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## Proton Therapy for Breast Cancer: A Consensus Statement from the Particle Therapy Cooperative Group (PTCOG) Breast Cancer Subcommittee

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## Abstract

Radiotherapy plays an important role in the multidisciplinary management of breast cancer. Recent years have seen improvements in breast cancer survival as well as a greater appreciation of potential long-term morbidity associated with the dose and volume of irradiated organs. Proton therapy reduces the dose to non-target structures while optimizing target coverage. However, there remain additional financial costs associated with proton therapy, despite reductions over time, and studies have yet to demonstrate that protons improve upon treatment outcomes achieved with photon radiotherapy. There remains considerable heterogeneity in proton patient selection and techniques, and the rapid technological advances in the field have potential to impact evidence evaluation given the long latency period for breast cancer radiotherapy recurrence and late effects. In this consensus statement we assess the data available to the radiation oncology community of proton therapy for breast cancer, provide expert consensus recommendations on indications and technique, and highlight ongoing trials cost-effectiveness analyses, and key areas for future research.

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## INTRODUCTION

Proton therapy (PT) for breast cancer has seen rapid growth due to improved access with expansion of proton centers across the globe, technical advances, and an increasing recognition of the potential late sequelae of breast radiotherapy in survivors. Proton beams have unique physical properties that enable reductions in dose deposition outside of the clinical target volume (CTV). Although patient-specific factors such as comorbidities and genetic makeup modify risk, the dose and volume of radiotherapy to individual organs are important determinants of normal tissue complication probability<sup>1</sup>. In addition, PT can improve target coverage because many breast cancer photon plans do not deliver the full prescribed dose to the CTV, especially the internal mammary chain, in order to limit heart and lung exposure<sup>2-4</sup>. Although the dosimetric advantages of PT are well-established, long-term clinical outcomes are only recently emerging. Conducting adequately powered randomized clinical trials directly comparing proton and photon therapy presents unique logistical, financial and medical-ethical challenges related to factors such as the rapid advances in proton and photon therapy technology, evidence of a dose-response relationship for cardiopulmonary toxicity from breast cancer radiotherapy, and prolonged latency of late effects<sup>5-10</sup>. The full potential and value of PT for breast cancer has yet to be realized. This evidence-based review from the breast subcommittee of the Particle Therapy Co-operative Group (PTCOG) summarizes the potential applications, published clinical data, optimal techniques and ongoing research initiatives of PT in the management of breast cancer.

## METHODS

The Institute of Medicine's Standard for Developing Trustworthy Clinical Practice Guidelines, which recommend that guideline development is led by a multidisciplinary expert panel with transparency where both conflicts of interest and funding sources are reported, were used as a model<sup>11</sup>. The panel was made up of a diverse international team of physicists and radiation oncologists with expertise in multimodality treatment of breast cancer, including proton therapy. In addition, the panel included one breast cancer survivor treated with photon radiotherapy and a second breast cancer survivor treated with PT, both well informed on both modalities prior to their treatment. All financial relationships and potential conflicts of interest were individually reported. There was no financial support for the development of the guidelines, outside of acknowledgement of protected research time as part of K12 HD065987 training grant (RWM).

The English language scientific articles were identified within a PubMed, MEDLINE, and EMBASE literature search. There were no date restrictions applied. Additional relevant articles were identified through targeted literature searching, reference lists of identified papers or by direct input from the authors. All articles were screened for suitability by the authors. To be included all articles were required to display sufficient detail on methodology, the patient cohorts, and clinical endpoints. Panel recommendations are based on literature evidence, where possible, and clinical experience, where appropriate<sup>11</sup>. Recommendations were refined in order to obtain the highest possible agreement among the experts. The minimum threshold for inclusion was pre-defined as 75% agreement among the authors. The entire panel contributed to the development of the guidelines and recommendations, provided critical review and approved the final manuscript.

## EVIDENCE RATING AND LIMITATIONS

The review is intended to provide guidance to practicing physicians and is not a substitute for professional judgement of individual providers. Level of evidence (LE) supporting recommendations and grade of recommendation was scored according to the Oxford Centre for Evidence-based Medicine (OCEBM) Levels of Evidence Working Group "The Oxford Levels of Evidence 2" (2016 version). A summary of the levels of evidence includes the following: Level 1, systematic review or meta-analysis; Level 2, randomized trial or observational study with dramatic effect; Level 3, non-randomized, controlled cohort or follow-up study; Level 4, case series, case-control or historically controlled study; Level 5, mechanism-based reasoning. A summary of grades of recommendation includes the following: A, consistent level 1 studies; B, consistent level 2 or 3 studies or extrapolations from level 1 studies; C, level 4 studies or extrapolations from level 2 or 3 studies; D, level 5 evidence or troublingly inconsistent or inconclusive studies of any level.

The panel acknowledges that there is no level 1 or level 2 evidence to support proton therapy for pediatric or adult malignancies, including breast cancer. Interpretation of the data must be met with caution, and all recommendations that follow are based on level 3, 4, and 5 evidence. In addition, the pace of technological advances, such as the transition from aperture and compensator-based delivery to pencil-beam scanning techniques, and

increasing clinical experience is leading to rapid changes in PT planning and delivery. Thus, clinical trial outcomes may not reflect current practice.

## RATIONALE: DOSIMETRIC ADVANTAGES TO ORGANS AT RISK

### Cardiac toxicity

**Recommendation:** There is a linear relationship between cardiac dose and major coronary events (MCEs) and no threshold below which there is an absence of risk. Therefore, cardiac sparing techniques should be employed for breast radiotherapy. PT reduces the dose to the heart compared to conventional radiotherapy (LE 3, Grade B).

Mean heart dose has been a principal planning parameter used in breast cancer radiotherapy since a seminal study reported a linear relationship between mean heart dose and MCEs<sup>12</sup>. For each 1 Gy increase in mean heart dose, a 7.4% relative increase in MCEs was observed. This translated to an estimated 0.3–0.6% per Gy absolute increase in MCEs by age 80, with variation mediated by the presence of cardiac risk factors and age at radiotherapy. No threshold was identified below which there was an absence of risk<sup>12</sup>. These findings have been validated by others<sup>13</sup>. The dose to the left ventricle and coronary artery subsegments have also been correlated with major coronary events<sup>13–15</sup>, and correlations between cardiac dose, right ventricular systolic dysfunction and development of heart failure with preserved ejection fraction have been reported<sup>16,17</sup>. Cardiac sparing is of particular importance in patients with baseline cardiac risk factors. Indeed, increasing age, presence of hypertension, diabetes, hypercholesterolemia and smoking history all increase the absolute risk associated with a given radiation dose to the heart<sup>12,13</sup>. Although advances have been made in photon cardiac sparing with techniques such as deep-inspiratory breath hold and intensity modulated radiotherapy (IMRT), the use of cardio-toxic systemic agents including anthracyclines and human epidermal growth factor receptor 2 (HER2) directed therapies may potentiate risk of cardiac exposure<sup>20</sup>.

Additional work is needed to better delineate the relationship between cardiac subsegment dose volume parameters, systemic therapy, and host factors with various cardiac endpoints<sup>21</sup>. In the future, the application of early markers of radiation-associated cardiac damage may enable improved prediction and ultimate mitigation of late cardiac toxicity from breast radiotherapy<sup>22,23</sup>. The available literature supports strategies to limit dose to all segments of the heart in order to reduce late radiation-related cardiac morbidity<sup>14</sup>. PT reduces the dose to the heart compared with 3-dimensional conformal radiotherapy (3DCRT) and intensity modulated radiotherapy (IMRT, Table 1, Figure 1)<sup>5,20,24–32</sup>.

### Radiation pneumonitis

A dose-volume relationship for radiation pneumonitis is established, and similar to radiation-induced coronary artery disease, there is no well-defined threshold under which the risk of toxicity disappears<sup>33</sup>. In a breast cancer systematic review and meta-analysis, predictors of radiation pneumonitis included supraclavicular fossa irradiation, older age (age > 55 years), ipsilateral lung  $V_{20Gy} > 30\%$  and ipsilateral mean lung dose > 15 Gy<sup>34</sup>. Patients with comorbidities such as interstitial lung disease that increase the risk of radiotherapy-

related pulmonary complications or simultaneously receiving systemic agents associated with pneumonitis may especially benefit from pulmonary sparing<sup>35,36</sup>. PT reduces the dose to the lungs in early stage and locally advanced breast cancer compared with 3DCRT and IMRT<sup>24,25,33,37–39</sup>.

Clinical pneumonitis is a rare complication of breast cancer radiotherapy with PT and photon therapy<sup>40,41</sup>. In a prospective PT trial of 69 patients treated to the breast or chest wall and regional lymph nodes with PT, the primary endpoint was incidence of grade 3 radiation pneumonitis or any grade 4 toxicity within 3 months of radiotherapy<sup>41</sup>. There were no grade 3 pneumonitis events. One patient developed grade 2 radiation pneumonitis and was treated successfully with oral steroids<sup>41</sup>. Enhanced linear energy transfer (LET) at the end of the proton range, as described in the section below, could lead to enhanced proton relative biologic effectiveness (RBE) for pneumonitis and should be taken into consideration during treatment planning<sup>42–44</sup>. Though to date, clinical data does not suggest a difference, large prospective studies will be needed to reliably compare pneumonitis rates across modalities.

### Lung cancer

The risk of secondary lung cancer in patients undergoing breast cancer radiotherapy is also associated with dose to the lungs<sup>5,45</sup>. Taylor et al. reported an excess rate ratio for incident lung cancer of 0.11 per Gy mean lung dose<sup>5</sup>. The absolute risk was particularly pronounced in active smokers<sup>5</sup>. Grantzau et al. reported that second primary lung cancer five years or more after breast cancer radiotherapy increased linearly by 8.5% per Gray; the increase in lung cancer risk was 17.5% per Gray for those with smoking histories<sup>45</sup>. Thus, strategies that reduce lung exposure are especially important in current and former smokers. Both low and high dose components of the dose volume histogram for the lungs are reduced with PT<sup>25</sup>, and dose modeling studies have suggested a lower risk of second lung cancer following PT compared with modern photon radiotherapy techniques<sup>5,46</sup>.

