Techniques for Treating Bilateral Breast Cancer Patients Using Pencil Beam Scanning Technology

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Abstract

Purpose: Patients with bilateral breast cancer (BBC), who require postmastectomy radiation therapy or radiation as part of breast conservation treatment, present a unique technical challenge. Even with modern techniques, such as intensity modulated radiation therapy or volumetric modulated arc therapy (VMAT), adequate target coverage is rarely achieved without the expense of increased integral dose to important organs at risk (OARs), such as the heart and lungs. Therefore, we present several BBC techniques and a treatment algorithm using intensity-modulated proton therapy (IMPT) for patients treated at our center.

Materials and Methods: We describe 3 different BBC treatment techniques using IMPT on patients treated at our center, with comparison VMAT plans to demonstrate the dosimetric benefit of proton therapy in these patients. Following RADCOMP (Radiation Therapy Oncology Group, Philadelphia, Pennsylvania) guidelines, a single physician approved all target volumes and OARs. Plans were designed so that /C21 95% of the prescribed dose covered /C21 95% of all targets. Parameters for dosimetric volume histograms for the clinical targets and OARs are reported for the 2 radiation methods.

Results: All methods demonstrated acceptable target coverage with 95% of the prescription planning target volume reaching a mean (± SD) of 98.0% (± 0.87%) and 97.5% (± 2.39%), for VMAT and IMPT plans, respectively. Conformity and homogeneity were also similar between the 2 techniques. Proton therapy provided observed improvements in mean heart dose (average heart mean [SD], 9.98 Gy [± 0.87 Gy] versus 2.12 Gy [± 0.96 Gy]) and total lung 5% prescription dose (V5; mean [SD] total lung V5, 97.9% [± 2.84%]), compared with 39.8% [± 9.39%]). All IMPT methods spared critical OARs; however, the single, 0° anterior-posterior plan allowed for the shortest treatment time.

Conclusion: Both VMAT and all 3 IMPT techniques provided excellent target coverage in patients with BBC; however, proton therapy was superior in decreasing the dose to OARs. A single-field optimization approach should be the IMPT method of choice when feasible.

Keywords: bilateral breast cancer; intensity modulated proton therapy; pencil beam scanning
Introduction

Breast cancer is the most common malignancy in women in the United States, with an estimated 266,120 new cases each year. The incidence of primary synchronous bilateral breast cancers (BBCs) ranges from 0.3% to 12%, but may be increasing because of the advent and acceptance of preoperative breast magnetic resonance imaging, which has shown a 3% to 5% rate of contralateral breast cancers. Patients with BBC who require postmastectomy radiation therapy or radiation as part of breast conservation therapy can present unique technical challenges. In this setting, using 3-dimensional conformal radiation therapy has been associated with complex, time-consuming techniques, which make it difficult to protect organs-at-risk (OARs), frequently sacrificing target coverage to do so. Newer methods using intensity modulated radiation therapy (IMRT) or volumetric modulated arc therapy (VMAT) have shown dosimetric improvement over 3-dimensional conformal radiation therapy in target coverage, but frequently at the cost of increasing the integral dose to critical structures, such as the heart and lungs.

Pencil-beam scanning (PBS) is the newest form of proton therapy, which uses 2 pairs of magnets near the beams exit to “paint” the target in layers, and multiple layers are used to cover the depth of the target. The treatment of breast cancer with PBS has been increasing in the past several years as PBS technology is being more widely implemented in proton centers. The PBS technology has been shown to be dosimetrically superior to photon treatment of localized and locoregional, unilateral breast cancers, offering improved target coverage as well as lower integral doses to OARs when compared with more traditional photon techniques. However, there is scant data describing the methods in treating patients with BBC with PBS proton therapy. Therefore, in this article, we describe different clinical scenarios and techniques for treating this unique cohort of patients with PBS and provide an algorithm that may be beneficial for other proton facilities when approaching treatment for these patients.

