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Proton Therapy for Breast Cancer

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Clinical Investigations

Proton Therapy for Breast Cancer: A Consensus Statement From the Particle Therapy Cooperative Group Breast Cancer Subcommittee

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Augmenix and Boston Scientific related to lecturing and training of new users of rectal spacers; R.A.A. reports being on the scientific advisory board and receiving honoraria from TAE Life Sciences; and X.D. has a patent related to spot-scanning proton arc therapy, and this patent has been licensed to IBA.

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

Abstract

Radiation therapy plays an important role in the multidisciplinary management of breast cancer. Recent years have seen improvements in breast cancer survival and a greater appreciation of potential long-term morbidity associated with the dose and volume of irradiated organs. Proton therapy reduces the dose to nontarget 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 the treatment outcomes achieved with photon radiation therapy. There remains considerable heterogeneity in proton patient selection and techniques, and the rapid technological advances in the field have the potential to affect evidence evaluation, given the long latency period for breast cancer radiation therapy 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. © 2021 Elsevier Inc. All rights reserved.

Introduction

Proton therapy (PT) for breast cancer has seen rapid growth because of improved access with expansion of proton centers across the globe, technical advances, and an increasing recognition of the potential late sequelae of breast radiation therapy in survivors. Proton beams have unique physical properties that enable reductions in dose deposition outside the clinical target volume (CTV). Although patient-specific factors such as comorbidities and genetic make-up modify risk, the dose and volume of radiation therapy to individual organs are important determinants of normal tissue complication probability.¹ 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, to limit heart and lung exposure.²⁻⁴ 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 radiation therapy, and prolonged latency of late effects.⁵⁻¹⁰ 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 Cooperative Group summarizes the potential applications, published clinical data, optimal techniques, and ongoing research initiatives of PT in the management of breast cancer.

Methods and Materials

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, was used as a model.¹¹ The panel was composed of a diverse international team of

physicists and radiation oncologists with expertise in multimodality treatment of breast cancer, including PT. In addition, the panel included one breast cancer survivor who underwent photon radiation therapy and a second breast cancer survivor treated with PT, both well informed on both modalities before their treatment. All financial relationships and potential conflicts of interest were reported individually. There was no financial support for the development of the guidelines, outside the acknowledgment of protected research time as part of K12 HD065987 training grant (R.W.M.).

The English-language scientific articles were identified within a search of PubMed, MEDLINE, and EMBASE. There were no date restrictions applied. Additional relevant articles were identified through targeted literature searching, reference lists of identified articles, or by direct input from the authors. All articles were screened for suitability by the authors. 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.¹¹ Recommendations were refined to obtain the highest possible agreement among the experts. The minimum threshold for inclusion was predefined 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 judgment of individual providers. Level of evidence (LE) supporting recommendations and grade of recommendation was scored according to the Oxford Center for Evidence-Based Medicine 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, nonrandomized,

controlled cohort or follow-up study; level 4, case series, case-control or historically controlled study; and 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; and 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 PT 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 might 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 used for breast radiation therapy. PT reduces the dose to the heart compared with conventional radiation therapy (LE 3, grade B).

Mean heart dose has been a principal planning parameter used in breast cancer radiation therapy since a seminal study reported a linear relationship between mean heart dose and MCEs.¹² 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% to 0.6% per 1-Gy absolute increase in MCEs by age 80, with variation mediated by the presence of cardiac risk factors and age at radiation therapy. No threshold was identified below which there was an absence of risk.¹² These findings have been validated by others.¹³ The dose to the left ventricle and coronary artery subsegments has also been correlated with major coronary events,¹³⁻¹⁵ and correlations among cardiac dose, right ventricular systolic dysfunction, and development of heart failure with preserved ejection fraction have been reported.^{16,17} 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.^{12,13} Although advances have been made in photon cardiac sparing with techniques, such as deep-inspiratory breath hold and intensity modulated radiation therapy (IMRT), the use of cardiotoxic systemic agents including anthracyclines and human epidermal growth factor receptor

2 (HER2)—directed therapies could potentiate the risk of cardiac exposure.¹⁸

Additional work is needed to better delineate the relationships among cardiac subsegment dose volume parameters, systemic therapy, and host factors with various cardiac endpoints.¹⁹ In the future, the application of early markers of radiation-associated cardiac damage might enable improved prediction and ultimate mitigation of late cardiac toxicity from breast radiotherapy.^{20,21} The available literature supports strategies to limit dose to all segments of the heart to reduce late radiation-related cardiac morbidity.¹⁴ PT reduces the dose to the heart compared with 3-dimensional conformal radiation therapy (3DCRT) and IMRT (Table 1, Fig. 1).^{5,18,22-30}

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.³¹ In a breast cancer systematic review and meta-analysis, predictors of radiation pneumonitis included supraclavicular fossa irradiation, older age (>55 years), ipsilateral lung $V_{20\text{Gy}} > 30\%$, and ipsilateral mean lung dose > 15 Gy.³² Patients with comorbidities, such as interstitial lung disease, that increase the risk of radiation therapy–related pulmonary complications or who are simultaneously receiving systemic agents associated with pneumonitis might especially benefit from pulmonary sparing.^{33,34} PT reduces the dose to the lungs in early-stage and locally advanced breast cancer compared with 3DCRT and IMRT.^{22,23,31,35-37}

Clinical pneumonitis is a rare complication of breast cancer radiation therapy with PT and photon therapy.^{38,39} In a prospective PT trial of 69 patients who underwent treatment 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.³⁹ There were no grade ≥ 3 pneumonitis events. One patient developed grade 2 radiation pneumonitis and underwent successful treatment with oral steroids.³⁹ Enhanced linear energy transfer (LET) at the end of the proton range, as described in the following section, could lead to enhanced proton relative biologic effectiveness (RBE) for pneumonitis and should be taken into consideration during treatment planning.⁴⁰⁻⁴² Although clinical data do not suggest a difference to date, large prospective studies will be needed for a reliable comparison of pneumonitis rates across modalities.