### Arm and shoulder function

Arm and shoulder motion impairment can result from breast and axillary surgery and/or radiotherapy, and the combination of surgery and radiotherapy appear to have the greatest functional impact<sup>47–50</sup>. The dose to the humeral head, scapula, and muscles involved in arm and shoulder movement are all reduced with PT<sup>51</sup>. Carefully designed prospective quality of life studies are warranted to test the hypothesis that PT can improve arm and shoulder functional outcomes in patients undergoing axillary and supraclavicular irradiation.

### Contralateral breast cancer

**Recommendation: The mean dose to all quadrants of the contralateral breast should be limited to < 1 Gy, particularly in women < 40 years (LE 4, Grade C).**—Dose to the contralateral breast increases the risk of developing second primary contralateral breast cancer, with risk being inversely related to age at exposure<sup>46,52,53</sup>. For example, in the Women's Environmental, Cancer, and Radiation Epidemiology (WECARE) study, women < 40 with quadrants of breast exposed to > 1.0 Gy mean dose had a 2.5-fold greater risk of contralateral breast cancer than unexposed women<sup>52</sup>.

Minimizing contralateral breast exposure is an important objective of breast radiotherapy planning, but may be especially challenging when administering internal mammary node (IMN) irradiation, treatment to medially located primary tumors, and in women with large contralateral breasts (Figure 1). Beyond dose and young age, breast cancer family history and pathogenic germline alterations in breast cancer susceptibility genes such as *BRCA1*, *BRCA2*, *PALB2*, *CHEK2*, *p53* and *ATM* have also been associated with an increased lifetime risk of contralateral second primary breast cancer, as well as other secondary malignancies<sup>52–56</sup>. The beam arrangements standardly used for proton therapy allows for near complete sparing of the contralateral breast to any dose of radiation. By reducing exposure to the contralateral breast, modelling studies suggest that PT will reduce the lifetime risk of contralateral second primary breast cancer over 3DCRT and IMRT<sup>46,57,58</sup>.

### Other secondary malignancy

**Recommendation: Patients with germline mutations that increase susceptibility to radiation-induced second cancers and are indicated to receive adjuvant radiotherapy should be considered for PT (LE 4, Grade C).**

—Pooled data from individual patients treated in historical trials suggest that breast cancer radiotherapy, as administered using the technology available at that time, was associated with increased risk of soft tissue sarcoma and esophageal cancer<sup>59</sup>. PT reduces soft tissue exposure outside of the CTV, and a modelling study has suggested reduced risk of soft tissue sarcoma following PT for breast cancer compared with 3DCRT and IMRT<sup>46</sup>. In addition, an analysis of patients in the National Cancer Database with a first cancer diagnosis of 9 tumor types between 2004–2015 who received 3DCRT, IMRT, or PT was reported. Among patients with breast cancer who had > 5 years follow-up, PT was associated with a significantly lower risk of second cancer compared with IMRT (adjusted odds ratio 0.62, 95% confidence interval, 0.41–0.95;  $p=0.029$ )<sup>60</sup>. Germline mutations in *p53*, *RB1*, and *NF1*, which result in Li-Fraumeni syndrome, hereditary retinoblastoma, and neurofibromatosis type I, respectively, increase the risk of radiation-induced second cancers<sup>56</sup>. The benefits of normal tissue sparing may be particularly pronounced in these patients when therapeutic radiation is indicated<sup>61</sup>.

Importantly, the dose to the esophagus can be increased with volumetrically planned radiotherapy as a result of more generous target coverage<sup>26,46</sup>. Therefore, careful supraclavicular CTV delineation as described below, and application of strict esophageal constraints are critical to limit the risk of esophageal toxicity and secondary malignancy with modern radiotherapy, including PT<sup>26,46,62</sup>.

## TREATMENT PLANNING CONSIDERATIONS, UNCERTAINTIES AND MITIGATION

### Targeting

**Recommendation: Meticulous, evidence-based CTV delineation is of high importance in PT treatment planning due to steep dose gradients (LE 5, Grade D).**—Precise CTV delineation all-inclusive of sites at risk of harboring microscopic disease is of high importance in PT due to the sharp dose fall off at the PT Bragg

peak<sup>6,63</sup>. For example, although the RTOG breast cancer atlas does not include coverage of the posterolateral supraclavicular fossa (i.e. the posterior triangle), historically delivered conventional anterior-oblique supraclavicular photon therapy fields deliver a considerable exit dose into this region. This exit dose into the posterior triangle is often at a magnitude that is expected to control microscopic disease due to the slow attenuation of photons through tissue<sup>64</sup>. Studies suggest that the posterior triangle is a common site of supraclavicular nodal metastases, with approximately half of supraclavicular nodes located marginal to or outside of the RTOG CTV in the posterior and lateral direction<sup>65–68</sup>. Therefore, more generous target delineation in this area should be considered in patients with indications for regional nodal irradiation (RNI), such as defined in the atlas for the RADCOMP trial (RTOG 3510)<sup>69</sup>. In contrast, paraesophageal and paratracheal nodes are infrequent sites of breast cancer nodal metastases<sup>65–68</sup>. In the absence of clinical nodal involvement, the medial border of the CTV should not extend medial of the internal jugular vein<sup>70</sup>, and an esophageal constraint should be applied during plan optimization in order to limit the risk of esophagitis and secondary esophageal cancer<sup>37,70,26,46,59</sup>. In cases for which gross adenopathy was visible on initial staging work-up, fusion of the pre-treatment PET and/or CT image sets with the CT simulation images can ensure that the high risk nodal areas are encompassed in the CTV. For the chest wall CTV, the posterior border should not extend into the intercostal muscles or ribs in the absence of direct clinical invasion, which enables rapid PT dose fall off anterior to the heart and lungs and reduced dose to the ribs (Figure 2A-C)<sup>71</sup>.

With the evolution of PMRT contouring guidelines, PT may be poised to further limit normal tissue exposure compared with photon delivery techniques. For example, ESTRO has recently revised its consensus guidelines for PMRT target delineation in the setting of immediate breast reconstruction. In this guideline, the chest wall CTV for implants in the retropectoral location is limited to the subcutaneous tissue ventral to the implant and pectoralis major muscle, and excludes the tissues posterior to the implant in the absence of “adverse factors” in patients undergoing PMRT<sup>72</sup>. If the safety of such an approach is ultimately confirmed prospectively, PT would be ideally suited to deliver radiation to these smaller volumes, thereby further reducing exposure to the heart, lungs, and ribs. However, recurrences within and posterior to the pectoralis muscles have been reported, and may be clinically occult<sup>71,73</sup>. Further, this area has been routinely treated in PMRT trials, and is at least partially covered in photon plans, even if not specifically delineated in the CTV. Finally, this technique has not been tested in the setting of pre-pectoral implant reconstruction, an increasingly common reconstruction technique<sup>37,74,75</sup>. Therefore, inclusion of the most posterior extent of the implant and immediately adjacent tissue anterior to the intercostal muscles and ribs in the PT chest wall CTV may be considered based on the currently available data<sup>71,76</sup>.

### LET and RBE heterogeneity

**Recommendation: Preclinical and clinical evidence suggests that the proton RBE for tumor control and toxicity is increased at the end of the proton range. Treating physicians should be mindful of these potential effects during treatment planning (LE: 4, Grade C).**—In clinical practice, a fixed proton RBE (the



dose of photons divided by the physical dose of protons to have the same biologic effect) of 1.1 is routinely employed. However, the RBE may be greater than 1.1 at the Bragg peak and distal falloff where the LET of the proton beam profile is greatest<sup>77</sup>. In typical breast or chest wall with RNI planning, the distal edge of the proton beam is located at the ribs and intercostal space, just distal to the target regions but proximal to the critical structures of the heart and lungs. This higher LET may lead to a greater RBE for normal tissue effects and tumor control than predicted when a constant physical dose to proton RBE conversion is assumed<sup>78</sup>. Indeed, the Massachusetts General Hospital (MGH) group has reported clinical data suggesting an RBE >1.1 for late-phase pulmonary radiographic changes as well as rib fractures<sup>41,42,44</sup>. At the Mayo Clinic, coverage with 90–95% of the physical prescription dose may be accepted in the most posterior few millimeters of the breast, chest wall, and IMN CTVs due to the higher LET and anticipated biologic range extension at those locations. Two to three fields are routinely employed, in order to limit potential biologic hot spots and biologic range extension into the ribs, chest wall, heart and lungs, and a constraint is applied to the brachial plexus with the goal of mitigating the risk of RBE heterogeneity on late brachial plexopathy<sup>43</sup>. In the future, advances in PT treatment planning and delivery such as LET/RBE optimization, variable RBE modelling, and Spot-scanning proton arc therapy (SPArc), may further mitigate the potential normal tissue effects of LET/RBE heterogeneity<sup>79–82</sup>.

### Range uncertainty

As with all PT planning, the potential effect of range uncertainty, usually quantified as a percentage of the proton's incident range, must be considered<sup>83,84</sup>. The required ranges to treat the typical breast CTV are relatively shallow and most of the traversed tissue for breast treatment consists of fatty, muscular or glandular tissues which have lower uncertainties for range calculations<sup>85</sup>. Therefore, the composite distal margins that are applied to account for range uncertainty in order to generate robust PT plans are often on the order of 2 to 3 mm, which enables exquisite sparing of the underlying heart and lungs.

### Adaptive re-planning

**Recommendation: Clinical exam, surface imaging and/or volumetric imaging may identify anatomical changes that impact dosimetry enough to warrant re-planning (LE: 4, Grade C).**—Reliable positioning of tissue is essential to maintain the consistent path length of the proton beam. The en face orientation of the proton beam in combination with the finite range of protons make the dose distribution along the chest wall interface sensitive to change. For example, contraction of the breast or chest wall such as from resolution of a seroma will decrease the proton path length, resulting in increased dose to the lung and heart<sup>86</sup>. In contrast, swelling from treatment can create a layer of under-dosing at the deepest portion of the target along the chest wall or IMN CTV<sup>87</sup>. Surface imaging can identify interfraction anatomical variation and has also been used for intra-fraction tracking<sup>37,88</sup>. In addition, periodic volumetric imaging evaluations with overlaying of the treatment plan may be considered to quantify the effects of anatomical changes during the course of PT<sup>87,88</sup>. Adaptive re-planning may be considered in instances where tissue changes lead to a breakdown in plan robustness<sup>89–92</sup>. Robust treatment planning with simulations of potential interfraction anatomical variation can be used to

minimize the need for replanning<sup>37,93</sup>. Thus, in addition to patient-specific factors, the need for adaptive re-planning may vary with planning parameters employed by the treating institution and the robustness of the original plan. In one study, 10% of PMRT patients with reconstruction underwent replanning to improve CTV coverage and/or homogeneity<sup>37</sup>. However, verification scans were acted upon 1% of the time at that institution for APBI and have since been abandoned in the absence of clinically apparent tissue changes at the time of treatment compared to simulation (RWM, unpublished observations).