Materials and Methods

Pretreatment Evaluation

All patients presented in this study were evaluated by a multidisciplinary team that included surgical oncologists, medical oncologists, and radiation oncologists at initial presentation. Patients underwent standard workups that included diagnostic mammograms, biopsies with pathology reviews, estrogen/progesterone (ER/PR) and ERBB2 (formerly HER2 or HER2/neu status). Patients were staged according to the 7th edition of the American Joint Committee on Cancer (Chicago, Illinois) staging criteria. Patients all received surgery and chemotherapy per National Comprehensive Cancer Network (Plymouth Meeting, Pennsylvania) guidelines for their American Joint Committee on Cancer stage. All patients had indications for adjuvant radiation therapy with ≥1 side requiring comprehensive nodal treatment.

Planning Technique

All patients underwent free-breathing noncontrast computed tomography (CT) simulation scans. Patients were immobilized in the supine position with both arms raised above their heads using an ArmShuttle (Qfix, Avondale, Pennsylvania) and Vac-Lok bag (Civco Radiotherapy, Orange City, Iowa) for immobilization. Each patient underwent treatment with intensity-modulated proton therapy (IMPT), where dose was calculated using Eclipse software (version 11.0.31, Ottawa, Ontario, Canada) and proton convolution superposition. Individualized clinical target volumes (CTVs) were delineated by a single physician using the RADCOMP (Radiation Therapy Oncology Group, Philadelphia, Pennsylvania) breast atlas. For IMPT, a proton planning target volume was generated with a 5-mm expansion from the CTV then edited 3 mm from the patient skin and lungs (no patient had skin involvement at presentation). The robustness of the CTV coverage was evaluated with combined 5-mm setup uncertainty and 3.5% range uncertainty. All IMPT plans were delivered with a nominal 4-mm spot size (r in air at 245 MeV) and field size of 30 cm by 40 cm as the isocentric plane. A range shifter of 5-cm physical thickness was used in all plans because of the shallow depth of targets in patients with BBC. Depending on the individualized patient-target size, a single-field (SFO) or multifield optimization (MFO) plan was used. In the SFO design, each field is optimized separately to cover the entire target to develop a more homogeneous plan with a decrease in steep gradients within the target. On the other hand, MFO techniques are used when only an individual beam is used to treat a portion of the clinical target, creating highly conformal dose distributions that tend to be more sensitive to range and setup uncertainties. In all MFO plans with multiple isocenters, gradient matching was used to minimize the formation of hot and cold spots generated by the offset of the 2 isocenters. For single-isocenter MFO plans, gradient matching was not used. In patients with breast implants, the product composition was

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obtained (saline versus silicone), typically through the operative notes, and the stopping power was accounted for during dose calculations. Daily VisionRT (London, England) with kilovolt x-rays and weekly cone-beam CT scans were used for image guidance. Quality assurance CT scans were performed ≥ 1 time during the course of therapy to assess for any soft-tissue changes during treatment and to determine whether those changes affected dose distribution. Weekly on-treatment visits were also performed to assess toxicities or any physical changes, such as truncal swelling in the midaxillary line, which could affect dose distribution.

For the purposes of this analysis, comparison photon plans were also performed for each case, using 6-MV VMAT fields. The CTV was the same as that used for the IMPT plans; however, an isometric 5-mm planning target volume (PTV) was used in the photon plans (3 mm at the chest wall-lung interface, splitting the ribs) and staying 3 mm off the skin. The VMAT plans were generated in RayStation (version 6.1.1.2, RaySearch Laboratories, Stockholm Sweden) with a single isocenter with 3 coplanar partial arcs (135° to 215°), not passing through the spinal cord.

