A Technical Guide for Passive Scattering Proton Radiation Therapy for Breast Cancer

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Abstract

Most patients treated with proton therapy have had eye tumors, sarcomas, or, more recently, pediatric, or prostate cancers. As more proton centers have developed globally, increased capacity will permit exploration of other potential indications for proton therapy, including for the treatment of breast cancer. The rationale for proton therapy in the treatment of breast cancer is reduced inadvertent radiation dose to the heart and lung, as well as improved target coverage. As with any new technology, multiple technical parameters require optimization to deliver safe and effective radiation therapy and to maximize the benefits of the new technology. The purpose of this report is to provide a technical guide for the treatment of breast cancer with passive-scattering proton therapy and an algorithm for selecting patients with breast cancer who would benefit from proton therapy.

Introduction

Landmark trials in postmastectomy radiation therapy to the chest wall and regional lymphatic vessels, including the internal mammary nodes (IMNs), the axillary nodes (AXNs), and the supraclavicular nodes (SCNs) [1–3], have demonstrated the significant effect of adjuvant radiation therapy on disease control and survival. A study of breast-conserving therapy, with or without radiation to those nodal regions [4], has also demonstrated significant advantages in disease control with regional node irradiation. Although meta-analyses have shown an overall positive survival effect from irradiation, a significant excess in cardiac and pulmonary mortality has also been observed. Cardiac morbidity and mortality have occurred more often in women with left-sided breast cancers [5, 6], presumably because of excess radiation dose to the heart via tangential photon beams. With tangential photon beams, it is difficult to treat left-sided IMNs without irradiating heart tissue, and there is substantial lung tissue irradiated with either right- or left-sided breast cancers. Breath-hold techniques for photon radiation therapy can decrease cardiac exposure [7, 8]. Hjelstuen et al [7] reported a decrease in mean heart dose from 6.2 Gy with free-breathing to 3.1 Gy using a breath-hold technique during treatment with IMN irradiation.

These data suggest that methods for delivering radiation therapy that minimize cardiac and pulmonary radiation doses will increase the therapeutic ratio of radiation therapy, further positively affecting overall survival. Recent studies have demonstrated a significant positive effect from treatment of the IMNs [9–11], suggesting that compromising IMN coverage to avoid exposing the heart and lung to radiation will decrease the therapeutic ratio of radiation therapy for breast cancer. It is unlikely that
further improvements in the delivery of photon-based radiation therapy can accomplish both goals of increasing coverage of regional nodes (particularly IMNs) and decreasing exposure to the heart and lung [12]. The basic difference between photons and protons is that the proton beam (and, therefore, dose deposition) stops at a predictable depth in tissue, with most of the dose deposited at the end of the beam range, thereby eliminating an exit dose beyond the target and significantly reducing entrance dose before the target. In the case of breast cancer, rather than the tangential fields necessary with photons, en face proton beams can be used, which stop before exposing underlying tissues, such as the heart and lung. Thus, there is a compelling rationale for exploring the potential role of proton therapy (PT) in patients with breast cancer.

The treatment of breast cancer is a relatively new application for PT. The earliest efforts focused on partial breast irradiation [13–15]. Recently, comparative treatment planning studies of PT for treatment of regional nodes with breast cancer have highlighted the significant advantage in cardiac and lung sparing as well as in target coverage over traditional photon-based radiation techniques [16, 17]. Three studies have demonstrated the clinical feasibility of PT in the postmastectomy and/or breast-conserving settings [18–20]. The goals of this report are to offer an algorithm for selecting patients who may benefit from PT and to describe techniques with passive-scattering PT for intact breast or postmastectomy settings. Although pencil-beam PT may provide some advantages [21, 22], many proton centers do not have access to pencil-beam scanning delivery, so knowledge of passive-scattering techniques may increase access to PT for patients with breast cancer who would benefit.