Lung cancer

The risk of secondary lung cancer in patients undergoing breast cancer radiation therapy is also associated with dose to the lungs.^{5,43} Taylor et al⁵ reported an excess rate ratio for incident lung cancer of 0.11 per Gray mean lung dose.⁵

Table 1 Dosimetric analyses of proton therapy for regional nodal irradiation (RNI).

Author	Technique	Laterality	Target	Heart			Lung			Contralateral Breast				
Ares (27)	3D	Left (n=20)	Metric (% Rx Dose)	3D	IM	IP	Metric (% Rx Dose)	3D	IM	IP	Metric (% Rx Dose)	3D	IM	IP
	IM	WB (n=10)	Max	121*	112	109	Mean	19	19	4	L Mean	41	26	14
	IP	CW (n=10)	Mean	102	101	101	V22.5	11	8	8	L V20	39	21	15
			Min	94	93	98	V5	40	68	12	L V5	76	80	28
			D95	94	93	98					R Mean	3 (CW)	13	1
Hernandez (28)	VM PP IP	Left (n=8)	V95	95	2	100					R V20	55 (WB)		
			V107	17	2	1					R V5	0	1	1
			Metric (%Rx Dose)	VM	PP	IP	Metric (%Rx Dose) <td>VM</td> <td>PP</td> <td>IP</td> <td>Metric (%Rx Dose)<td>VM</td><td>PP</td><td>IP</td></td>	VM	PP	IP	Metric (%Rx Dose) <td>VM</td> <td>PP</td> <td>IP</td>	VM	PP	IP
			D95 (Gy)	47.8	48.6 [#]	49.4	V5	88	2.02	3.05	V5	53.2	13.1	19.0
			V107	0.2	0.1	0.003	V22.5	12	0.49	0.56	V20	14.7	8.73	8.72
Jimenez (31)	P/E WT IP	Left CW (n=5) Right CW (n=5)	DHI	0.13	0.09	0.58								
			CI	0.72	0.81	0.86								
			Metric (%Rx Dose)	P/E	WT	IP	Metric (%Rx Dose) <td>P/E</td> <td>WT</td> <td>IP</td> <td>Metric (%Rx Dose)<td>P/E</td><td>WT</td><td>IP</td></td>	P/E	WT	IP	Metric (%Rx Dose) <td>P/E</td> <td>WT</td> <td>IP</td>	P/E	WT	IP
			Mean to PTV	99	100	100	L V5	26.6	19.7	2.8	L V5	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
MacDonald (32)	P/E WT PP	Left CW (n=11)	D2	124	116	114	L V20	7.8	13.6	0.4	L V20	31.9	36.7	4.3
							R V5	11.5	1.2	0.3	R V5	65.1	53.2	13.5
							R V10	4.6	0.5	0.1	R V10	52	44.6	8.6
							R V20	1.2	0.3	0.1	R V20	36.4	38.3	4.1
							Metric (%Rx Dose) <td>P/E</td> <td>WT</td> <td>PP</td> <td>Metric (%Rx Dose)<td>P/E</td><td>WT</td><td>PP</td></td>	P/E	WT	PP	Metric (%Rx Dose) <td>P/E</td> <td>WT</td> <td>PP</td>	P/E	WT	PP
Ranger (24)	WT-DIBH VMAT-DIBH IMPT-FB	Left WB (n=10) CW (n=4)	Metric (%Rx Dose)	PP			Metric (%Rx Dose) <td>PP</td> <td></td> <td></td> <td>Metric (%Rx Dose)<td>PP</td><td></td><td></td></td>	PP			Metric (%Rx Dose) <td>PP</td> <td></td> <td></td>	PP		
			PTV	85	96	100	Mean	2.5	2.6	1.0	V17Gy (%)	28	28	17
							V17Gy (%)	2	1.8	1.3	Mean	0.8	0.7	0.2
							LAD Max	38.3	36.2	17.4				

(Continued)

(Continued)

Table 1 (Continued)