### Partial breast planning considerations

Reproducible setup has been achieved for APBI with prone positioning and supine positioning in arms up or down position<sup>39,86,94–96</sup>. Many of the initial planning techniques used for treatment of proton APBI included 3–4 fields using fixed spread out Bragg peak (SOBP), aperture and compensator-based double scattering<sup>94</sup>. Depending on the target position within the breast, the process of avoiding skin overlap with these techniques must be accomplished by using larger hinge angles between treatment fields. These more tangential fields can spare skin dose but treat larger volumes of breast tissue to low doses and demonstrate more sensitivity to alignment errors and respiratory motion<sup>97</sup>. A patient-specific multi-field approach representing compromise between integral dose, skin sparing, and end-of-range uncertainty is desirable<sup>39,97</sup>.

The implementation of PBS for APBI provides the planner with spot by spot intensity control of the proton field. This added degree of freedom can be used to optimize proximal conformity to provide skin sparing, even in the case of overlapping enface fields. In addition, advanced spot optimization methods (Multi Field Optimization, MFO) can be used to increase overall plan robustness to set-up and range uncertainties and further reduce OAR doses when compared to the aperture and compensator methods described above<sup>95</sup>.

### Breast/chest wall and RNI planning considerations

To avoid excessive dosing of surrounding tissues, en face fields are most commonly utilized, which allow for distal sparing of the heart and lung and a beam path in the direction of respiratory motion. In this case, the distal fall-off of the Bragg peak is placed within the ribs, intercostal spaces and IMNs where the full advantage of the sharp distal falloff of the proton beam is achieved. Regional lymphatics, including the axillary and supraclavicular nodes, are also treated with enface fields. For aperture and compensator-based PT, the size of the treatment area generally requires multiple matched fields and match line changes. Traditional methods of verifying match lines on the skin surface clinically are difficult with typical PT delivery systems<sup>98</sup>. The control of spot intensity offered by PBS delivery enables PT delivery without the need for collimator matching. PBS field edges are designed to be insensitive to set-up errors with slow gradient dose fall-off, thus eliminating the need for junction changes which can be particularly advantageous for treatment of large targets, as in bilateral breast cancer (Figure 2). In addition, PBS allows photon-like skin sparing throughout the entire treatment field (Figures 3, 4). In plans where the target dose is optimized to deliver a uniform dose to the entire target region (Single Field, Uniform Dose, SFUD), the maximal magnitude of the skin sparing in the breast/chest wall region is dependent on the modulation across the target, with less surface sparing achievable in

regions where large modulations are required. This presents a situation where the maximum extent of skin sparing will be non-uniformly distributed across the treatment field. By using more than a single field for treatment and not requiring a uniform dose from each individual field (MFO), the combined field spot patterns can be optimized together to achieve a more optimal solution with more uniform skin sparing<sup>37,93</sup>. Given these significant differences for breast cancer PT, attention to the techniques employed (i.e. PBS versus aperture and compensator-based PT treatments) is critical in evaluating and interpreting PT treatment outcomes.

Tissue expanders are commonly placed at the time of mastectomy as part of two-stage immediate breast reconstruction. These expanders contain metallic ports made of high atomic number materials which create considerable artifact on the CT planning images, raising the complexity of accurately predicting the stopping powers through and around the port<sup>99</sup>. Several planning strategies have been implemented to address this challenge including metal artifact reduction algorithms, MFO techniques to treat around the port (Figure 4), and careful characterization of the port and use of Monte Carlo methods to improve accuracy of dose calculation, thus enabling treatment through the port<sup>37,99–102</sup>. The resulting proton plans have superior dosimetric characteristics over photon plans.<sup>99,102</sup>

Deep inspiratory breath hold (DIBH) has been shown to be an effective method to reduce heart dose in photon planning by displacing the heart and coronary arteries away from the treatment beams<sup>103</sup>. DIBH may also facilitate displacement of cardiac structures inferiorly and posteriorly away from the IMN CTV and areas of high LET in some cases of breast PT. However, routine use of DIBH to reduce heart dose in unselected patients does not appear to be beneficial<sup>24,104</sup>. The physical displacement of the heart created by the DIBH process is usually replaced with low density lung tissues. Since breast proton treatment uses en face proton fields, this results in minimal change of the water equivalent path length to the heart, and typically little additional sparing of the heart is achieved in the absence of significant inferior cardiac displacement. With photon tangents, respiratory motion has the effect of oscillating the deep edges of the target regions in and out of the high dose areas. With the en face fields used in proton delivery, the proton path is typically in the direction of the respiratory movement. Although these tissues are moving as part of the respiratory cycle, the proton path length from the skin to the distal edge of the target does not change significantly with respiratory motion<sup>24,105</sup>. Thus, typical respiratory patterns are not a major source of intrafraction uncertainty relative to the uncertainties for beam range and setup which should be accounted for during routine treatment planning process<sup>105</sup>.

## CLINICAL EVIDENCE AND INDICATIONS

### Regional nodal irradiation

**Recommendation: PT is a treatment option for patients with indications for RNI. Patients in whom recognized target coverage and/or organ at risk constraints cannot be achieved with a robust photon plan may be most likely to derive benefit. Clinical trial enrollment should be considered if available (LE: 3, Grade B).**—RNI encompassing axillary, supraclavicular, and IMN basins is routinely indicated in lymph node positive, locally advanced, or medially located breast

cancers<sup>40,63,106–109</sup>. Delivery of RNI poses dosimetric challenges due to the large CTV size and location of the CTV in close proximity to the heart, lungs, and other organs at risk. 3DCRT techniques have several well-recognized limitations for RNI. Traditional 4- or 5-field photon and electron 3DCRT approaches introduce uncertainties at match lines and potential for cold spots at abutting fields<sup>2</sup>. Partially wide tangents and IMRT improve homogeneity but also result in additional compromises, including increased dose to the contralateral breast<sup>57,110</sup>. IMRT has excellent conformality but increases low and intermediate dose spread to tissues outside of the CTV (Figure 1)<sup>46,57,111</sup>. Regardless of technique, the dose to organs at risk can only be reduced so much after which compromises in CTV coverage arise, which can lead to suboptimal disease control<sup>2–4,40,63,109</sup>. PT addresses these limitations. Modern photon techniques such as DIBH and IMRT can typically provide homogeneous target coverage while limiting doses to organs at risk to levels expected to result in low rates of late adverse events. Nevertheless, multiple dosimetric analyses have demonstrated that PT improves CTV coverage, including of the IMNs, while simultaneously decreasing dose to organs at risk and overall integral dose (Table 1).

These promising early PT planning studies spurred a number of prospective clinical studies in patients with indications for RNI (Table 2)<sup>25,37,41,112–114</sup>. Initial reports from clinical trials from the University of Florida and MGH demonstrated favorable early toxicity outcomes, and confirmed that PT was associated with significantly lower heart and lung dose compared with 3DCRT using either photon-electron matched fields or partially wide tangents<sup>25,32,112</sup>.

In a publication from the Procure Proton Therapy Center in New Jersey, 42 patients with breast cancer received adjuvant chest wall and RNI using single field uniform dose optimized PT<sup>113</sup>. Dosimetric parameters to the heart, lungs, contralateral breast, spinal cord, and esophagus were low, consistent with those seen in previous planning studies. With a median follow-up of 35 months, no grade 3 or higher acute toxicities were noted and only 1 (2%) grade 3 late complication, in the form of pneumonitis, developed in a patient who had prior contralateral RNI and a stem cell transplant. Three-year outcomes included 97.2% overall survival and 97.6% local control.

Retrospective outcomes of 91 patients treated with uniform scanning or pencil beam scanning (PBS) PT at Northwestern Medicine Chicago Proton Therapy Center have been described<sup>114</sup>. Grade 2 or higher toxicities were limited, with 5% developing grade 3 esophagitis, rib fracture in 3%, and clinically evident lymphedema in 3%. With a median follow-up of 16 months, twelve patients experienced disease failure, and the crude locoregional control was 96%.

A prospective trial with long-term follow-up of breast cancer patients undergoing RNI was recently published<sup>41</sup>. Between 2011 and 2016, 69 patients were treated with passive scattering PT (prior to 2013) or PBS PT (2013 and later). 93% of patients were treated post-mastectomy<sup>41</sup>. The heart mean, LAD max, and ipsilateral lung V20 Gy were 0.5 Gy, 4.7 Gy (RBE), and 14.5%, respectively<sup>43</sup>. With a median follow-up of 55 months, 5-year locoregional control and overall survival rates were 98.5% and 91%, respectively<sup>41</sup>. Acute

toxicities included grade 2 radiation dermatitis and fatigue in 83% and 35% of patients, respectively, and grade 3 radiation dermatitis in 4%. The acute dermatologic adverse events were comparable to what has recently been reported with conventionally fractionated photon patients<sup>40</sup>. Five patients (7%) experienced grade 1 rib fracture, a higher rate than other PT and photon experiences reported to date. This may be due to close attention due to a perceived potential increased risk with low threshold for imaging, use of a single field, and lack of chest wall constraint to limit end of range LET/RBE effects during the treatment planning process<sup>43</sup>. Research is ongoing that is examining potential differences between photons and protons with respect to chest wall toxicity ([NCT03270072](#)).