Evaluation Tools

Evaluation of all plans were based on a dose-volume histogram (DVH) analysis. The target coverage goal was 95% of the PTV (for photons) and proton PTV (for protons) received ≥ 95% of the prescribed dose. For IMPT plans, the CTV receiving ≥ 95% of the dose ($V_{95}$), and the robustness of the IMPT plan was evaluated, where the “worst-case scenario” CTV coverage was reported as a combination effect from the setup and proton range uncertainties of the plan. The $V_{100}$ of the CTV was also reported for both photons and proton plans. Hot spots were limited to < 110% of the prescribed dose. The conformity index ($CI$) and homogeneity index ($HI$) were also described and defined as follows:

\[
CI = \frac{V_{R95}}{TV},
\]

where $V_{R95}$ is the volume of the reference isodose (95%)/CTV, and

\[
HI = \frac{D_2 - D_{98}}{D_P},
\]

where $D_2$ is the minimum dose to 2% of the CTV, $D_{98}$ is the minimum dose to 98% of the CTV, and $D_P$ is the prescribed dose. For the OARs, the mean dose to the heart, as well as the $V_{15}$, $V_{25}$, and $V_{30}$, was assessed. The mean dose, $V_5$, and $V_{20}$ of each lung and the total lung were also considered. Maximum dose to 0.03 cm³ to the esophagus was also reported. At our institution, we used the following dose constraints for IMPT: $V_{30} < 5\%$ and mean < 1.7 Gy for the heart, $V_{20} < 15\%$, $V_5 < 40\%$ for the individual lung, and the 70% isodose line was kept off the esophagus.

Results

Case 1

Patient 1 is a 61-year-old woman, who was found to have bilateral cT2N1M0 invasive ductal carcinomas (IDCs) with possible radiographic involvement of the internal mammary lymph nodes of the right breast. Both lesions tested positive for ER/PR and ERBB2 (right: ER 62%, PR 5%, Ki-67 41%; left: ER 100%, PR 44%, Ki-67 59%). She underwent neoadjuvant chemotherapy with docetaxel, caboplatin, trastuzumab, and pertuzumab, followed by bilateral mastectomy and axillary lymph node dissection. Pathology on the right revealed minimal residual ductal carcinoma in situ (DCIS) in a background of treatment effect, with no residual invasive carcinoma and negative margins. Three of 10 lymph nodes were involved with IDC in the axillary dissection, and she was staged as ypTisN1aM0. On the left, she had residual, multifocal, invasive carcinoma with 2 foci measuring 3.5 cm and 0.8 cm along with high-grade DCIS, as well as evidence of treatment effect. She had lymphovascular space invasion (LVI) present, negative margins, and 13 of 19 lymph nodes involved with evidence of extracapsular extension, which was, thus, staged as ypT2N3aM0.

For her postmastectomy radiation therapy, the CTV included bilateral chest wall and comprehensive nodal regions (axilla, supraclavicular [SCLV] and internal mammary [IM]). The medial chest wall above the sternum was included to ensure adequate coverage of both mastectomy scars, especially in the setting of extensive LVI. A dose of 50.4 Gy relative biological effectiveness (RBE) in 1.8-Gy (RBE) fractions was prescribed. An SFO technique was used in this clinical scenario, with an anterior-posterior (AP) beam positioned at 0° (Figure 1A). With a single field, the entire CTV was adequately covered (Figure 2A, Table 1) with acceptable robustness, where in the worst-case scenario, 96.65% of the CTV received 91.67% of the
prescribed dose and 89.70% of the PTV received 93.41% of the dose. Individual clinical volumes were assessed for robustness on both sides, and the left side was as follows: 94.48% of the chest wall received 46.8 Gy (RBE), 95.30% of the axilla received 46.1 Gy (RBE), 90.59% of the SCLV nodes received 46.7 Gy (RBE), and 94.85% of the IM nodes received 46.7 Gy (RBE). On the right, the worst-case scenario for the chest wall (93.36% of the volume received 46.8 Gy [RBE]), axillary nodes (85.91% of the volume received 46.9 Gy [RBE]), SCLV (88.48% of the volume received 46.0 Gy [RBE]), and IM nodes (89.09% of the volume received 46.0 Gy [RBE]) were also clinically acceptable.

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Case 2

Patient 2 is a 62-year-old female diagnosed with an ER/PR⁺, ERRB2⁺ IDC of the bilateral breast, both staged as a cT2N0M0. The patient underwent neoadjuvant chemotherapy with adriamycin and cyclophosphamide (Cytoxan, Bristol-Myers Squibb, New York, New York), followed by dose-dense paclitaxel (Taxol, Bristol-Myers Squibb). She underwent bilateral mastectomy.