Author	Technique	Laterality	Target	Heart			Lung			Contralateral Breast				
Fleijmer (29)	3D-DIBH	Left WB or CW (n=10)	Metric	3D	UP	IP	Metric	3D	UP	IP	3D	UP	IP	
	UP-DIBH		PTV Mean (Gy)	50.1	50.0	50.0	Mean (Gy)	2.1	0.2	0.2	L Mean (Gy)	12.3	7.3	6.9
	IP-DIBH		PTV V95 (%)	93.9	97.1	99.0	D2% (Gy)	16.7	3.2	3.2	L D2%	46.9	32.9	33.6
			PTV V105 (%)	5.0	0.1	0.1	V20 (%)	1.6	0	0.1	L V20 (%)	23.3	13.1	11.3
			PTV D98 (%)	46.7	47.0	48.2	V5 (%)	4.9	1.3	1.3	L V10 (%)	30.1	28.8	26.8
			PTV D2% (Gy)	52.8	51.4	51.2	LAD Mean (Gy)	14.6	3.2	3.3	Integral Dose (Gy)	114.1	67.0	67.0
			HI	12.3	8.8	6.0	LAD D2% (Gy)	29.9	10.2	10.3				
Fagundes (30)	3D	Left CW (n=10)	Metric	3D	VM	IP	Metric	3D	VM	IP	Metric	3D	VM	IP
	VM		PTV V100 (%)	69.2	85.8	81.9	Mean (Gy)	6.8	8.2	1.2	L V20 (%)	40.4	27.3	28.4
	IP		PTV V95 (%)	86.5	95.6	91.6	V25 (%)	6.3	7.4	1.2	L V10 (%)	53.3	40.6	35.9
					PTV V90 (%)	92.2	98.4	95.8	LAD Mean (Gy)	20.9	15.5	7.0	L V5 (%)	66.4

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 breast 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.

Fig. 1. Axial computed tomography dose color wash from an IMRT plan (A) and multifield optimized pencil-beam scanning 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. *Abbreviations:* IMRT = intensity-modulated radiation therapy; PT = proton therapy.

The absolute risk was particularly pronounced in active smokers.⁵ Grantzau et al⁴³ reported that second primary lung cancer 5 years or more after breast cancer radiation therapy increased linearly by 8.5% per Gray; the increase in lung cancer risk was 17.5% per Gray for those with smoking histories.⁴³ Thus, strategies that reduce lung exposure are especially important in current and former smokers. The low- and high-dose components of the dose volume histogram for the lungs are reduced with PT,²³ and dose-modeling studies have suggested a lower risk of second lung cancer after PT compared with modern photon radiation therapy techniques.^{5,44}

Arm and shoulder function

Arm and shoulder motion impairment can result from breast and axillary surgery or radiation therapy, and the combination of surgery and radiation therapy appear to have the greatest functional effect.^{45–48} The dose to the humeral head, scapula, and muscles involved in arm and shoulder movement are all reduced with PT.⁴⁹ 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 the risk being inversely related to age at exposure.^{44,50,51} For example, in the Women's Environmental, Cancer, and Radiation Epidemiology study, women <40 years old 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 did.⁵⁰

Minimizing contralateral breast exposure is an important objective of breast radiation therapy planning, but it can be especially challenging when administering internal mammary node (IMN) irradiation, during treatment to medially located primary tumors, and in women with large contralateral breasts (Fig. 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 and other secondary malignancies.^{50–54} 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, modeling studies suggest that PT will reduce the lifetime risk of contralateral second primary breast cancer over 3DCRT and IMRT.^{44,55,56}

Other secondary malignancy

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

Pooled data from individual patients treated in historical trials suggest that breast cancer radiation therapy, as administered using the technology available at that time, was associated with increased risk of soft tissue sarcoma and esophageal cancer.⁵⁷ PT reduces soft tissue exposure outside the CTV, and a modeling study has suggested a reduced risk of soft tissue sarcoma after PT for breast cancer compared with 3DCRT and IMRT.⁴⁴ In addition, an analysis of patients in the National Cancer Database with a first cancer diagnosis of 9 tumor types during 2004 to 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* = .029).⁵⁸ 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.⁵⁴ The benefits of normal tissue sparing might be particularly pronounced in these patients when therapeutic radiation is indicated.⁵⁹

Importantly, the dose to the esophagus can be increased with volumetrically planned radiation therapy because of more generous target coverage.^{24,44} Therefore, careful supraclavicular CTV delineation, as described in the following section, and the application of strict esophageal constraints are critical for limiting the risk of esophageal toxicity and secondary malignancy with modern radiation therapy, including PT.^{24,44,60}

Treatment Planning Considerations: Uncertainties and Mitigation

Targeting

Recommendation: Meticulous, evidence-based CTV delineation is of high importance in PT treatment planning because of 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 because of the sharp dose fall-off at the PT Bragg peak.^{6,61} For example, although the RTOG breast cancer atlas does not include coverage of the posterolateral supraclavicular fossa (ie, 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 because of the slow attenuation of photons through tissue.⁶² 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 the RTOG CTV in the posterior and lateral directions.^{63–66} Therefore, more generous target delineation in this area should be considered in patients with indications for regional nodal irradiation (RNI), as defined in the atlas for the RADCOMP trial (RTOG 3510).⁶⁷ In contrast, paraesophageal and paratracheal nodes are infrequent sites of breast cancer nodal metastases.^{63–66} In the absence of clinical nodal involvement, the medial border of the CTV should not extend medial of the internal jugular vein,⁶⁸ and an esophageal constraint should be applied during plan optimization to limit the risk of esophagitis and secondary esophageal cancer.^{24,35,44,57,68} In cases for which gross adenopathy was visible on initial staging workup, fusion of the pretreatment positron emission tomography or computed tomography (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 (Fig. 2A-2C).⁶⁹

With the evolution of post-mastectomy radiation therapy (PMRT) contouring guidelines, PT could be poised to

Fig. 2. (A) Axial, (B) coronal, (C) and sagittal 25% color-wash images demonstrating comprehensive clinical target volume 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 clinical target volume.