The pragmatic randomized phase III proton versus photon breast trial for RNI in nonmetastatic breast cancer patients (RADCOMP, RTOG 3510) is currently accruing ([NCT02603341](#))<sup>69</sup>. The primary objective of this study is to assess the effectiveness of proton versus photon therapy in reducing MCEs. The hypothesis of the trial is that PT will reduce the 10-year rate of MCEs after radiation from 6.3% to 3.5%, a relative reduction of 45%. The predicted 6.3% 10-year event rate in the photon arm was estimated from the Surveillance Epidemiological End Results (SEER) database and is higher than that reported in the study by Darby and colleagues<sup>69</sup>. Using the 7.4% estimated relative increase in MCEs per gray mean heart dose from Darby et al., a 45% relative reduction would require an absolute difference in mean heart dose between the photon and proton arms of > 6 Gy<sup>12</sup>. Modern photon irradiation has seen improvements in cardiac sparing. For example, a mean heart dose > 5 Gy in the RNI arm of the ongoing NRG Oncology/NSABP B-51/RTOG 1304 trial would be a protocol violation. The heart doses observed in the photon arm, along with the age and comorbidities of the participants, may ultimately determine whether the RADCOMP trial is adequately powered to detect a clinically meaningful reduction in MCEs with PT at 10 years<sup>6</sup>. Secondary objectives of the RADCOMP trial include to assess the non-inferiority of proton versus photon therapy in reducing locoregional and any recurrence, to assess health-related quality of life (HRQOL) and adverse events, and to develop predictive models to examine the association of radiation dose distribution to heart and MCEs and HRQOL. The Danish Breast Cancer Group is also conducting a phase III randomized breast cancer trial. In this study eligible patients are those with indications for adjuvant radiotherapy for breast cancer where standard photon planning shows a mean heart dose of 4 Gy or more and/or an ipsilateral lung V20 Gy of 37% or more<sup>117</sup>. The primary endpoint is radiation associated ischemic and valvular heart disease at 10 years after radiotherapy. Much larger studies will be required to test the hypothesis that the improved CTV coverage observed with PT can reduce breast cancer recurrence events over modern photon-based techniques<sup>6,63</sup>. The optimal dose/fractionation for PT in patients undergoing RNI is not known. Hypofractionation is an area of ongoing investigation, including a randomized phase 2 trial investigating conventional versus moderate hypofractionation in patients undergoing PMRT ([NCT02783690](#))<sup>37,115,116</sup>.

## Reconstruction

**Recommendation: PT is a treatment option for patients who have undergone a mastectomy with immediate breast reconstruction and have indications for PMRT. Clinical trial enrollment should be considered if available (LE:**

**3, Grade C).**—Rates of mastectomy, contralateral prophylactic mastectomy (CPM), and immediate breast reconstruction are increasing<sup>118–120</sup>. Reconstructed breast mounds may preclude comprehensive coverage of the postmastectomy CTV with photon techniques<sup>121</sup>. For example, among women who undergo CPM with direct-to-implant or tissue expander reconstruction, the breast prosthesis often retains a medial chest wall position, even when the patient is supine. This medial positioning may result in wide tangent or IMRT fields traversing the contralateral prosthesis, particularly when the IMNs are targeted. An en face electron strip can limit contralateral chest wall dose, but differences in chest wall tissue thickness created by the reconstructed breast may limit chest wall and IMN CTV coverage<sup>31,121</sup>. Typically delivered with one or more en face fields, PT improves CTV coverage and sparing of the contralateral breast mound and other organs at risk in reconstructed women<sup>2,31,99</sup>. Another potential advance of PT among patients undergoing autologous flap reconstruction is improved sparing of the region of the internal mammary vessel anastomosis<sup>122,123</sup>.

PT clinical outcomes have been reported in women following mastectomy with IBR<sup>25,99,112</sup>. Smith et al. described outcomes of 51 reconstructed patients treated with multi-field optimized PBS PT (intensity modulated PT [IMPT]) at the Mayo Clinic<sup>37</sup>. As expected, PT increased the risk of implant-based reconstruction complications compared with non-irradiated contralateral reconstructed breasts, but acute toxicity and reconstruction outcomes compared favorably with previously published photon studies<sup>124</sup>. These results were promising given the exceptional normal tissue sparing and target coverage afforded by PT, with a median mean heart, ipsilateral lung V20 Gy (RBE) and IMN CTV V95% of 0.6 Gy (RBE), 13.9%, and 97.4%, respectively<sup>37</sup>. Interestingly, the rate of reconstruction complications was higher in those receiving a moderately hypofractionated PT regimen (40.05 Gy [RBE] in 15 fractions) compared with conventional fractionation, although this subset analysis was limited by small patient numbers and could be a chance finding. Nevertheless, caution may be warranted when extrapolating novel fractionation regimens to PT based on photon experiences alone due to potential LET/RBE differences between the modalities, and additional investigation into altered dose fractionation regimens is warranted.

The aforementioned phase II trial from MGH included 39 patients who underwent mastectomy with immediate implant-based reconstruction and 14 patients who underwent delayed reconstruction<sup>41</sup>. Among this cohort of 53 patients who attempted reconstruction, 15 (28%) experienced an RT-related complication and just two (4%) experienced reconstructive loss. These outcomes compared favorably with recent reports of patients treated with photon therapy from that institution<sup>125</sup>.

### Partial breast irradiation

**Recommendation: PT is a treatment option for patients with indications for PBI. Clinical trial enrollment should be considered if available (LE: 3, Grade B).**—Accelerated partial breast irradiation (APBI) has emerged as a standard of care for selected patients with favorable early stage breast cancer<sup>126–129</sup>. Favorable treatment outcomes have been achieved with modern short course photon therapy and

brachytherapy<sup>126,128</sup>. Numerous studies have demonstrated that PT reduces non-target breast, heart, and lung exposure compared with photon techniques, and reduces heart and lung exposure and dose inhomogeneity compared to brachytherapy APBI<sup>94,130–134</sup>. Normal tissue sparing may be most pronounced in patients with medially located tumors. Reducing dose to non-target breast tissue with photon therapy has been associated with improved cosmesis following APBI<sup>135</sup>.

Outcomes from several prospective proton APBI studies have been reported (Table 3). Investigators at Loma Linda conducted a phase II trial of 100 patients treated with a multi-field, prone, passive scattered technique to a dose of 40 Gy (RBE) in 10 daily fractions. With a median follow-up of 5 years, the in-breast recurrence free-survival was 97%, and there were no grade 3 or higher acute skin toxicities. Late toxicity consisted of just 7 cases of grade I telangiectasia. Provider assessed cosmesis was good to excellent in over 90% of patients in annual follow-up through 5 years; patient-reported cosmesis was comparably favorable, with no evidence of deterioration over time<sup>39,136</sup>. Comparably favorable three-year outcomes have also been presented from a multi-center phase II Proton Collaborative Group study utilizing the same dose-fractionation regimen<sup>137</sup>.

Long-term results from the first dose cohort of a phase I APBI trial conducted at MGH that included a small number of patients treated with PT are available. APBI was administered with either aperture and compensator-based, double scattering PT (n=19) or photon 3DCRT (n=79)<sup>38</sup>. The prescription was 32 Gy (RBE) in 8 fractions given twice daily. The heart mean and maximum dose, D5%, D10%, and D20% were all significantly less with PT. In addition, PT had a lower ipsilateral lung mean and maximum dose, D5%, D10%, and D20% and greater non target breast sparing. No significant difference in 7-year incidence of local failure or in patient reported cosmetic outcomes between the two arms was found. However, PT APBI was associated with significantly worse provider-reported late skin toxicity and adverse cosmesis, likely related to the use of a single proton field and insufficient time for repair between the large, twice daily fractions<sup>38,138,139</sup>. The authors favored two fields treated daily based on these results.

The National Cancer Center in Korea has reported long term results of a phase 2 trial of 30 patients, aged 40 years with primary tumors 3 cm and pathologically negative nodes, treated with aperture and compensator-based proton APBI<sup>140</sup>. The prescription was 30 Gy (RBE) in 5 daily fractions. A single field was used for the first 15 patients and a two-field technique for the remaining 15 patients to limit entrance skin dose. There have been no recurrences, with a median follow-up of 59 months. Physician-assessed cosmetic outcomes were good or excellent in 69% at 3 years but increased to 89% for patients treated with 2 fields; no late toxicities grade 2 were observed amongst the patients treated with two fields<sup>140</sup>.

Results of an interim analysis of a phase 2 trial from the MD Anderson Cancer Center of 100 patients with node negative early stage breast cancer and DCIS<sup>141</sup>. Patients were treated with a minimum of two passively scattered proton fields to achieve minimal beam overlap on the patient surface and the prescription was 34 Gy in 10 fractions delivered twice daily. With a median follow-up of 24 months there have been no local recurrences or acute or late

toxicities grade 3 or higher. Cosmesis was reported as good or excellent at 12 months by 91% of patients and 94% of physicians<sup>141</sup>.

Early outcomes of 76 patients treated with PBS APBI at the Mayo Clinic have also been reported<sup>95</sup>. PBS is attractive due the capacity to constrain the dose at the skin surface, which may limit the risk of acute and late skin toxicity (Figure 3). In this study, a three fraction regimen of 7.3 Gy (RBE) per fraction was administered with a median of two multi-field optimized PBS beams. The median of the maximum dose to 1 cc of the skin volume (D1cc), defined as the first 3 mm beneath the body surface, was 89% of prescription. The median mean heart dose was 0.0 Gy (RBE) and the median volume of ipsilateral breast receiving 50% or more of the prescribed dose was 28%. With a median follow-up of 12 months there was no grade 2 acute skin toxicity reported, and no grade 2 late adverse events to date<sup>95</sup>. Additional follow-up will be necessary to fully evaluate late effects and long-term cosmetic outcomes with this approach. In summary, given these prospective clinical outcomes demonstrating safety and efficacy of PT with the improved dosimetry over other APBI alternatives, PT is an attractive option for the delivery of APBI.

### Whole breast irradiation

**Recommendation: Photon whole breast irradiation can typically be administered with favorable normal tissue sparing. PT may be considered an option, particularly for patients with complex anatomy resulting in higher doses to organs at risk or necessitating compromises in target coverage. Clinical trial enrollment should be considered if available (LE: 3, Grade C)—**

Modern photon therapy typically delivers radiotherapy to the whole breast with excellent normal tissue sparing<sup>142–145</sup>. Nevertheless, dosimetric studies have demonstrated potential for improvements in target coverage and reductions in dose to the heart and lungs with PT, including complete or near complete cardiac sparing<sup>143,146,147</sup>. The absolute improvement in normal tissue sparing may be most pronounced in patients with complex anatomy such as pectus excavatum or pectus carinatum, medially located tumor beds, and in those unable to perform cardiac sparing maneuvers such as DIBH or prone positioning (Figure 5)<sup>148</sup>. The potential clinical importance of normal tissue sparing may be greater in patients with active cardiopulmonary conditions<sup>12,35</sup>.