### Methods and Findings

#### An Algorithm for Selecting Patients with Breast Cancer for Proton Therapy

The goal of treatment planning for patients with breast cancer at risk for nodal disease is to create a treatment plan that provides the best target coverage with minimal dose to organs at risk (OARs), such as heart and lung (Figure 1). Because of the higher cost, increased complexity, and limited availability of PT, a proton-based plan should be used only if it improves at least one of these treatment planning goals over the best available conventional technique (Figure 2). The sequential steps in

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**Table 1:** Organs at risk (OAR) parameters and target coverage stratified as ideal, goal, acceptable, minor, and unacceptable. Note: The RTOG terminology has been modified from PTV_Eval to PTV because we have accounted for the adjustments in creation of the PTV.

| OAR parameters | Ideal | Goal | Acceptable | Marginal | Unacceptable |
|----------------|-------|------|------------|----------|--------------|
| Heart, V25     | 0     | 0    | 0          | ≤5       | >5           |
| Heart, D5%, Gy | ≤1    | ≤2   | ≤10        | ≤25      | >25          |
| Heart, V15, %  | 0     | ≤5   | 0          | ≤10      | >30          |
| Heart, mean dose, Gy | ≤0.1 | ≤2   | ≤4          | ≤5       | >5           |

| OAR parameters | Ideal | Goal | Acceptable | Marginal | Unacceptable |
|----------------|-------|------|------------|----------|--------------|
| Ipsilateral lung, V5, % | ≤5    | ≤50  | ≤65        | ≤70      | >70          |
| Ipsilateral lung, V10, % | ≤1    | ≤20  | ≤50        | ≤60      | >60          |
| Ipsilateral lung, V20, % | ≤1    | ≤25  | ≤30        | ≤35      | >35          |
| Contralateral lung, V5, % | 0     | ≤5   | ≤10        | ≤15      | >15          |
| Contralateral breast, D5%, Gy | 0     | ≤1   | ≤3         | ≤4.1     | >4.1         |

**Legend:**
- **Ideal:** DVH parameters should be an achievable goal regardless of whether the nodes are treated.
- **Goal:** DVH parameters are considered acceptable by RTOG 1304/NSABP B51 for right sided breast cancer with nodal irradiation.
- **Acceptable:** DVH parameters are considered acceptable by RTOG 1304/NSABP B51 for left sided breast cancer with nodal irradiation.
- **Marginal:** DVH parameters are considered to be minor variation on RTOG 1304/NSABP B51 for left sided breast cancer with nodal irradiation.

**Figure 1:** Organs at risk (OAR) parameters and target coverage stratified as ideal, goal, acceptable, minor, and unacceptable. Note: The RTOG terminology has been modified from PTV_Eval to PTV because we have accounted for the adjustments in creation of the PTV.

**Abbreviations:** DVH, dose-volume histogram; PTV, planned target volume.

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Bradley et al. (2017), *Int J Particle Ther*
the algorithm for selecting patients who may benefit from PT are simulation, target and OAR delineation, treatment planning, and plan evaluation and comparison.

**Simulation**

**Patient Positioning**

The first step in simulation is selecting a treatment position that will be reproducible and minimize the risk of intrafraction motion. Targeted tissue should be stable, and skin folds in the treatment field should be avoided. With PT, en face, rather than tangential, fields are used, so it is not necessary to place the patient’s arms above the head. The optimal arm positioning may vary among patients: the akimbo arm position can minimize the supraclavicular and axillary folds (Supplemental Figure 1A–1D), whereas the overhead arm position can minimize inframammary folds and is most commonly used (Supplemental Figure 1E). Positioning the arms akimbo is incompatible with delivery of photon therapy, which should be considered for comparative plans. Thermoplastic body molds were tried early on but were abandoned because of the lack of reproducibility.

**Treatment Planning Computed Tomography and Deep-Inspiration Breath Hold**

A 4-dimensional (4D) treatment-planning computed tomography (CT) image should be obtained at initial simulation for evaluation of respiratory motion and plan robustness. Deep-inspiration breath hold (DIBH) has been useful in left-sided patients with breast cancer treated with photon-based techniques to reduce the heart dose [7, 8, 23, 24]. With PT in left-sided patients with breast cancer, the mean heart dose is typically < 1 Gy without DIBH. Therefore, DIBH may not provide additional significant dose reduction to the heart and may increase the volume of irradiated lung (Supplemental Figure 2A–2D).