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 it excludes the tissues posterior to the implant in the absence of “adverse factors” in patients undergoing PMRT.⁷⁰ 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 they might be clinically occult.^{69,71} Furthermore, this area has been treated routinely in PMRT trials, and it 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 prepectoral implant reconstruction, an increasingly common reconstruction technique.^{35,72,73} 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 should be considered on the basis of currently available data.^{69,74}

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 used routinely; however, the RBE could be greater than 1.1 at the Bragg peak and distal falloff where the LET of the proton beam profile is greatest.⁷⁵ 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 can 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.⁷⁶ Indeed, the Massachusetts General Hospital (MGH) group has reported clinical data suggesting an RBE > 1.1 for late-phase pulmonary radiographic changes and rib fractures.^{39,40,42} At the Mayo Clinic, coverage with 90% to 95% of the physical prescription dose can be accepted in the most posterior few millimeters of the breast, chest wall, and IMN CTVs because of the higher LET and anticipated biologic range extension at those locations. Two to 3 fields are usually used, to limit potential biologic hot spots and biologic range extension into the ribs, chest wall, heart, and lungs. In addition, a constraint is applied to the brachial

plexus with the goal of mitigating the risk of RBE heterogeneity on late brachial plexopathy.⁴¹ In the future, advances in PT treatment planning and delivery such as LET/RBE optimization, variable RBE modeling, and Spot-scanning proton arc therapy, could further mitigate the potential normal tissue effects of LET/RBE heterogeneity.^{77–80}

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.^{81,82} 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.⁸³ Therefore, the composite distal margins that are applied to account for range uncertainty 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 replanning

Recommendation: Clinical examination, surface imaging, and volumetric imaging can identify anatomic changes that affect dosimetry enough to warrant replanning (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 makes the dose distribution along the chest wall interface sensitive to change. For example, contraction of the breast or chest wall (eg, from resolution of a seroma) will decrease the proton path length, resulting in increased dose to the lung and heart.⁸⁴ In contrast, swelling from treatment can create a layer of underdosing at the deepest portion of the target along the chest wall or IMN CTV.⁸⁵ Surface imaging can identify interfraction anatomic variation, and it has been used for intrafraction tracking.^{35,86} In addition, periodic volumetric imaging evaluations with overlaying of the treatment plan can be considered to quantify the effects of anatomic changes during the course of PT.^{85,86} Adaptive replanning can be considered in instances where tissue changes lead to a breakdown in plan robustness.^{87–90} Robust treatment planning with simulations of potential interfraction anatomic variation can be used to minimize the need for replanning.^{35,91} Thus, in addition to patient-specific factors, the need for adaptive replanning can vary with planning parameters used by the treating institution and the robustness of the original plan. In one study, 10% of patients who underwent PMRT with reconstruction underwent replanning to improve CTV coverage or homogeneity, or both.³⁵ However, verification scans were acted upon ≤1% of the time at that institution for APBI, and they have since been abandoned in the absence of clinically apparent tissue changes at the time of treatment

compared with simulation (R.W.M., 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.^{37,84,92–94} Many of the initial planning techniques used for treatment of proton APBI included 3 to 4 fields using fixed spread-out Bragg peak (SOBP), aperture, and compensator-based double scattering.⁹² Depending on the target position within the breast, the process of avoiding skin overlap with these techniques must be accomplished 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 they demonstrate greater sensitivity to alignment errors and respiratory motion.⁹⁵ A patient-specific multifield approach representing compromise between integral dose, skin sparing, and end-of-range uncertainty is desirable.^{37,95}

The implementation of pencil-beam scanning (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 conformality to provide skin sparing, even in the case of overlapping enface fields. In addition, advanced spot optimization methods (eg, multifield optimization [MFO]) can be used to increase overall plan robustness to setup and range uncertainties and further to reduce OAR dose compared with the aperture and compensator methods described previously.⁹³

Breast and chest wall and RNI planning considerations

To avoid excessive dosing of surrounding tissues, en face fields are most commonly used; they allow for distal sparing of the heart and lung and a beam path in the direction of respiratory motion. In this case, the distal falloff 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 en face fields. For aperture- and compensator-based PT, the size of the treatment area generally requires multiple matched fields and matched line changes. Traditional methods of verifying match lines on the skin surface clinically are difficult with typical PT delivery systems.⁹⁶ 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 setup errors with slow gradient dose falloff, thus eliminating the need for junction changes, which can be particularly advantageous for treatment of large targets, as in bilateral breast cancer (Fig. 2). In addition, PBS allows photon-like skin sparing throughout the entire treatment field (Figs. 3 and 4).

Fig. 3. Axial computed tomography dose color-wash images from a pencil-beam scanning (PBS) proton therapy acceleration partial breast irradiation plan. (A) The 90% color wash 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 nontarget breast tissue.