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and sentinel lymph node dissection with implant reconstruction. Pathology revealed residual invasive disease measuring 0.8 cm with 0 of 1 lymph nodes involved and negative margins, so the right breast was staged as a ypT1bN0M0. In the left breast, she was found to have residual invasive disease measuring 1.9 cm with isolated tumor cells present in 3 lymph nodes, staged as a ypT1cN0(1+)(sn). There were negative margins bilaterally and no evidence of LVSI. Despite surgical recommendations, the patient refused additional lymph node evaluation on the right where only 1 sentinel was seen.

The CTV was defined as the right chest wall, including axillary levels I and II and left chest wall with comprehensive lymph node regions (axilla, supraclavicular, and internal mammary chains). A dose of 50 Gy (RBE) in 2 Gy (RBE) fractions was prescribed. For this patient, a 2-field, 2-isocenter plan was designed in such a fashion that only 1 lateral shift was required for treatment (Figure 1B). An MFO plan was used, and the contribution to the dose coverage of the medial breast tissue was split between the beams. This beam arrangement was chosen because of the patient’s size because she was unable to fit within one portal. The $V_{95}$ of the CTV was calculated to be 99.92% of the prescribed dose (Figure 2B, Table 1). The robustness of the plan was acceptable in which the worst-case scenario was 95.49% of the entire CTV received 98.60% of the dose and 90.52% of the total PTV received 96.55% of the dose. The robustness for the individual CTV structures on the left were as follows: 98.68% of the chest wall received 49.7 Gy (RBE), 99.90% of the axilla received 49.9 Gy (RBE), 82.53% of the SCLV nodes received 45.8 Gy (RBE), and 89.43% of the IM nodes received 47.3 Gy (RBE). On the right, 91.69% of the chest wall received 48.3 Gy (RBE), and 77.72% of the axilla received 49.9 Gy (RBE).

### Case 3

Patient 3 is a 50-year-old woman who was initially diagnosed with an ER/PR$^+$, ERRB2$^-$, cT2N2aM0 IDC of the left breast at the age of 36. She underwent an excisional biopsy of the primary and neoadjuvant chemotherapy, followed by axillary lymph node dissection (0 of 8 involved nodes) and comprehensive radiation therapy to the left breast and axillary, supraclavicular, and internal mammary nodes completed in November 2004. She also completed 5 years of adjuvant tamoxifen therapy. In June 2010, she had biopsy-proven, grade 3, ER/PR$^+$ DCIS in her left breast, treated with mastectomy and immediate autologous tissue reconstruction. She developed recurrent disease in the inferior medial aspect of the left reconstructed breast, measuring 4.7 cm, and the biopsy was consistent with an ER$^+$, PR$^-$, grade 3 IDC. On positron emission tomography–CT, she was found to have a cluster of avid right axillary nodes, the largest measuring 2 cm, but no systemic evidence of disease elsewhere. She underwent a left mastectomy with expander placement, and sentinel node sampling was performed, with the tracer leading to the contralateral axilla. Pathology from her latest surgery depicted a 2.3-cm IDC from the left reconstructed breast, negative margins, but the tumor did extend to the dermis. There was 1 of 4 right axillary nodes involved.

| Parameter | Case 1 | Case 2 | Case 3 |
|-----------|--------|--------|--------|
| $V_{95}$ (%) | 94.78 | 99.07 | 98.75 |
| $V_{100}$ (%) | 95.78 | 97.55 | 96.89 |
| $V_{95}$ (%) | 99.85 | 99.91 | 99.65 |
| CI | 1.01 | 1.37 | 1.28 |
| HI | 0.057 | 0.043 | 0.059 |
| Delivery$^b$ | 188 | 0.057 | 0.130 |

Abbreviations: IMPT, intensity modulated proton therapy; VMAT, volumetric modulated arc therapy; PTV, planning target volume; $V_{XX}$, percentage of target (CTV or PTV) that received $\geq XX$% of prescribed dose; CTV, clinical target volume; CI, conformity index; HI, homogeneity index.