**Target and Organs at Risk Delineation**

The second step in the algorithm is to delineate the clinical target volumes (CTVs) and OARs on the average 4D CT. For the breast, the breast tissue ≤ 5 mm from the skin surface constitutes the CTV_breast. The lumpectomy cavity plus a 1- to 1.5-cm expansion for potential microscopic disease constitutes the CTV_tumor bed. After mastectomy, the chest wall contour (CTV_chest wall) extends from the costosternal junction medially to the midaxillary line or anterior edge of the latissimus dorsi laterally, the anterior rib surface posteriorly, and to 3 mm beneath the skin surface anteriorly. All nodal CTVs, including the level I to III AXNs, SCNs, and IMNs, should be delineated. Several atlases exist to guide target delineation, including ones by the Radiation Therapy Oncology Group (RTOG), the Danish Cooperative Group, and the Project on Cancer of the Breast [25–27]. The atlases are intended to serve as guidelines that can be tailored to individual cases. It is important to review and, when possible, fuse the patient’s diagnostic imaging, particularly if regional nodes are present on those scans, to ensure adequate target delineation. Brown et al [28] reported that only 59% of supraclavicular recurrences were located in the supraclavicular volume suggested by the RTOG atlas. In PT, if gaps exist between contours, those regions may not receive the dose. If the
surgery has left clips at a biopsy site, tumor resection bed, or nodal dissection bed, those should be included in the contours. Omission of the dissected axilla falls to the treating physician's judgment. If the low axilla is omitted when treating with protons, there will be no dose to those regions, unlike with photons, when the low axilla remains largely captured in the tangent fields. All standard OARs [29] should be contoured, including the heart, ipsilateral lung, contralateral lung, and contralateral breast. In addition, the left-anterior descending coronary artery should be contoured in left-sided patients with breast cancer to permit optimization of plan parameters, such as beam angle, radiation modality (electrons, photons, or protons), and evaluation of DIBH and compensator design to minimize coronary artery injury. Often, the left-anterior descending artery can be defined without contrast administration. If contrast is given, either a separate, noncontrast scan must be obtained for treatment planning because of the difference in density and proton stopping power between the contrast and normal blood-filled vessels, or the contrast density must be over-ridden in the proton treatment planning process. If the SCNs are treated, the brachial plexus and esophagus should be contoured to permit dose reduction and optimization of plan parameters, such as aperture margin, beam angles, and compensator design. The axillary vessels can be contoured as a surrogate for the brachial plexus to avoid potential dose “hot spots” over the brachial plexus. Skin is defined as the rind between the surface of the body and the CTV (5 mm rind for intact breast, 3 mm rind for chest wall).

**Treatment Planning**

The proton beam travels only a finite distance, which is dependent on the proton stopping power of the material through which it passes; proton stopping power is correlated with CT Hounsfield units (HUs), which vary with tissue type. It is important to select beam angles that will likely result in a stable radiologic path length, that is, the same path composition and length from day to day. According to the depth of the target within a field, a spread-out Bragg peak (SOBP), comprising a series of proton energies whose Bragg peaks of energy deposition will fall within the targeted depth, is designed to fully cover the target with a prescribed dose metric, for example, CTV100% covered by $\geq$ D95%. With passive-scattering PT, the beam is shaped perpendicular to its axis, with an aperture and the distal edge or stopping position for the beam modified by a range compensator placed in the beam path, which increases conformity of the dose distribution to the distal edge of the target [30].

Treatment planning should be done on the average 4D CT reconstruction that combines all 10 phases of the 4D CT scan so that the beam range and compensator calculations can be optimized to ensure target coverage for all phases. Additionally, the dose distribution can be calculated on each phase to ensure adequate coverage throughout the respiratory cycle.

**Beam Angle Selection**

En face fields angled at $0^\circ$ to $60^\circ$ generally approximate the axis of respiratory motion and thereby result in minimal changes in the radiologic path length for protons through the respiratory cycles (Figure 3A–3C). When possible, treatment of a given target volume through at least 2 fields using beam angles $> 5^\circ$ apart increases dose homogeneity and robustness (Figure 3D–F) and may minimize skin doses because of decreased hot spots. It is rarely possible to achieve fully nonoverlapping
beams in whole-breast or chest wall targets, but it is typically achievable and critical for cosmetic outcome in partial breast irradiation or tumor bed boosts.