In plans where the target dose is optimized to deliver a uniform dose to the entire target region (eg, single-field uniform dose), the maximal magnitude of the skin sparing in the breast and 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 in which the maximum extent of skin sparing will be nonuniformly distributed across the treatment field. By using more than a single field for treatment and not requiring a uniform dose from each individual field (ie, MFO), the combined field spot patterns can be optimized together to achieve a more optimal solution with more uniform skin sparing.^{35,91} Given these significant differences for breast cancer PT, attention to the techniques used (ie, 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 2-stage immediate breast reconstruction. These expanders contain metallic ports made of high-atomic-number materials that create considerable artifact on the CT planning images, raising the complexity of

Fig. 4. (A, B, E) Axial, (C, F) sagittal, (D, G) and coronal 50% color-wash images demonstrating a 2-proton field, multifield optimization 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.

accurately predicting the stopping powers through and around the port.⁹⁷ Several planning strategies have been implemented to address this challenge, including metal artifact reduction algorithms, MFO techniques to treat around the port (Fig. 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.^{35,97–100} The resulting proton plans have superior dosimetric characteristics over photon plans.^{97,100}

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.¹⁰¹ DIBH can 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.^{22,102} The physical displacement of the heart created by the DIBH process is usually replaced with low-density lung tissues. Because breast proton treatment uses en face proton fields, it 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.^{22,103} 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.¹⁰³

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 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.^{38,61,104–107} Delivery of RNI poses dosimetric challenges because of 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 the potential for cold spots at abutting fields.² Partially wide tangents and IMRT improve homogeneity but also result in additional compromises, including increased dose to the contralateral breast.^{55,108} IMRT has excellent conformality but increases low and intermediate dose spread to tissues outside the CTV (Fig. 1).^{44,55,109} Regardless of technique, the dose to organs at risk can be reduced only so much, after which compromises in CTV coverage arise and can lead to suboptimal disease control.^{2–4,38,61,107} 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 several prospective clinical studies in patients with indications for RNI (Table 2).^{23,35,39,110–112} Initial reports from clinical trials from the University of Florida and MGH demonstrated favorable early toxicity outcomes, and they 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.^{23,30,110}

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.¹¹¹ 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 greater acute toxicities were noted, and only 1 (2%) grade 3 late complication, in the form of pneumonitis that 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 who underwent uniform scanning or PBS PT at Northwestern Medicine Chicago Proton Therapy Center have been described.¹¹² Toxicities of grade 2 or greater 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, 12 patients experienced disease failure, and the crude locoregional control was 96%.

A prospective trial with long-term follow-up of patients with breast cancer and undergoing RNI was published recently.³⁹ Between 2011 and 2016, 69 patients underwent passive scattering PT (before 2013) or PBS PT (2013 and later); 93% of patients underwent postmastectomy.³⁹ The heart mean, LAD max, and ipsilateral lung V20 Gy values were 0.5 Gy, 4.7 Gy (RBE), and 14.5%, respectively.⁴¹ With a median follow-up of 55 months, 5-year locoregional control and overall survival rates were 98.5% and 91%, respectively.³⁹ Acute toxicities included grade 2 radiation dermatitis and fatigue in 83% and 35% of patients, respectively, and grade 3 radiation dermatitis in 4% of patients. The acute dermatologic adverse events were comparable to what has been reported recently with conventionally fractionated photon therapy.³⁸ Five patients (7%) experienced grade 1 rib fracture, a higher rate than other PT and photon experiences reported to date. This finding could be the result of close attention because of a perceived potential increased risk with low threshold for imaging, use of a single field, and lack of a chest wall constraint to limit end-of-range LET/RBE effects during the treatment planning process.⁴¹ Research is ongoing to examine potential differences between photons and protons in regard to chest wall toxicity (NCT03270072).

A pragmatic, randomized phase 3 proton versus photon breast trial for RNI in patients with nonmetastatic breast cancer (RADCOMP, RTOG 3510) is currently accruing (NCT02603341).⁶⁷ 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 Epidemiologic End Results (SEER), database and it is higher than that reported in the study by Darby et al.⁶⁷ 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.¹² 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, could ultimately determine whether the RADCOMP trial is adequately powered to detect a clinically meaningful reduction in MCEs with PT at 10 years.⁶ Secondary objectives of the RADCOMP trial include to assess the noninferiority of PT versus photon therapy in reducing locoregional and any recurrence, to assess health-related quality of life and adverse events, and to develop predictive models to examine the association of radiation dose distribution to heart and MCEs and health-related quality of life. The Danish Breast Cancer Group is also conducting a phase 3 randomized breast cancer trial. In this study, eligible patients are those with indications for adjuvant radiation therapy for breast cancer where standard photon planning shows a mean heart dose of 4 Gy or more or an ipsilateral lung V20 Gy of 37% or more.¹¹³ The primary endpoint is radiation-associated ischemic and valvular heart disease at 10 years after radiation therapy. 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.^{6,61} The optimal dose and 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).^{35,114,115}

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.^{116–118} Reconstructed breast mounds can preclude comprehensive coverage of the postmastectomy CTV with photon techniques.¹¹⁹ For example, among women who undergo CPM with direct-to-implant or tissue expander reconstruction, the breast prosthesis often retains