Thorpe and colleagues recently reported early outcomes of 82 patients treated with whole breast irradiation with or without RNI, as part of the multi-institutional prospective Proton Collaborative Group (PCG) Registry<sup>149</sup>. Grade 3 adverse events were observed in 7% of patients, dermatitis and/or breast pain, and the authors concluded PT to be well tolerated. Similar to the case of APBI, skin-sparing PBS technology may make PT more attractive for whole breast irradiation<sup>95</sup>.

### Bilateral Breast Cancer

**Recommendation: PT is a treatment option for patients with indications for bilateral breast/chest wall irradiation. The benefit may be most pronounced when bilateral breast/chest wall with comprehensive RNI is indicated. Clinical trial enrollment should be considered if available (LE: 3, Grade C).—**The



incidence of synchronous bilateral breast cancer is 1–3 % of all patients affected by breast cancer<sup>150,151</sup>. Bilateral breast cancer radiotherapy increases the heart and lung dose when compared to unilateral treatment<sup>152</sup> which puts patients at increased risk for cardiac and pulmonary adverse events<sup>5,20</sup>. In addition, uniform target coverage of the bilateral internal mammary chains and medial breast tissue is limited with traditional 3DCRT techniques due to overlap of the tangent fields. PT enables a homogeneous and highly conformal dose distribution with improved normal tissue sparing (Figure 2)<sup>153,154</sup>.

### Reduced Arm Mobility

**Recommendation: If available, PT may be considered a preferred treatment option for breast radiotherapy that must be delivered in the arms down position, particularly when RNI is indicated. Clinical trial enrollment should be considered if available (LE: 3, Grade C).**—Patients with reduced arm mobility may require treatment in the arms down position. Photon tangents, delivered alone or in combination with matched electron fields, must be directed through the arm in such situations to achieve CTV coverage. Breast brachytherapy is an option but is not routinely utilized to treat the regional nodes. IMRT can improve arm sparing, but at the price of elevated heart and lungs doses from concentrated delivery of anteriorly directed fields or arcs to avoid the arm. In contrast, anterior PT fields are routinely administered, and achieve exquisite CTV coverage and normal tissue sparing in an arms down/akimbo position (Figure 2)<sup>93,99</sup>. Therefore, the dosimetric advantages of PT over photon techniques are particularly pronounced when breast radiotherapy must be administered in the arms down position<sup>155</sup>. The technique of arms down PT has been described, and favorable long-term disease control and toxicity outcomes have been reported<sup>37,41,93,99</sup>.

### Reirradiation

**Recommendation: PT is a treatment option for patients with indications for reirradiation. Clinical trial enrollment should be considered if available (LE: 3, Grade C).**—Locoregional recurrence from breast cancer represents a broad spectrum of disease with differing natural history, but has generally been associated with poor prognosis<sup>156</sup>. The role and optimal approach to reirradiation, such as part of salvage treatment of recurrent breast cancer or in the management of second primary breast cancer or primary breast cancer following thoracic radiotherapy, has yet to be defined. Traditionally, options have included photon 3DCRT or IMRT, electrons, and brachytherapy<sup>157–162</sup>. In-field complications of reirradiation such as soft tissue fibrosis cannot be avoided with PT. However, when indicated, reirradiation may be made safer with PT by lowering cumulative doses to sensitive organs such as heart, lung, ribs, brachial plexus, and other soft tissue outside of the target volume or reducing dose heterogeneity from brachytherapy<sup>24,163</sup>.

Thorpe and colleagues have reported outcomes of 50 patients who in a multi-institutional prospective registry underwent PT reirradiation between 2011 and 2016<sup>164</sup>. The median time between RT courses and cumulative dose was 103.8 months and 100.6 Gy (RBE), respectively. With a median follow-up of 13 months from reirradiation, any (acute or late) grade 3 adverse events were observed in 16% of patients, including 4 patients (8%) with late grade 3 toxicities. Grade 3 adverse events were significantly associated with

body mass index, bilateral recurrence, and bilateral reirradiation. One-year locoregional recurrence free and overall survival was 93% and 97%, respectively. These promising outcomes mirror prospective PT series in other disease sites<sup>165–167</sup>. Fattahi et al. reported outcomes of a series of 72 patients who underwent reirradiation between 1999 and 2019 at a single institution, including 52 patients treated with photons and 20 with protons. Any grade 3 adverse events were observed in 13% of patients, including 10% with acute skin toxicity. Two patients (3%) had grade 3 late adverse events, both treated with photon therapy<sup>168</sup>. These proton outcomes are comparable to prior photon reports<sup>169</sup>. Given the favorable dosimetric profile and early outcomes, PT is an attractive option for breast cancer reirradiation and further clinical evaluation is warranted.

## COST EFFECTIVENESS AND MODEL-BASED PATIENT SELECTION

Due to the increased capital investment required to build and operate proton facilities, the cost of PT per fraction is greater than conventional photon radiotherapy. In addition, depending on the geographic location of the patient relative to PT centers, there may be additional unique costs related to travel, lodging, and time away from work. In the absence of phase III data, decision-analysis methodology and cost-effectiveness analyses (CEAs) can leverage known data to provide decision-makers with evidence to improve management. As such, different CEAs have been published examining the cost-effectiveness of PT<sup>170–173</sup>. For example, Mailhot Vega et al. published a contemporary CEA using an American framework informed by cardiac dose-toxicity relationships presented by Darby et al.<sup>9</sup> Guidelines estimating mean heart dose thresholds for photon plans above which PT may be cost-effective comparatively were presented<sup>173</sup>. In the base case, it was assumed that cost of cardiac toxicity management would be exclusive medical management, an assumption that may severely underestimate the true cost of heart disease. Nevertheless, PT favorability mean heart dose thresholds approximating 7–9 Gy (RBE) for women without cardiac risk factors and 4–5 Gy (RBE) for women with at least one cardiac risk factor were calculated. In light of a systematic review of mean heart doses for photon-based regional nodal radiation<sup>20</sup>, the authors noted that PT may be cost-effective for more than 95% of women with 1 cardiac risk factor undergoing RNI for left breast cancer.

As an alternative to randomized controlled clinical trials comparing photons and protons, which the authors note may be impractical in many scenarios given the rapidly evolving technology and prolonged latency of radiation-associated late effects, Langendijk et al. have proposed and implemented a two phase model-based approach for patient selection for PT in the Netherlands<sup>9</sup>. The first phase aims to select patients who may benefit most from PT by integrating comparative planning studies with normal tissue complication probability (NTCP) models, and the second phase involves prospective observational cohort studies using historical comparisons as validation. The implemented model uses the calculated life-time risk for a cardiovascular event according to the publication by Darby et al<sup>12</sup>. The threshold for reimbursement of proton treatment is an absolute reduction of at least 2% in lifetime risk of a cardiovascular event.

Another area of exploration has been the cost favorability of proton APBI. While no CEAs with effectiveness endpoints have been captured, a cost analysis noted comparable cost of

proton APBI versus other APBI techniques<sup>174</sup>. Hypofractionated and ultra-hypofractionated regimens have emerged as new standards in early stage breast cancer patients treated with photon therapy<sup>175–177</sup>. If also proven acceptable for PT, or if the improved normal tissue sparing of PT facilitates further treatment acceleration, the reduction in costs may further improve the cost-acceptability of PT<sup>95,178</sup>.

## CONCLUSION

PT is being investigated as an adjuvant radiotherapy alternative for both early-stage and locally advanced breast cancer. Access to this modality has improved with the construction of PT centers throughout the globe. Long term clinical data will continue to become available in the years ahead, including the results from ongoing randomized trials, and these studies are expected to inform which patients are most likely to benefit from PT. Still, the field of PT for breast cancer remains in its infancy, and rapid technological advances are poised to further improve treatment delivery. These advances and potential variability in techniques across institutions also present challenges for evidence development. Close attention to the PT techniques employed is vital in evaluating available and burgeoning PT outcomes. Additional research is needed to fully explore the distinct physical and biological characteristics of PT<sup>179</sup>, including optimizing dose-fractionation schedules, in order to improve cure rates and optimize quality of life.

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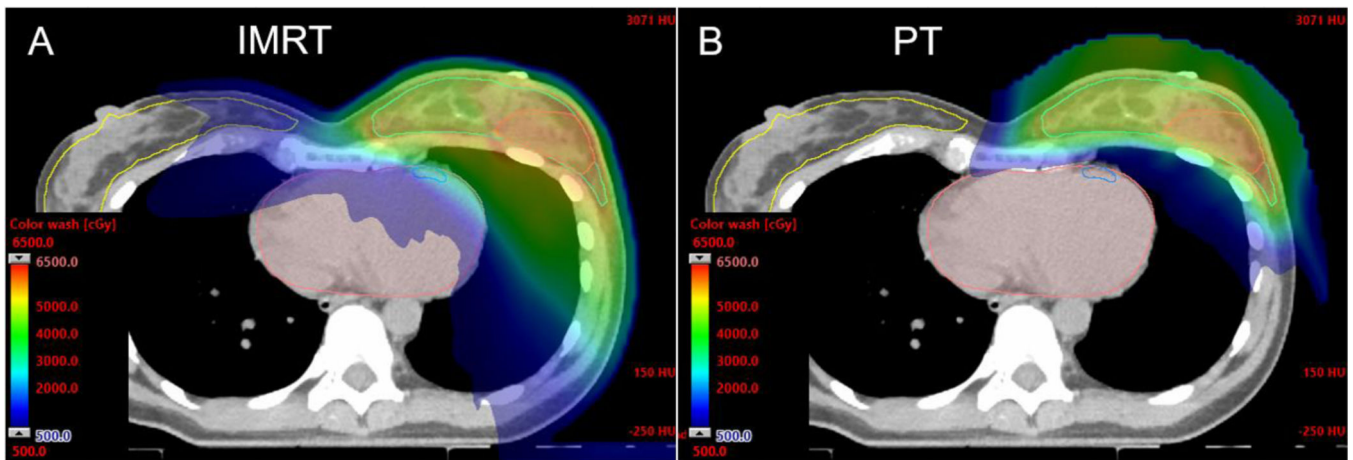