**Expansion of the Target Volume for Uncertainty in Target Location, Shape, and Beam Range**

The principles underlying the expansion of the CTV to a planning target volume (PTV) differ somewhat from those used in photon treatment planning. The need for target volume expansion is related to uncertainty regarding beam range as well as target location and is, therefore, beam specific. Target location (depth and shape) varies with intrafraction and interfraction motion, physiologic changes (eg, seromas), and individual anatomic stability (large or pendulous breasts). Beam-range uncertainties vary with changes in radiologic path length (physical length and tissue composition that may affect proton stopping power), which are related to target depth and shape, intrafraction and interfraction variations in target position, and treatment planning parameters, such as the beam angle and smearing margin. For breast and chest wall targets, because beam angles are selected to approximately coincide with the direction of respiratory motion and because a smearing margin is applied to the range compensator to account for potential variations in radiologic path length, a PTV expansion along the beam axis is not routinely performed. Expected interfraction and intrafraction setup errors perpendicular to the beam axis are accounted for in aperture margin calculations, as discussed below. Therefore, CTV_breast/chest wall equals PTV_breast/chest wall. An additional expansion could be considered if the daily setup is expected to be less reproducible, as in a patient with large or mobile breasts. Because of potential variability in the clavicle and chin positioning, a 5-mm uniform expansion is applied to the AXN and SCN CTVs, which is then edited to exclude the lung plus 3 mm, skin, esophagus, and thyroid, resulting in PTV_nodal. Similar to the chest wall and breast, the IMN CTV is not expanded, so CTV_IMN equals PTV_IMN. Some centers may prefer to use the PTV to account for setup errors, similar to the use of the PTV for conventional radiation therapy.
However, a uniform PTV expansion may unnecessarily increase the target volume along the beam axis, potentially resulting in greater doses to the lung and heart. Therefore, care should be taken when using the PTV to account for setup errors, and a nonuniform PTV margin should be considered to omit larger-than-necessary expansion in the beam path.

If both nodal and chest wall/breast targets are to be treated in a single treatment field, distal and proximal margins of the proton field can be specified to only one target. It is, therefore, necessary to create a combined PTV from the PTV_breast/chest wall, PTV_IMN, and PTV_nodal from which lung and heart incursions are removed by binary subtraction. To further increase dose homogeneity, the contours of the resulting combined PTV, especially in the volumes between the PTV_IMN and PTV_breast/chest wall, are connected and smoothed. Beam range and range compensator calculations are based on that combined PTV. Implementation of compensator smearing in some treatment planning systems (TPSs) may increase beam range, which can be tested by observing TPS-calculated beam ranges versus smearing values. In such cases, no distal or proximal margin should be considered.

Figure 5. Dose-volume histogram goal sheet for depicting the category of OAR parameter and target coverage as per the Table. (A) A postmastectomy radiation therapy plan without reconstruction (free-breathing for proton and electron plans), (B) a breast-conserving radiation therapy plan (free-breathing for proton plan and DIBH for photon plan), and (C) a postmastectomy radiation therapy plan with bilateral expander reconstruction (free-breathing for proton and IMRT plans).
proximal margins are applied to the combined PTV for patients with smaller breasts (the beam range in the chest wall/breast target is < 6.0 g/cm²). For patients with larger breasts, which may present with additional setup and organ motion concerns, an additional distal margin (DM) is applied (DM = [Maximum CTV range in mm] × 2.5% + 1.5 mm), but no additional proximal margin is applied.

Field and Compensator Design

With PT for small- to medium-sized patients, the AXN and SCN PTVs, as well as IMN and breast/chest wall PTVs, may be treated using a single field, if the combined field size does not exceed field size limitations for the machine and if the range requirements for the nodal and breast/chest wall targets are similar. The single field avoids matchlines but allows for only a single modulation over various target depths (Figure 4A). With passive-scattered PT, the width of the SOBP for a given beam must cover all water-equivalent thicknesses of the PTV. If there are significant differences in the SOBP width requirements for different parts of the target within a field, the SOBP may overexpose proximal, nontargeted tissue. For example, a breast may span 7 cm in depth from skin to chest wall, whereas the nodal CTVs may range from 3 to 5 cm. This difference in target depth may lead to a less-conformal high dose proximal to the nodal targets. In such a case, the nodal PTV may be better treated in a separate abutting field, even though the beam angle may be identical. Split fields also allow adjustment of field weighting (dose normalization) separately to improve homogeneity, including decreasing the skin dose. Consequently, in most patients with medium to large breast sizes, separate abutting proton fields with customized apertures and/or range compensators are used to treat the AXN and SCN volumes (Figure 4B).