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 (41)	2011-2016	69	L (n=63) R (n=4) B/I (n=2) CW (n=64) WB (n=5) 45-50.4 Gy +/- III (36%) 14.4 Gy Boost	Metric (Median, Gy) Mean	PP/PBS 0.5	Metric (Median) Mean (Gy)	PP/PBS 7.7	Heart Mean LAD Max LAD Mean Ipsi Lung V20 Esophagus Max	— Grade 2 Dermatitis 83% Dysphagia 7% Fatigue 35% Grade 3 Dermatitis 4% Late: Unplanned Sx -33% Grade 1 Rib fracture 1% Grade 2 Pneumonitis 1% Acute: Grade 2 Dermatitis 33% Esophagitis 2% Fatigue 2% Decreased Joint ROM 2% Br. Plexop. 2% Grade 3 Esophagitis 4% Late: Reconst. Cx - 39% Acute: Grade 2 Dermatitis 74% Esophagitis 17% Skin Pain 24% Fatigue 2% Late: Reconst. Cx - 27% Grade 3 Pneumonitis: 2% Grade 2 Dermatitis 72% Esophagitis 33% Skin Pain 21% Fatigue 15% Grade 3 Dermatitis 5%	
				Min	0.1	Min (Gy)	0.1	Mean	<1.5 Gy	5-year LRC 98.5% OS 91%
				Max	16.6	Max (Gy)	45.9	LAD Max	<10 Gy	
				LAD Mean	1.16	V20 (%)	14.5	LAD Mean	<20Gy	
				LAD Min	0.1			LAD Min	<20%	
LAD Max	4.7			LAD Max	<40 Gy					
Mayo (37)	2015-2017	51	CW+Immed. Reconst. L (n=35) R (n=14) B/I (n=2) 50 Gy (n=37) 40.5 Gy (n=14) III (39%)	Metric (Median) Mean (Gy)	IP (IQR) 0.6 (0.4-0.9)	Metric (Median) Ipsi Mean (Gy)	IP (IQR) 7.3 (6.5-8.3)	—		
				V25 (%)	0.1 (0.0-0.3)	Ipsi V20 (%)	13.9 (10.1-14.9)			
				LAD Mean (Gy)	2.8 (1.5-4.0)					
				RCA Mean (Gy)	0.8 (0.4-2.7)					
				Metric (Median) Mean (Gy)	UP (Range) 0.7 (0.0-3.2)	Metric (Median) V20 (%)	7.1 (0.1-19.1)	OAR Metric C/I Breast V5 (%)	UP (Range) 7.1 (0.0-9.9)	3-year LR DFS 96.3% MFS 84.1% OS 97.2% LC 97.6%
MSK (113)	2013-2015	42	L CW (n=36) R CW (n=6) *IMN 76% Median 50 Gy +/-Boost	Metric (Median) Mean (Gy)	UP (Range) 0.7 (0.0-3.2)	Metric (Median) V20 (%)	UP (Range) 7.1 (0.1-19.1)	OAR Metric C/I Breast V5 (%)	UP (Range) 7.1 (0.0-9.9)	
				V20 (%)	0.5 (0.0-6.0)	Ipsi V20 (%)	16.1 (2.1-30.3)	C/I Breast Mean (Gy)	0.3 (0.0-3.5)	
				V5 (%)	4.3 (0.16-2)	Ipsi V5 (%)	34.0 (16.4-53.8)	Spinal Cord Max (Gy)	0.8 (0.0-18.2)	
				Max (Gy)	16.3 (0.1-51.9)	C/I V5 (%)	0.3 (0-42.4)	Esophagus Mean (Gy)	7.5 (0.0-26.9)	
				Constraint Used		Constraint Used		Constraint Used		
NWM (114)	2011-2016	91	WB (n=27) CW (n=66) L (n=56) R (n=33) Median 50.4 Gy +/- 8.0-19.8 Gy Boost	Constraint Used		Constraint Used		Constraint Used		
				V20	≤21%	Ipsi V20	≤33%	Esophagus Max Ipsi Humeral Head Max Skin PTV V110	<40Gy <45 Gy <3.5%	OS 93.4% DF 11% LC 95.6%
				V5	≤50% (Left-sided) ≤40% (Right-sided)	Ipsi V5	≤42%			

(Continued)

Table 2 (Continued)

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=11) L (N=9) R (N=9)	Metric (Median; L, R)	PP	3D	Metric (Median)	3D	PP	PP	20 mo	Other Rib Fracture - 3% Lymphedema - 3% Grade 2 Pneumonitis 6% Grade 3 Dermatitis 22% Infection 6%	—	
				V5 (%)	2.7% [#]	34.0	Ipsi V5 (%)	60.5	35.3	Integral Dose (Gy-L)	193			92.7
				Mean (Gy)	0.3	13.2	Ipsi V20 (%)	35.5	21.6	C/I Breast	0			0
				V20 (%)	0.5	2.9	Ipsi Mean (Gy)	17.5	11.0	V3 (%)				
				Ventricle Mean (Gy)	0.0	6.1								
				LAD Max (Gy)	0.1	1.6								
				LAD Mean (Gy)	0.2	5.4								
					30.5	1.2								
					1.7	44.6								
						27.0								
MGH (112)	—	12	L CW (n=11) R CW (n=1)	Metric (Mean, L)	PP (Range)	Metric (Mean, PP (Range)				6 mo	Acute: Grade ≥1 — 0%	—		
				Mean (Gy)	0.4	Mean (Gy)	6							
				V20 (%)	(0.1-1.2)	V20 (%)	(2.4-10.1)							
				LV Mean (Gy)	0.01	LV Mean (Gy)	12.7							
				LV V20 (%)	(0.0-2.4)	LV V20 (%)	(4.4-22.1)							
					0.1									
					(0.0-0.4)									
					0.0004									
					(0.0-0.2)									