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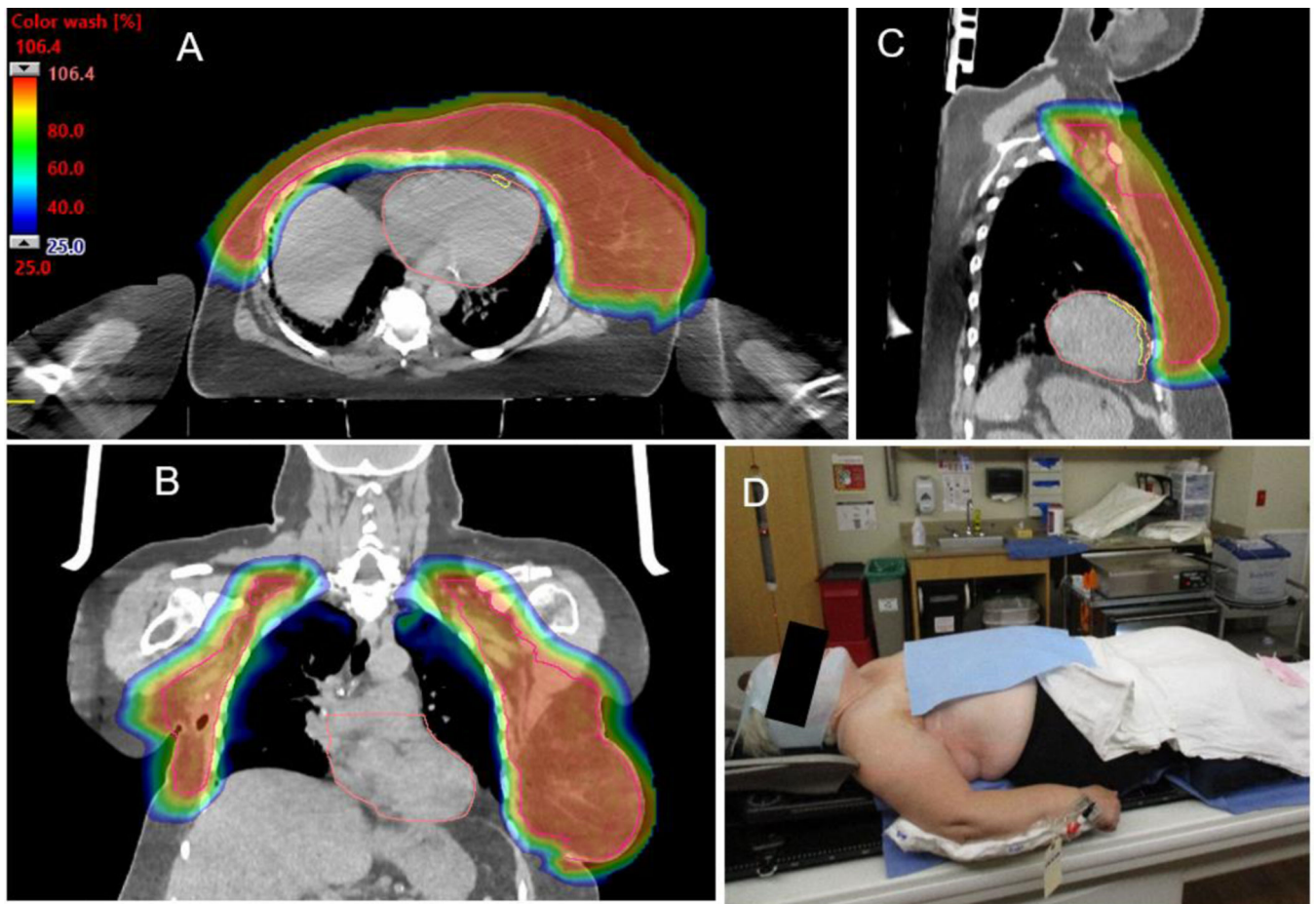
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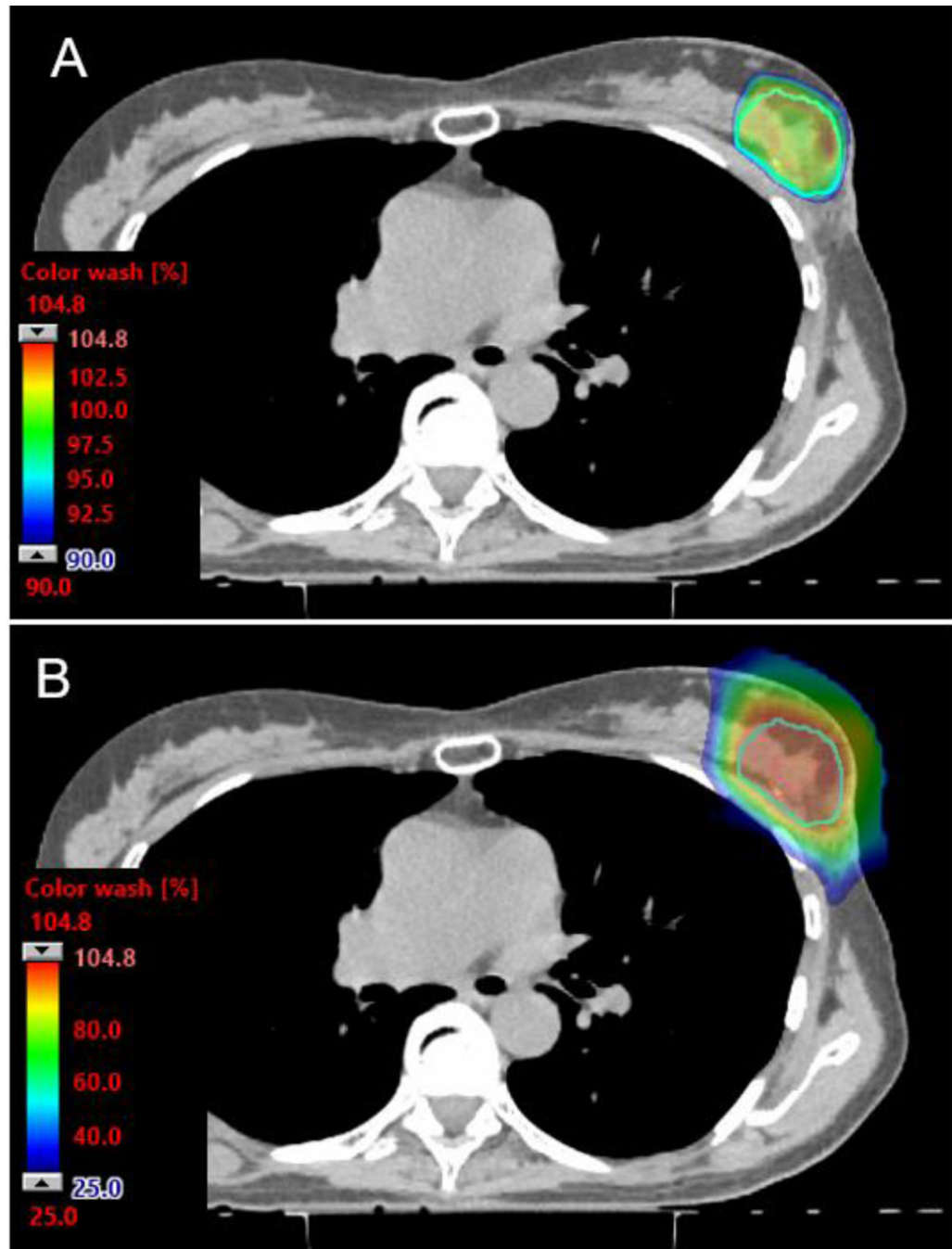
**Figure 1:**

Axial CT dose color wash from an IMRT plan (A) and multi-field optimized PBS PT plan (B) for whole breast and RNI demonstrating improved heart, lung, contralateral breast, and other soft tissue sparing with PT. The lumpectomy cavity CTV is highlighted in orange where a simultaneous integrated boost is administered to 56.26 Gy in 25 fractions, with the breast and nodal volumes (not shown) receiving 50 Gy.



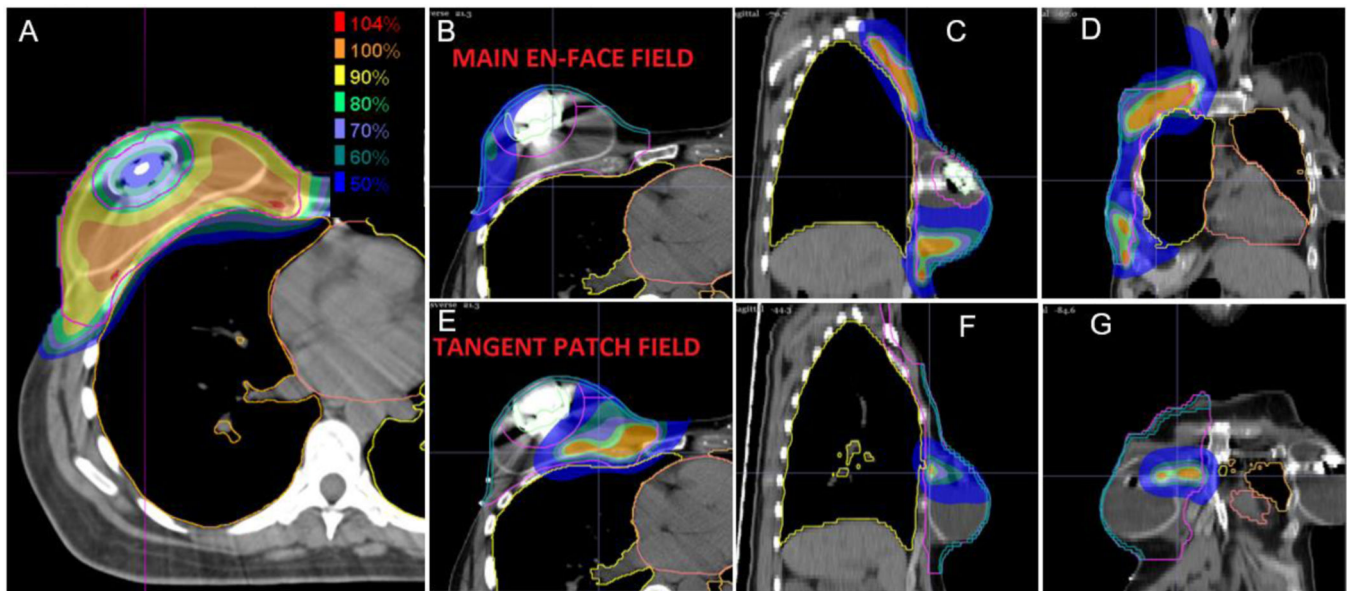
**Figure 2:**

Axial (A), coronal (B), and sagittal (C) 25% color wash images demonstrating comprehensive CTV coverage (pink) with a homogeneous dose (maximum dose 106.4% of prescription) and excellent normal tissue sparing for recurrent breast right breast cancer with ipsilateral and contralateral axillary metastases. (D) Medical comorbidities necessitated an arms down immobilization. The arm is in an akimbo position to attempt to maximize separation between the arm and CTV.