Aperture Margins

For most breast cases, the beam range is between 4 cm and 15 cm, resulting in a 90% to 50% penumbra of about 5 mm. The internal margin (IM) to account for target intrafraction motion and deformation is 3 mm, and the setup margin (SM) with daily image guidance setup tolerance at our institution is 2 mm. Note that instead of accounting for the IM and SM in the PTV expansions, as is usually the case for photon treatments, they are accommodated in the aperture margin (AM) calculations. The distance to the AM from the PTV is derived from the formula in equation 1 and is thus typically 1 cm:

\[
AM = IM + SM + (90\% \ to \ 50\% \ penumbra)
\] (1)

Compensator Design

Compensators are used with double-scattering PT to shape the distal edge of the dose distribution within a given field. To account for potential variations in setup and intrafraction motion affecting the range within the target, a smearing margin of 6 to 8 mm is used based on equation 2 [31]:

\[
\text{Smearing} = \sqrt{(IM + SM)^2 + [0.03 \times (\text{Distal CTV depth} + \text{Bolus thickness})]^2}
\] (2)

The compensator plan can be edited to decrease the proton range in critical areas, such as the left-anterior descending coronary artery or the brachial plexus, a technique sometimes called distal blocking. In addition, to account for setup and intrafraction motion affecting the borders of the field outside of the target volume, a 1-cm border-smoothing margin is added for all range compensators to calculate the compensator thicknesses between the PTV and the aperture border, when considered together with the smearing values of 6 to 8 mm [30].

Dose Prescription

The treatment plan is normalized such that 95% of the combined PTV receives 95% to 100% of the prescribed dose. Skin dose and plan heterogeneity are considered when selecting the optimal normalization. When multiple treatment fields are used, individual field weights may be adjusted to maximize CTV and PTV coverage and minimize exposure of OARs.

Plan Optimization and Evaluation

Both proton and conventional radiation plans should be designed independently to first achieve target coverage goals and then maximize OAR sparing (Figure 1). If adequate OAR sparing cannot be achieved, then an iterative process occurs wherein either coverage or OAR protection is prioritized. However, this should be done explicitly and recorded clearly to
simplify plan evaluation. Each treatment-planning result for target coverage and protection of OAR can be easily evaluated as ideal, good, acceptable, marginal, or unacceptable according to the predetermined treatment planning goals (Figure 1). If any of the planning goals with conventional radiation are evaluated as marginal or unacceptable, then referral to a proton center should be considered for comparative planning. Skin dose is not accurately measured by treatment-planning systems for either protons or photons. However, despite that limitation, dose to skin (as defined in this article) should remain < 105%. The goal maximum point dose of the plan is ≤ 110%, with ≤ 115% acceptable.

Plan Comparison

The fourth step in the algorithm is to compare the PT plan and the best conventional radiation therapy plan (photons and/or electrons) using objective criteria from Figure 1 (see examples in Figure 5A–C). If the proton plan is worse or shows no improvement in any of the target coverage or OAR-avoidance goals, then conventional radiation is recommended. If important PT plan evaluation metrics are superior to the conventional radiation metrics, PT should be considered.

Special Considerations

Seromas

Seromas must be identified and monitored with weekly or every 2 weeks verification CTs from treatment planning through treatment completion because of potential changes in dose distribution (Supplemental Figure 3A–3E). Although seromas are not a contraindication to PT, adaptive replanning may be required.

Breast Implants

Care must be taken with breast implants to account for differences in density of the implant expansion material (silicone and saline). Not accounting for the actual physical density and proton stopping power of the implant material may result in significant unintended dose to underlying OARs or underdosage of the target volume (Supplemental Figure 3F and 3G). The manufacturer specifications of the implant should be verified, and if the stopping power of that particular implant has not been previously measured at the treating institution, a sample implant should be obtained for stopping-power evaluation to determine whether an override of the apparent CT-based stopping power value is needed in the treatment planning process. During treatment planning, the entire implant is contoured, and its CT number is overridden to match the measured stopping-power value.

Breast Expanders

In patients with breast expanders, a metal port (valve) may cause significant perturbations in the dose distribution. In such cases, photon tangents for the reconstructed breast mound can be matched to proton fields for the nodal targets. It is important to ensure that the metal port is completely contained within the photon field and that matchline management (see section below) ensures minimal-dose inhomogeneity at the field junctions.