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; DIBH = deep inspiratory breast hold; Gy = Gray (Relative Biological Effectiveness [RBE]); IQR = interquartile range; LAD = 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

a medial chest wall position, even when the patient is supine. This medial positioning can result in a 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 can limit chest wall and IMN CTV coverage.^{29,119} 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.^{2,29,97} Another potential advance of PT among patients undergoing autologous flap reconstruction is improved sparing of the region of the internal mammary vessel anastomosis.^{120,121}

PT clinical outcomes have been reported in women after mastectomy with immediate breast reconstruction.^{23,97,110} Smith et al³⁵ described outcomes of 51 reconstructed patients treated with multifield optimized PBS PT (intensity modulated PT [IMPT]) at the Mayo Clinic.³⁵ As expected, PT increased the risk of implant-based reconstruction complications compared with nonirradiated contralateral reconstructed breasts, but acute toxicity and reconstruction outcomes compared favorably with previously published photon studies.¹²² 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.³⁵ 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 this could be a chance finding. Nevertheless, caution is warranted when extrapolating novel fractionation regimens to PT based on photon experiences alone because of potential LET/RBE differences between the modalities, and additional investigation into altered dose fractionation regimens is warranted.

The aforementioned phase 2 trial from MGH included 39 patients who underwent mastectomy with immediate implant-based reconstruction and 14 patients who underwent delayed reconstruction.³⁹ Among this cohort of 53 patients who attempted reconstruction, 15 patients (28%) experienced an RT-related complication, and just 2 patients (4%) experienced reconstructive loss. These outcomes compared favorably with recent reports of patients treated with photon therapy from that institution.¹²³

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.^{124–127} Favorable

treatment outcomes have been achieved with modern short-course photon therapy and brachytherapy.^{124,126} Numerous studies have demonstrated that PT reduces nontarget breast, heart, and lung exposure compared with photon techniques, and it reduces heart and lung exposure and dose inhomogeneity compared with brachytherapy APBI.^{92,128–132} Normal tissue sparing could be most pronounced in patients with medially located tumors. Reducing dose to nontarget breast tissue with photon therapy has been associated with improved cosmesis after APBI.¹³³

Outcomes from several prospective proton APBI studies have been reported (Table 3). Investigators at Loma Linda conducted a phase 2 trial of 100 patients who underwent a multifield, 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 greater acute skin toxicities. Late toxicity consisted of just 7 cases of grade 1 telangiectasia. Provider-assessed cosmesis was good to excellent in greater than 90% of patients in annual follow-up through 5 years; patient-reported cosmesis was comparably favorable, with no evidence of deterioration over time.^{37,134} Comparably favorable 3-year outcomes have also been presented from a multicenter phase 2 Proton Collaborative Group study using the same dose-fractionation regimen.¹³⁵

Long-term results from the first dose cohort of a phase 1 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).³⁶ 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 nontarget breast sparing. No significant difference in 7-year incidence of local failure or in patient reported cosmetic outcomes between the 2 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.^{36,136,137} The authors favored 2 fields treated daily on the basis of these results.

The National Cancer Center in Korea has reported long-term results of a phase 2 trial of 30 patients, age ≥ 40 years with primary tumors measuring ≤ 3 cm and pathologically negative nodes, treated with aperture- and compensator-based proton APBI.¹³⁸ The prescription was 30 Gy (RBE) in 5 daily fractions. A single field was used for the first 15 patients and a 2-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 of grade ≥ 2 were observed among the patients who underwent treatment with 2 fields.¹³⁸

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) EB or P/E (n=79)	32 Gy (RBE) / 4 Gy x 8 fx BID	1-3 fields for PP (1 field treated per fx) 1.5-2.0 cm margin to PTV <5 mm from skin	7yr Good-excellent: 62% PP 94% EB or P/E	7yr Good-excellent: 92% PP 96% photon, NSS	PP vs. EB or P/E Telangiectasias 69% vs. 16% (<i>p</i> =0.03) Pigmentation changes 54% vs. 22% (<i>p</i> =0.02) Other late skin tox 62% vs. 18% (<i>p</i> =0.029) Increased toxicity with single field plan	7yr LF: 11% PP 4% EB or P/E, NSS
NCC, Korea (140)	PP (n=30)	30 Gy (RBE) / 6 Gy x 5 fx QD	1-2 fields PBT	3yr Good-excellent: 69% (~100% with 2-field plan)	–	Acute: Gr 1-2 - RT dermatitis 62% No grade 3 AE Late: Gr 1 - telangiectasia 7% Fat necrosis 1% Gr 2 – 7 events ≥Gr 3 – none	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: Gr 1-2 - RT dermatitis 62% No grade 3 AE Late: Gr 1 - telangiectasia 7% Fat necrosis 1% Gr 2 – 7 events ≥Gr 3 – none	5yr IBTR-FS 97% 5yr OS 95%
PCG BRE007 (137)	UP (n=37) PP (n=1)	40 Gy (RBE) / 4 Gy (RBE) x 10 fx QD	≥3 fields (≥2 treated daily) for PP 1.5 cm margin to CTV	3yr Good-excellent: 100%	BCTOS Score of 4: 13.2% (nipple appearance, breast shape, scar tissue)	Gr 2 – 7 events ≥Gr 3 – none	3yr LF 0% 3yr DF 0%
MDACC (141)	PP (n=100)	34 Gy (RBE) / 3.4 Gy x 10 fx BID	≥2 fields (3 or 4 fields used for 80% of patients)	2yr Good-excellent: 84%	2yr Good-excellent: 96%	Acute Gr 2 - 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: PP = 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