$^a$The PTV for IMPT plans were beam specific and were generated with a 5-mm setup uncertainty and a 3.5% range uncertainty.

$^b$This time solely reflects the “beam-on” time of treatment and does not take into consideration patient setup time or image guidance.
with disease, measuring 0.8 cm, with extracapsular extension. She had a final implant placement on the left side in January 2018.

The CTV for this case included the left reconstructed breast, chest wall, and the medial, postoperative bed, as well as the right breast and chest wall with right comprehensive nodes. The total dose to this initial target was 50.4 Gy in 1.8 Gy per fraction. The skin was not spared because of involvement of the dermis. An MFO plan with 3 noncoplanar beams sharing a single isocenter was used (2 anterior obliques on the left and right, respectively, as well as an AP beam). As with case 2, the patient’s treatment volume did not fit within the field size. A single isocenter setup with 3 beams resulted in a qualitative faster treatment time than the dual isocenter approach because no shifts were required (Figure 1C, Table 1). The robustness of the CTV and PTV coverage was 85.36% of the optimized CTV receiving \( 94.21\% \) of the dose and 85.95% of the PTV receiving \( 93.32\% \) of dose (Figure 2C). The robustness for the left reconstructed breast was 92.88% of the target, receiving 46.8 Gy (RBE), and 90.51% the right breast and chest wall, which received 46 Gy (RBE). The following describes the “worse-case scenarios” for the right nodal areas: 88.62% of the axilla received 47.5 Gy (RBE), 87.50% of the SCLV nodes received 45.1 Gy (RBE), and 59.56% of the IM nodes received 39.42 Gy (RBE).

**Table 2. Comparison of organs-at-risk parameters for IMPT and VMAT plans.**

| Parameter | Case 1 VMAT | IMPT | Case 2 VMAT | IMPT | Case 3 VMAT | IMPT |
|-----------|-------------|------|-------------|------|-------------|------|
| Heart     |             |      |             |      |             |      |
| Mean (Gy) | 9.10        | 1.02 | 10.02       | 1.59 | 10.83       | 2.55 |
| \( V_{15}\% \) | 6.38        | 2.38 | 8.96        | 3.37 | 11.53       | 6.25 |
| \( V_{15}\% \)* | —          | 3.22 | —           | 8.02 | —           | 9.31 |
| \( V_{25}\% \) | 2.45        | 1.53 | 2.79        | 1.65 | 5.59        | 4.02 |
| \( V_{25}\% \)* | —          | 2.09 | —           | 4.73 | —           | 6.60 |
| \( V_{30}\% \) | 1.63        | 1.23 | 1.38        | 1.12 | 3.77        | 3.14 |
| \( V_{30}\% \)* | —          | 1.78 | —           | 3.60 | —           | 5.49 |
| Left lung |             |      |             |      |             |      |
| Mean (Gy) | 17.90       | 9.37 | 17.18       | 8.72 | 22.15       | 4.61 |
| \( V_{5}\% \) | 97.65       | 50.07 | 100.00     | 38.84 | 99.77       | 23.72 |
| \( V_{5}\% \)* | —          | 50.98 | —           | 50.67 | —           | 34.22 |
| \( V_{20}\% \) | 31.52       | 21.18 | 29.42      | 19.57 | 53.06       | 8.20 |
| \( V_{20}\% \)* | —          | 31.90 | —           | 34.11 | —           | 17.52 |
| Right lung |             |      |             |      |             |      |
| Mean (Gy) | 17.20       | 9.22 | 16.94       | 8.04 | 21.53       | 7.46 |
| \( V_{5}\% \) | 92.44       | 42.51 | 98.68      | 36.77 | 100.00      | 37.12 |
| \( V_{5}\% \)* | —          | 49.53 | —           | 49.85 | —           | 52.75 |
| \( V_{20}\% \) | 32.11       | 20.29 | 29.57      | 17.79 | 44.75       | 14.49 |
| \( V_{20}\% \)* | —          | 28.66 | —           | 33.00 | —           | 33.89 |
| Total lung |             |      |             |      |             |      |
| Mean (Gy) | 17.50       | 9.28 | 17.05       | 8.35 | 21.77       | 6.30 |
| \( V_{5}\% \) | 94.68       | 50.07 | 99.25      | 37.83 | 99.91       | 31.62 |
| \( V_{5}\% \)* | —          | 49.85 | —           | 42.29 | —           | 44.98 |
| \( V_{20}\% \) | 31.86       | 21.18 | 29.51      | 18.63 | 48.08       | 11.92 |
| \( V_{20}\% \)* | —          | 29.69 | —           | 32.49 | —           | 27.23 |
| Esophagus |             |      |             |      |             |      |
| Mean (Gy) | 9.27        | 1.09 | 16.98       | 5.70 | 16.81       | 1.77 |
| Max (Gy)  | 51.12       | 43.12 | 48.76      | 46.41 | 48.49       | 37.99 |
| Max (Gy)* | —          | 46.39 | —           | 48.26 | —           | 46.20 |