PT may be used alone if the material composition and dimensions of the expander port are known so that the beam range effect can be accurately calculated, and plan-robustness analysis demonstrates confidence in the reproducibility of daily plan delivery. The metal composition and dimensions vary among manufacturers and expander models. The saline-filled expander volume, as well as all imaging artifacts of chest tissues, should be overridden with the correct HU values corresponding to their relative stopping-power ratios. The metal, and especially the magnetic alloy, components of the port need to be contoured to the dimensions acquired from the vendor, and the relative stopping-power ratios of the high-Z port materials need to be accurately defined in the TPS. The metal cup of the port is usually a submillimeter in thickness and, therefore, does not require HU overrides. At least 3 en face beams are used to reduce the overall uncertainties generated by the metal in the proton plan. The beam angles are chosen to maximize the distance between the magnet shadow and the chest wall and are separated to maximize the angular distance between the beams. If matched fields are used, the match planes should be ≥ 2 cm from the expander port.

Large and/or Pendulous Breasts

For all intact breasts, verification scans are recommended during weeks 2 and 4 of therapy to ensure adequate range and positioning. Adjustment of parameters, such as range, may be necessary in the setting of breast edema. Replanning of the
boost on the fourth week verification scan can be done in cases of breast edema during the course of therapy. Nonetheless, in pendulous breasts, because of the nonreproducibility in positioning (Supplemental Figure 4), the best solution may be shallow photon tangents matched to en face proton nodal fields, similar to photon tangents matched to a medial IMN electron field and a photon AXN and SCN field (Supplemental Figure 5A–5D). Using protons, rather than electrons, for the SCN-AXN and IMN fields offers several advantages. First, the range of electrons is uniform throughout the field, leading to areas of overshoot and undershoot, but the compensator for a proton field allows variation in range providing full coverage of the IMNs without overshoot into the lung in areas at which the chest wall is thinner. Second, the depth of the IMN target in a thick chest wall (or with a protuberant expander) often exceeds 4 cm; beyond which, adequate electron energies deliver significantly greater doses to the skin than to the target and overshoot into the lung. The range of the proton beam is significantly greater, permitting excellent and homogenous coverage of deeper targets, and there is less skin dose than with high-energy electrons (> 10 MEV). Additionally, because a proton beam has a sharper penumbra compared with an electron beam, the difference in beam angle at the proton-photon junction (typically 5°) is less than that for a photon-electron junction (typically 15°). This reduction in the interbeam angle results in a much smaller “cold triangle” of underdosed tissue that complicates the photon-electron technique.

**Matchlines**

Because of the limitation of snout size or significant target depth variations, matching fields are needed in most cases with nodal irradiation. To minimize the dose-distribution uncertainty inherent to any matchline, >2 matchline changes for each proton-photon and any proton-proton junctions are recommended (Supplemental Figure 6A–6D). The beam angles for each matchline are changed by ≥ 5° to increase plan robustness, and different apertures and compensators are used on alternating days. The matchlines are separated from each other by at least 1 to 1.5 cm. The field edges for matchline A and B are drawn in different colors and documented in the treatment notes to avoid day-to-day confusion. Fields are matched on the skin. One set of matched fields is treated daily, and matchlines are alternated daily. Light fields are verified clinically daily to confirm that matchlines align with both the proton and photon setups.

In a combined proton-photon plan, the photon field is treated first. Limited-angle cone-beam CT is used for setup on the linear accelerator. At a specific point in the respiratory cycle (typically during expiration), lines are drawn on the skin to indicate the field borders. Then, the patient is set up in the proton treatment room using the same immobilization devices and kilovolt orthogonal x-ray imaging. The field borders are reviewed during the same point of the respiratory cycle (typically expiration). If the patient is setup correctly, those lines should match perfectly on the skin. If there is a difference in a few millimeters, the patient can be shifted up to 5 mm to align the light fields clinically on the skin. If > 5-mm shift is required, the setup and isocenters should be verified. A block check before the start of this combined modality is prudent. Isocenters for the proton supraclavicular fields and the photon tangent fields can be placed at the superior aspect of the field, as with a monoisocenter conventional technique. Alternatively, a dual-isocenter technique can be used. In contrast to photon techniques, PT does not require a couch kick. Imaging is performed daily for setup with both the photon and proton treatments.

