose in the brachial plexus, which may put patients at greater risk of brachial plexophathy.[42] A similar arms-down technique was first described by Depauw et al[32] but was used in only 1 patient in their series. Otherwise, published reports of PBT for breast cancer most commonly reference simulation in the supine position with arms raised above the head, as is done in photon radiation therapy.[26,28,30] In our practice, unique patient factors and anatomic considerations for target coverage determine the most appropriate setup. Additionally, no respiratory gating or DIBH techniques were used with IMPT in this study. In our experience, select patients with unfavorable cardiac anatomy undergoing IMPT may have a dosimetric improvement with DIBH from displacement of the heart and coronary arteries away from the IMN CTV.[44] However, owing to excellent target volume coverage and normal-tissue sparing achieved with IMPT, we infrequently use DIBH and only when there is an indication for additional benefit in normal-tissue sparing that outweighs the increase in complexity and time of treatment delivery.

Acute toxic effects in the study patients compared favorably with previously published reports of proton therapy for breast cancer.[27-29,31,45,46] For example, a recently published phase 2 trial reported an 86% incidence of acute grade 2 to 3 skin toxic effects using passively scattered and pencil-beam scanning proton therapy.[27] We applied skin dose constraints to limit hot spots at the surface but made adjustments based on the risk profile of individual patients. Skin in the supraclavicular region was contoured as a separate OAR because dermal lymphatics are not at risk and a lower skin dose can routinely be achieved without compromising coverage of the underlying nodal basins. Additionally, only 1 patient in our study developed dysphagia, compared with more than 70% in a series of patients treated with photon radiation therapy for SBBC.[4] At a median follow-up of 22 months, no patient had developed rib fractures, symptomatic pneumonitis, or cardiac disease.

Although the clinical benefit of proton therapy has not been proven in randomized trials, there is compelling data that superior normal-tissue sparing may be associated with reduced late toxic effects. Owing to proximity of the IMNs to the heart and coronary vessels, there is concern that increased risk of late cardiac mortality may outweigh the potential disease-control benefits.[47] Dose to the heart has been associated with increased risk of ischemic heart disease and cardiac mortality.[21,22] More recently, the mean dose to cardiac substructures, including the coronary vessels, has been associated with an increase of nearly 5% per Gy in coronary artery stenosis and need for revascularization.[48-50] There is no known safe dose to the coronary vessels. We were able to achieve adequate target coverage while keeping the mean heart dose to 0.7 Gy and the maximum dose to the coronary vessels <12 Gy. Patients treated for breast cancer have increased incidence of and mortality from lung and esophageal cancer,[24] which may be reduced with sparing of the lungs and esophagus with IMPT. Further prospective evaluation is needed to confirm whether IMPT will reduce the risk of pneumonitis and other late toxic effects.

We selected VMAT as a gold standard comparison to IMPT in this study because multiple planning studies have shown that VMAT and hybrid techniques achieve superior normal-tissue avoidance compared with 3-dimensional techniques.[5,6,8-10,13] Respiratory management with DIBH or respiratory gating also reduces the dose to the heart and lungs.[11] Two clinical series of adjuvant photon radiation therapy for SBBC reported good oncologic outcomes and low rates of radiation-associated lung toxic effects. Twenty-one patients were treated with tomotherapy and assessed with pulmonary function tests and high-resolution CT scans.[36] At 3 years, 14 patients had subclinical grade 1 to 2 radiographic changes, and 1 patient had grade 3 radiographic changes. No patient had a significant change in pulmonary function tests. In a series of 25 patients treated with RapidArc and followed with high-resolution CT scans, there was a 30% rate of grade 1 radiation-induced lung fibrosis at 3 years.[45] These studies had a relatively short follow-up and did not report late toxic effects. Advanced planning techniques, including IMRT and respiratory management, should be considered when treating patients with SBBC when proton therapy is unavailable.

This study has several limitations. Photon plans for 7 patients were generated solely for the purposes of this study. We attempted to minimize differences between plans intended for clinical use and for research by having an experienced photon breast dosimetrist generate VMAT plans with the objective of achieving comparable CTV coverage. Computed tomography simulation scans in DIBH for photon comparison planning were available for only 3 patients, and 2 patients had simulation scans with only arms-down immobilization, which is not ideal for VMAT planning. The heterogeneous use of DIBH and immobilization positioning for VMAT comparison plans limits the interpretation of the results of the dosimetric comparisons. The number of patients in this study was small. However, owing to the relative rarity of SBBC requiring bilateral adjuvant radiation therapy, this is, to our knowledge, the largest reported series of IMPT in this setting. Long-term toxic effects and outcome data in this study are limited, and follow-up is ongoing.

Conclusion

To our knowledge, this is the first report of adjuvant IMPT for SBBC. Delivery of bilateral IMPT was technically feasible and well-tolerated in 11 patients treated at our institution; it was associated with significantly improved sparing of the lungs, heart, coronary vessels, and esophagus compared with VMAT and should be considered an excellent treatment option for SBBC. Additional research to determine the potential long-term benefits of proton therapy compared with photon radiation therapy is ongoing.

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