Abbreviations: IMPT, intensity modulated proton therapy; VMAT, volumetric modulated arc therapy; \( V_{xx}\% \), percentage of target (clinical or planning target volume) that received \( XX\% \) of prescribed dose; Max, maximum.

*Parameters with an asterisk (*) are values that denote the “worse-case scenario” in IMPT plans using 0.5-cm isocenter shifts and 3.5% range uncertainty.

bMaximum dose (Gy) is defined as dose to 0.03 cm\(^3\) of target.
Comparison of IMPT and VMAT Techniques

A comparison the VMAT plan was done to qualitatively compare target coverage (Table 1, Figures 1a–c) and dose to OARs (Figure 2a–c, Table 2). Both methods provided acceptable target coverage to the PTV (VMAT, average $V_{95}: 98.0\% \pm 0.87$ versus IMPT, 97.5\% $\pm 2.39$) and CTV (VMAT, average $V_{100}: 95.3\% \pm 1.64$ versus IMPT, 96.7\% $\pm 0.89$) (Table 1). Conformity and homogeneity were also observably similar between IMPT and VMAT plans. However, integral dose to the heart and lungs was visibly less for IMPT techniques (Table 2). Mean dose to the heart was superior for all IMPT plans when compared with VMAT techniques, with an mean heart dose of $9.98 \pm 0.87$ Gy and $2.12 \pm 0.96$ Gy for VMAT and IMPT methods, respectively. There was an appreciable difference between lung dose, especially when the low dose ($V_5$) to the lungs were considered (Table 2). The total averaged $V_5$ for the VMAT plans was $97.9\% \pm 2.84$, compared with $39.8\% \pm 9.39$ for all IMPT techniques. Radiation delivery time was also reported, and total delivery time was recognizably less for all VMAT plans (Table 1).

Discussion

Patients with BBC are rare and present technical challenges, especially when comprehensive nodal irradiation is required. Three-dimensional methods often result in sacrificing coverage to clinical targets to meet dose constraints for OARs, and although IMRT or VMAT approaches can improve target coverage in patients with BBC (Table 1), they often result in higher doses of radiation to the lungs, heart, and esophagus (Figure 2, Table 2).\textsuperscript{18,19} Although the incidence of symptomatic radiation pneumonitis for patients undergoing unilateral comprehensive nodal radiation is low,\textsuperscript{20} there are limited data describing the incidence in patients with BBC. In a BBC case, mean lung dose can reach approximately 20 to 30 Gy, and total lung $V_{20}$ is typically 20\% to 40\% with IMRT and VMAT methods (Table 2).\textsuperscript{8} Both lung constraints have been associated with higher rates.
(> 30%) of symptomatic pneumonitis in patients with lung cancer\textsuperscript{21,22} and pose an increased risk in this unique breast cancer group. Furthermore, radiation dose to the heart has been linked to increased risk of cardiovascular events in women treated for breast cancer, where there was no apparent threshold for dose.\textsuperscript{23} Mean dose to the heart from advanced photon techniques for women with BBC can be significant, ranging from 8 to 15 Gy,\textsuperscript{19} potentially increasing the relative risk of cardiovascular events by approximately 56\% to 105\%.