To date, we have not observed matchline fibrosis or telangiectasia in any patient treated with matched photon-proton or proton-proton fields (Supplemental Figure 7A and 7B).

**Image-Guided Treatment Delivery**

Digital radiography is the standard technology currently used in proton treatment centers. Cone-beam CT systems are beginning to be used in a few proton centers [32, 33]. Batin et al [34] reported that surface imaging, such as AlignRT (Vision RT, Columbia, Maryland), may assist in the daily positioning of patients with breast disease. An orthogonal kilovolt x-ray imaging system is used at our institution for the image-guided delivery of breast PT treatments. This system delivers significantly smaller imaging doses compared with cone-beam CT or a photon electronic portal imaging device guidance. Because soft tissue is not visualized, bony anatomy contours and radio-opaque surgical clips are used for daily patient alignment. Contours of the sternum, humeral head, clavicles, and spine are overlaid on the digitally reconstructed radiographs (DRRs) of setup and portal fields, created in the TPS. The DRRs are created from the average 4D CT as well so that orthogonal x-ray images obtained at different breathing phases can be aligned correctly to the DRR images. Supplemental Figure 8 demonstrates a discrepancy that can be seen with the use of 3-dimensional CT, rather than 4D CT. The 3-dimensional CT captured the patient during a part of the respiratory cycle that was different than that captured by the daily setup films on the first day of treatment, resulting in poor sternal alignment (Supplemental Figure 8A). A 4D verification CT
was obtained, and excellent reproducibility of daily sternal alignment (Supplemental Figure 8B) was achieved using the average sternal position. For patients with expanders, it is recommended that the port location on the daily x-ray images be reviewed to ensure that the applied compensator smearing margins are adequate to accommodate the interfraction location variations of the port.

Discussion
The Early Breast Cancer Trialists' Cooperative Group documented an excess in mortality in patients from cardiac disease, pulmonary embolism, and lung cancer, despite an overall survival advantage associated with radiation therapy [5]. Darby et al [35] demonstrated a linear relationship between cardiac mortality and mean heart dose based on historical data and reconstructed mean heart dose estimates. It is difficult to know the absolute risks, given uncertainties in historical data, but estimates found a 7.4% increase in relative risk for cardiac mortality for each incremental increase in mean heart dose of 1 Gy, with no dose threshold. In our experience [17, 18], PT has almost universally provided better avoidance of the heart and lung in both left-sided and right-sided patients with breast cancer. In addition, when nodal radiation therapy is indicated, there is frequently better target coverage particularly in the IMNs and level II axillary node regions [18]. Figure 1 provides an objective method of comparing proton and conventional radiation therapy options in patients with breast cancer. If PT equipment or treatment planning systems are not available, an institution could evaluate the best conventional radiation treatment plan against the target coverage and OAR protection goals detailed in Figure 1 to determine whether a patient might benefit from referral to a proton center for comparative treatment planning and/or treatment.

There are important differences among patient positioning, management of uncertainties, and treatment planning between conventional radiation therapy and PT, as described above. The skin dose is higher with double-scattered PT compared with photons, and the skin dose cannot be modulated to a lower dose with double-scattered PT as it can with pencil-beam delivery. Although pencil-beam delivery may be beneficial in some circumstances, passive-scattering PT is likely to provide clear benefits over conventional radiation therapy for many patients with breast cancer and will provide additional access to PT for patients.

The OAR protection criteria in the RTOG 1304/NSABP B51 trial are complicated and vary for left-sided and right-sided breast cancers as well as breast-only and regional nodal irradiation. This adjustment in constraints based on tumor laterality and extent of the radiation field is indicative of the compromises made to balance target coverage and OAR exposure. With advanced radiation therapy techniques, it should not usually be necessary to compromise either OAR protection or target coverage.

Conclusion
Proton radiation therapy for breast cancer shows great promise for reduced late effects and increased disease control, but it is technically complex with a multitude of variables that can affect dose distribution and plan robustness. Careful attention to planning parameters is essential to ensure safe and effective radiation therapy, with optimal target coverage and maximization of OAR sparing.

ADDITIONAL INFORMATION AND DECLARATIONS

Conflicts of Interest: The authors have no conflicts to disclose

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