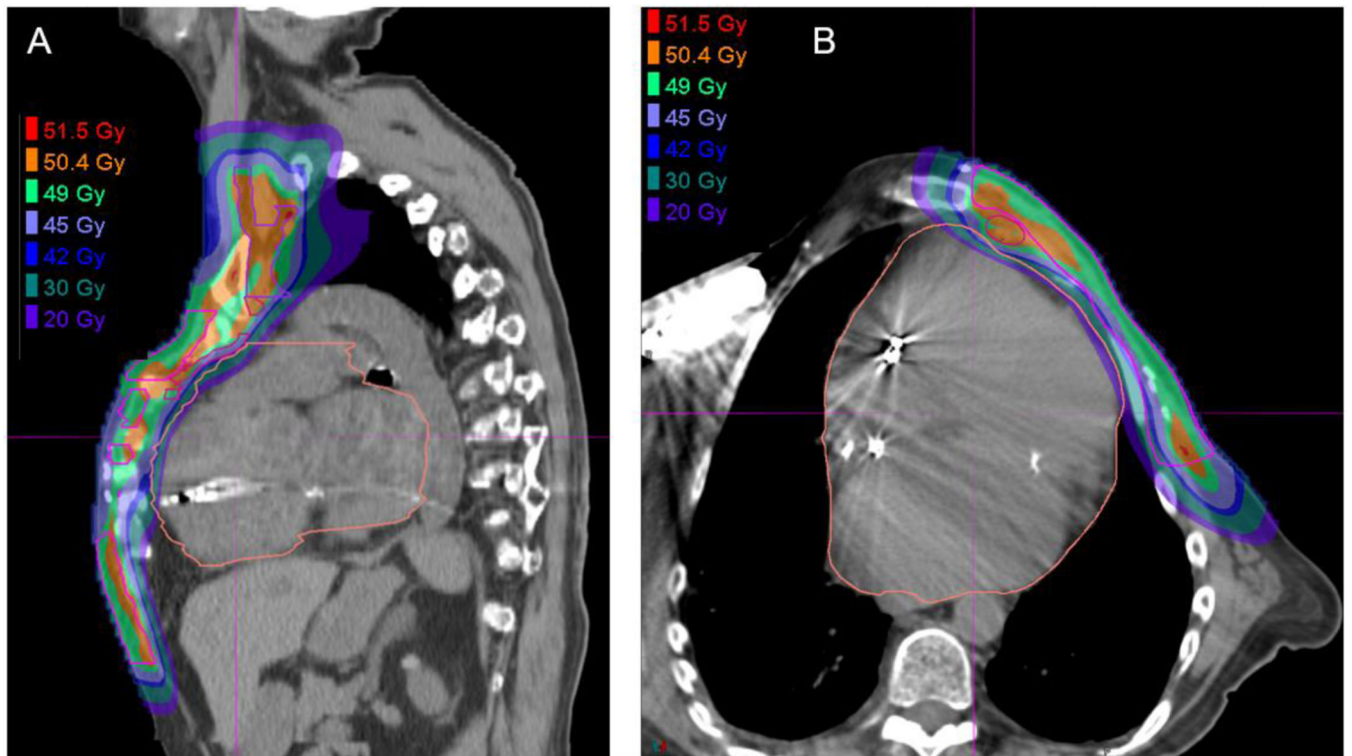
**Figure 3:**

Axial CT dose color wash images from a PBS PT APBI plan. The 90% color wash (A) demonstrates the high level of conformality and skin-sparing properties of the PBS technique. (B) The 25% color wash at the same level demonstrates exquisite normal tissue sparing, including of non-target breast tissue.



**Figure 4:** Axial (A, B, E), sagittal (C, F), and coronal (D, G) 50% color wash images demonstrating a two proton field, multi field optimization (MFO) plan avoiding delivery through the magnetic expander port of the reconstructed breast while achieving comprehensive target coverage. Individual dose deposition profiles from the en face field (B-D) and the more tangential beam angle (D-F) are displayed.





**Figure 5:** Sagittal (A) and axial (B) 20 Gy color wash images of a patient with locally advanced left breast cancer and pectus carinatum, a deformity of the chest characterized by protrusion of the sternum and ribs, demonstrating excellent coverage of the chest wall (pink) and IMN (red) CTV and normal tissue sparing despite the unfavorable anatomy.

**Table 1**

Dosimetric analyses of proton therapy for regional nodal irradiation (RNI).

Author	Technique	Laterality	Target				Heart				Lung				Contralateral Breast			
			Metric (% Rx Dose)	3D	IM	IP	Metric (% Rx Dose)	3D	IM	IP	Metric (% Rx Dose)	3D	IM	IP	Metric (% Rx Dose)	3D	IM	IP
Ares (27)	3D IM IP	Left (n=20) WB (n=10) CW (n=10)	Max	121*	112	109	Mean	19	19	4	L Mean	41	26	14	Max	15-84	42	12
			Mean	102	101	101	V22.5	11	8	8	LV20	39	21	15	Mean	3	10	0
			Min	94	93	98	V5	40	68	12	LV5	76	80	28				
			D95	94	93	98	R Mean	3(CW) 55(WB)	13	1								
			V95	95	2	100	R V20	0	1	1								
Hernandez (28)	VM PP IP	Left (n=8)	V107	17	2	1	RV5	1	63	1								
			Metric (%Rx Dose)	VM	PP	IP	Metric (%Rx Dose)	VM	PP	IP	Metric (%Rx Dose)	VM	PP	IP				
			D95 (Gy)	47.8	48.6 <sup>#</sup>	49.4	V5	88	2.02	3.05	V5	53.2	13.1	19.0	V5	57	0.99	2.1
Jimenez (31)	P/E WT IP	Left CW (n=5) Right CW (n=5)	V107	0.2	0.1	0.003	V22.5	12	0.49	0.56	V20	14.7	8.73	8.72	Mean	7.3	0.17	0.34
			DHI	0.13	0.09	0.58												
			CI	0.72	0.81	0.86												
			Metric (%Rx Dose)	P/E	WT	IP	Metric (%Rx Dose)	P/E	WT	IP	Metric (%Rx Dose)	P/E	WT	IP				
			Mean to PTV	99	100	100	LV5	26.6	19.7	2.8	LV5	53.6	49.2	14.9				
			Max	133	120	115	L V10	15.8	16.2	1.0	L V10	43.6	42.2	9.5				
			D2	124	116	114	L V20 R	7.8	13.6	0.4	LV20	31.9	36.7	4.3				
							V5 R V10	11.5	1.2	0.3	RV5	65.1	44.6	13.5				
							RV20	4.6	0.5	0.1	RV10	52	38.3	8.6				
								1.2	0.3	0.1	RV20	36.4		4.1				
MacDonald	P/E				Metric (%Rx)	P/E	WT	PP	Metric	P/E								
					Left CW (n=11)													

Author	Technique	Laterality	Target	Heart				Lung				Contralateral Breast																																			
				WT	PP	P/E	WT	PP	Dose)	Metric (%Rx Dose)	WT	VM	IP	Metric (Gy)	WT	VM	IP	Metric (Gy)	WT	VM	IP	Metric (Gy)																									
(32)	(32)	WT PP	PP	Dose)	94	99	V5	35.6	20.9	V90 92	4.1	L V5	46.3	33.2	14.9	2.8	L V10	32.2 28.5	21.3	89	91	98	20.9																								
																								V20	12.4	1.6	LV20	21.7	25.3	16.2																	
																															V45 2.2	6.9	0.3														
																																		Metric (Gy)	WT	VM	IP	Metric (Gy)	WT	VM	IP	Metric (Gy)					
																																											Metric (%Rx Dose)	WT	VM	IP	Metric (Gy)
(24)	WT-DIBH VMAT-DIBH IMPT-FB	Left WB (n=10) CW (n=4)	Metric (%Rx Dose)	Metric (Gy)	IP	VM	WT	Metric (Gy)	85	96	100	Mean V17Gy (%) LAD Max	2.5 2 38.3	2.6 1.8 36.2	1.0 1.3 17.4	V17Gy (%) Mean	28 0.8	28 0.7	17 0.2	Mean	1.4	1.5	0.2																								
																								Metric (Gy)	IP	VM	WT	Metric (Gy)																			
																													Metric (Gy)	IP	VM	WT	Metric (Gy)														
																																		Metric (Gy)	IP	VM	WT	Metric (Gy)									
																																							Metric (Gy)	IP	VM	WT	Metric (Gy)				
																																												Metric (Gy)	IP	VM	WT
(29)	3D-DIBH UP-DIBH IP-DIBH	Left WB or CW (n=10)	Metric	Metric (Gy)	IP	UP	3D	Metric	50.1	50.4	50.0	Mean (Gy)	2.1	0.2	0.2	L Mean (Gy)	12.3	7.3	6.9	32.9	33.6	11.3																									
																							Metric (Gy)	IP	UP	3D	Metric																				
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																																											Metric (Gy)	IP	UP	3D	Metric
(30)	3D VM	Left CW (n=10)	Metric	Metric (Gy)	IP	VM	3D	Metric	52.8	51.4	51.2	LAD Mean (Gy)	14.6	3.2	3.3	Integral Dose (Gy)	114.1	67.0	67.0	Metric 3D VM	IP	Metric 3D VM	3.8																								
																								Metric (Gy)	IP	VM	3D	Metric																			
																													Metric (Gy)	IP	VM	3D	Metric														
																																		Metric (Gy)	IP	VM	3D	Metric									
																																							Metric (Gy)	IP	VM	3D	Metric				
																																												Metric (Gy)	IP	VM	3D

Author	Technique	Laterality	Target	Heart	Lung	Contralateral Breast
	IP		PTV V95 (%)	V25 (%) <sup>*</sup>	L V10 (%)	Mean (Gy)
			86.5	91.6	1.2	35.9
				95.6	7.4	40.6
				6.3	53.3	58
			PTV V90(%)	LAD Mean (Gy)	L V5 (%)	41.3
			92.2	20.9	66.4	
			98.4	15.5		
			95.8	7.0		

Abbreviations: VM = volumetric modulated arc therapy; PP = passively scattered proton therapy; WT = 3D conformal wide tangents; IM = intensity modulated radiation therapy; IP = intensity modulated proton therapy; UP = single field uniform proton therapy; WB = whole breast; CW = chest wall; 3D-CRT = 3D conformal radiotherapy; DHI = dose homogeneity index; CI = conformity index; DIBH = deep inspiratory breath hold; Gy = Gray (Relative Biological Effectiveness [RBE]); LAD = left anterior descending artery.