In our study, proton therapy with PBS technology, has allowed the physician to treat the clinical target effectively and alleviate the dose to the surrounding healthy tissue in patients with BBCs. When compared with VMAT plans, our IMPT methods had equivalent target coverage, conformity, and homogeneity (Table 1), but significantly decreased the dose to critical OARs. Although randomized data are still underway to quantify the benefits of protons versus photons in decreasing the risk of major cardiovascular events (RADCOMP; ClinicalTrials.gov identifier: NCT02603341), we found that IMPT was able to decrease mean heart dose 4-fold to 9-fold when compared with a VMAT approach (Table 2), a benefit that is hard to ignore, especially in women who already have preexisting cardiac morbidities from chemotherapy and who have potential other health conditions.

To our knowledge, we are the first group to compare IMPT to VMAT methods\textsuperscript{24} in patients with cancer and bilateral breast involvement and to provide a treatment algorithm to decide which beam arrangements should be used with PBS technology. Based on our experience, we recommend proceeding with a single-field optimized plan whenever possible because it offers an acceptable dose distribution with an expected shorter overall treatment time as compared with the other 2 IMPT methods described (Figure 3). However, this technique has a field-size limitation, in which a target volume has to be < 28 cm by 38 cm for this method to be feasible for our specific proton center. In scenarios in which the target volume is larger than that limit, our next recommendation is to use a 3-field, single-isocenter approach. From a treatment delivery viewpoint, this technique offers an easier setup, however, it requires increased treatment planning time and may sacrifice target or OAR robustness (Figure 2C). Although radiation delivery time is longer when compared with a single or 2-field IMPT technique, total treatment time would theoretically be less than a 2-isocenter plan because no shifts or re imaging is required during delivery (Figure 3). Finally, the 2-isocenter approach is hypothetically the most challenging setup, resulting in the longest “in-room” time of the 3 methods but can be beneficial in patients with larger implant or expander reconstruction in which the body contour is quite convex (Figure 1B).

Despite the dosimetric benefit seen with IMPT, this study does have limitations. First, a relatively small sample size was available for comparison between proton techniques. To date, we have treated 11 patients with BBC at our proton center, and most (n = 6) were treated with the SFO IMPT method. Our few study participants are inadequate for further defining dosimetric differences that may be present between the proton plans, such as overall robustness among patients, meaningful differences in OAR dose, or reproducibility issues. From Figure 2B, it appears that the 2-isocenter approach provides the best clinical target robustness; however, that comes at the cost of increase uncertainty to important OARs, including the lung, heart, and esophagus. In addition, although we can qualitatively report that overall treatment time would be longer for the 2-isocenter IMPT approach (Figure 1B) because of the retrospective nature of the analysis, we could not accurately quantify the total treatment time, taking into consideration image-guidance, patient setup, etc, between IMPT techniques or even compared with VMAT plans. However, we can infer qualitative differences among the 3 scenarios and can extrapolate the longer treatment time with the 2-isocenter plan (Figure 3), which would require 2 image-guidance captures per fraction. Future work is underway to prospectively compare dosimetric and treatment parameters in this unique set of patients employing all 3 IMPT techniques.

Nonetheless, we have successfully treated a number of patients with BBC with PBS technology, in which a solitary AP (0\textdegree), SFO IMPT plan provided the ideal beam arrangement in this unique clinical scenario, providing adequate target coverage, sparing important OARs, and qualitatively ensuring the shortest overall treatment time among the 3 IMPT methods. The PBS technology offers identical target coverage when compared with VMAT plans but has the added benefit of decreased the integral dose to the heart and lungs. We await the results of the RADCOMP trial to determine whether this superior dosimetric advantage translates to a clinical benefit in women with BBC.

**ADDITIONAL INFORMATION AND DECLARATIONS**

**Conflicts of Interest:** The authors have no relevant conflicts of interest to disclose.

**Ethical Approval:** All patient data have been collected under an internal review board–approved protocol.

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