\* When a range was given, the average value is shown.

# Bolded and italicized values have an associated p-value less than 0.05, indicating a statistically significant difference versus the comparative group, when these data were available.

Table 2

Prospective clinical trials of proton therapy for regional nodal irradiation (RNI)

Series	Year/ Modality	N/ Stage	Target/ Dose	Heart	Lung	Other Metric	Median F/u	Toxicity	Disease Control
MGH(4I)	2011– 2016	69	L <n=63 R(n=4)	Metric (Median, Gy)	Metric (Median)	Constrain Used	—	Acute: Grade 2	5-year LRC 983% OS 91%
			B/I (n=2) CW (n=64)	Mean	Mean (Gy)	Heart Mean		Dermatitis 83% Dysphagia 7%	
			WB(n=5)	Min	Min (G)	LAD Max		Fatigue 35%	
PP(n=23)		1(6%)	45–50.4 Gy	Max	Max (Gy)	LAD Mean		Grade 3	
PBS (n=46)		11(58%)	+/-	LAD Mean	V20 (%)	Ipsi Ioin V20		Dermatitis 4%	
		nn (36%)	14.4 Gy Boost	LAD Mb		Esophagus Max		Late: Unplanned Sx –33%	
				LAD Max				Grade 1 Rib fracture 1%	
Mayo (37)	2015– 2017	51	CW+Immmod. Reconst. L (n=35) R (n=14) B/I (n=2)	Metric (Median) Mean (Gy) V25(%)	Metric (Median) Ipd Mean (Gy) IpdV20(%)	—	19 mo	Grade 2 Dermatitis 33% Esophagitis 2% Fatigue 2% Decreased Joint ROM 2% Br. Plexop. 2%	—
		1(12%)	50Gy(n=37)					Grade 2 Dermatitis 33%	
		11(49%)	403Gy(n=14)					Esophagitis 2% Fatigue 2% Decreased Joint ROM 2% Br. Plexop. 2%	
		ID (39%)		LAD Mean (Gy)				Grade 3 Esophagitis 4%	

Series	Year/Modality	N/ Stage	Target / Dose	Heart	Lung	Other Metric	Median F/u	Toxicity	Disease Control	
MSK (113)	2013–2015	42	RCA Mean (Gy)	0.8 (0.4–2.7)				Late: Roconst. Cx - 39%		
			LCW (n=36)	UP	Metric	UP	OAR	35 mo	Acute:	3-year
			R CW (n=6)	(Range)	(Median)	(Range)	Metric	I Range)	Grade 2	LR DFS 96.3%
			◆IMN76%	0.7	V20 (%)	7.1	C/I Breast	7.1	Dermatitis 74%	MFS 84.1%
NWM (114)	2011–2016	—		0.0–6.0				Esophagitis 17%	«5 97.2%	
			Malian 50 Gy +/-Boost	43	V5(%)	34.0	Spinal Cord	0.8	Late:	LC 97.6%
				0–162	V20(%)	16.1	C/I Breast	03	Skin Pain 24%	
				0.1–51.9	Max (Gy)	03	Esophagus	73	Fatigue 2%	
UP (n=72)	T1-2 (n=55)	91	WB (n=27)	Constraint Ised	Constraint Used	Constrakrit	153 mo	Roconst.Cx -27%	OS 93.4%	
			CW (n=66)	V20	V20	Used	Esophagus Max	Grade 2	Pneumonitis: 2%	DF 11%
			L (n=56)	£21%	Ipsi V20	<33%	Esophagus Max	<40Gy	Dermatitis 72%	LC 95.6%
			R (n=33)	£50% (Left-sided)	Ipsi V5	<42%	Ipsi Humeral Head Max	<45 Gy	SkinPain21%	
PBS (n=21)	T3-4 (n=38)	N+ (n=83)		<40% (Right-sided)		Skin PTVVII0	<33%	Grade 3		
			Gy Boo a							
Series	Year / Modality	N / Stage	Target / Dose	Heart	Lung	Other Metric	Median F/u	Toxicity	Disease Control	

Series	Year/Modality	N/Stage	Target / Dose	Heart	Lung	Other Metric	Median F/u	Toxicity	Disease Control
UF (25)	2012–2014	18	WB (n=7) CW (n=1) L (N=9) R (N=9)	Metric (Median; L, R) V5 (%) Mean (Gy) V20 (%)	3D PP 34.0 2.7%# 13.2 0.3	Metric (Median) 3D PP 60.5 35.3 Ipsi V5 (%) Ipsi V20 (%) Ipsi Mean (Gy)	3D OAR Metric 193 Integral Dose (Gy-L) C71 Breast V3(%) 0	Rib Fracture - 3% Lymphedema - 3% PP 20 mo Grade 2 Pneumonitis 6% Grade 3 92.7 Dermatitis 22% Infection 6%	
MGH (112)		12	L CW (n=1) R CW (n=1) 50Gy CW 45–50.4 Gy LN TI+2 (n=9) T3 (n=3) N+ (n=1)	Metric (Mean, L) Mean (Gy) V20 (%) V20 (%) V20 (%) LV Mean (Gy) LV V20 (%) 0.0004 (0.0–0.2)	PP (Range) 0.4 (0.1–1.2) 0.01 (0.0–2.4) 0.1 (0.0–0.4) 0.0004 (0.0–0.2)	Metric (Mean) Mean (Gy) V20 (%) PP (Range) 6 (2.4–10.1) 12.7 (4.4–22.1)	6 mo Acute: Grade > 1 — 0%		

Abbreviations: VM = volumetric modulated arc therapy; PP = passively scattered proton therapy; WT = 3D conformal wide tangents; IM = intensity modulated radiation therapy; PBS = pencil beam scanning proton therapy; UP = single field uniform proton therapy; 3D-CRT = 3D conformal radiotherapy; WB = whole breast; CW = chest wall; IMN = internal mammary nodes; Ax = axilla; HI = homogeneity index; C/I = contralateral; DIB H = deep inspiratory breast hold; Gy = Gray (Relative Biological Effectiveness [RBE]); IQR = interquartile range; L:AD = left anterior descending artery; LV = left ventricle; N = number of patients; mo = months; OS = overall survival; LC = local control; DF = distant failure; MFS = metastasis-free survival; LR DFS = local recurrence disease free survival; Reconstr. Cx = reconstruction complications; Br. Plexop. = brachial plexopathy; ROM = range of motion.

# Bolded and italicized values have an associated p-value less than 0.05, indicating a statistically significant difference versus the comparative group, when these data were available

**Table 3**

Clinical investigations of proton therapy for partial breast irradiation (PBI)

Institution	Technique (N)	Dose	RT Details	MD-Reported Cosmesis	Patient-Reported Cosmesis	Toxicity	Disease Control
MGH (38,96)	PP (n=19)	32 Gy (RBE)/4 Gy x	1–3 fields for PP (1)	7yr Good-excellent	7yr Good-excellent	PPvs. EBorP/E	7yr LF:
	EB or P/E (n=79)	8 fx BID	field treated per fx) 1.5–2.0 cm margin to PTV <5 mm from skin	62% PP 94% EB or P/E	92% PP 96% photon, NSS	Telangiectasias 69% vs. 16% ( $\zeta=0.03$ ) Pigmentation changes 54% vs. 22% ( $\zeta=0.02$ ) Other late skin tox 62% vs. 18% ( $\zeta=0.029$ )	11% PP 4% EBorP/E, NSS
NCC, Korea (140)	PP (n=30)	30 Gy (RBE) / 6 Gy x 5fx QD	1–2 fields PBT	3yr Good-excellent 69% (–100% with 2-fieldplan)		Increased toxicity with single field plan	3yr LF 0% 3yr DF 0%
LLU (39,136)	PP(n=90)	40 Gy (RBE)/4 Gy x 10 fx QD	2–4 fields PP 1.0 cm tumor bed margin to CTV	5yr Good-excellent 90%	5yr Good-excellent 90%	Acute: Gr1-2-RT dermatitis 62% No grade 3 AE Late: Gr 1 - telangiectasia 7% Fat necrosis 1%	5yr IBTR-FS 97% 5yr OS 95%
PC G BRE007 (137)	UP(n=37)	40 Gy (RBE)/4 Gy	>3 fields (>2 treated	3yr Good-excellent	BCTOS Score of 4:	Gr 2 — 7 events	3yr LF 0%
	PP(n=1)	(RBE) x 10fxQD	daily) for PP 1.5 cm margin to CTV	100%	13.2% (nipple appearance, breast shape, scar tissue)	>Gr 3 — none	3yr DF 0%
MDACC (141)	PP (n=100)	34 Gy (RBE)/ 3.4 Gy x 10fx BID	>2 fields (3 or 4 fields used for 80% of patients)	2yr Good-excellent 84%	2yr Good-excellent: 96%	Acute Gr2 - Breast pain (1%), Hyperpigmentation (2%), Pruritus (1%), Dermatitis (12%) Late Gr 2 - Fatigue (5%), Hyperpigmentation (1%), Dermatitis (2%) >Gr 3 — none	2yr LF 0% 2yr OS 100%

Abbreviations: FP = passively scattered proton therapy; EB = photon external beam radiotherapy; P/E = photons with electrons; UP = uniform scanning proton therapy; RT = radiotherapy, fx = fractions; Gy = Gray; RBE = Radiobiological effective dose; NSS=not statistically significant; yr ) year; Gr = grade; LF = local failure; DF=distant failure; IBTR-FS ipsilateral breast tumor recurrence-free survival; OS = overall survival