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.¹³⁹ Patients underwent a minimum of 2 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 of grade 3 or higher. Cosmesis was reported as good or excellent at 12 months by 91% of patients and 94% of physicians.¹³⁹

Early outcomes for 76 patients who underwent PBS APBI at the Mayo Clinic have also been reported.⁹³ PBS is attractive because of the capacity to constrain the dose at the skin surface, which might limit the risk of acute and late skin toxicity (Fig. 3). In this study, a 3-fraction regimen of 7.3 Gy (RBE) per fraction was administered with a median of 2 multifield optimized PBS beams. The median of the maximum dose to 1 cm³ of the skin volume, 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.⁹³ Additional follow-up will be necessary to 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 radiation therapy to the whole breast with excellent normal tissue sparing.^{140–143} 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.^{141,144,145} The absolute improvement in normal tissue sparing might 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 (Fig. 5).¹⁴⁶ The potential clinical importance of normal tissue sparing could be greater in patients with active cardiopulmonary conditions.^{12,33}

Thorpe et al.¹⁴⁷ recently reported early outcomes of 82 patients who underwent whole-breast irradiation with or without RNI, as part of the multi-institutional prospective Proton Collaborative Group Registry.¹⁴⁷ Grade 3 adverse events were observed in 7% of patients, dermatitis, or breast pain, and the authors found PT to be well tolerated. Similar to the case of APBI, skin-sparing PBS technology could make PT more attractive for whole-breast irradiation.⁹³

Bilateral breast cancer

Recommendation: PT is a treatment option for patients with indications for bilateral breast and chest wall irradiation. The benefit might be most pronounced when bilateral breast and chest wall with comprehensive RNI is indicated.

Fig. 5. (A) Sagittal and (B) axial 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.

Clinical trial enrollment should be considered if it is available (LE: 3, grade C).

The incidence of synchronous bilateral breast cancer is 1% to 3% of all patients affected by breast cancer.^{148,149} Bilateral breast cancer radiation therapy increases the heart and lung dose compared with unilateral treatment,¹⁵⁰ which puts patients at increased risk for cardiac and pulmonary adverse events.^{5,18} In addition, uniform target coverage of the bilateral internal mammary chains and medial breast tissue is limited with traditional 3DCRT techniques because of the overlap of the tangent fields. PT enables a homogeneous and highly conformal dose distribution with improved normal tissue sparing (Fig. 2).^{151,152}

Reduced arm mobility

Recommendation: If available, PT may be considered a preferred treatment option for breast radiation therapy 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 might 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 it is not used routinely 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 (Fig. 2).^{91,97} Therefore, the dosimetric advantages of PT over photon techniques are particularly pronounced when breast radiation therapy must be administered in the arms-down position.¹⁵³ The technique of arms-down PT has been described, and favorable long-term disease control and toxicity outcomes have been reported.^{35,39,91,97}

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 a differing natural history, but it is generally associated with poor prognosis.¹⁵⁴ 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 occurring after thoracic radiation therapy, has yet to be defined. Traditionally, options have included photon 3DCRT or IMRT, electrons, and brachytherapy.^{155–160} 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 the heart, lung, ribs, brachial plexus, and other soft tissue outside of the target volume or reducing dose heterogeneity from brachytherapy.^{22,161}

Thorpe et al¹⁶² have reported outcomes of 50 patients who underwent PT reirradiation between 2011 and 2016 in a multi-institutional prospective registry. The median time between RT courses and cumulative dose were 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 were 93% and 97%, respectively. These promising outcomes mirror prospective PT series in other disease sites.^{163–165} Fattahi et al¹⁶⁶ reported outcomes of a series of 72 patients who underwent reirradiation between 1999 and 2019 at a single institution, including 52 patients who received 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.¹⁶⁶ These proton outcomes are comparable to prior photon reports.¹⁶⁷ 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

Because of the increased capital investment required to build and operate proton facilities, the cost of PT per fraction is greater than conventional photon radiation therapy. 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 3 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.^{168–171} For example, Mailhot Vega et al¹⁷¹ published a contemporary CEA using an American framework informed by cardiac dose–toxicity relationships presented by Darby et al.⁹ Guidelines were presented estimating mean heart dose thresholds for photon plans above which PT is cost-effective, comparatively.¹⁷¹ In the base case, it was assumed that cost of cardiac toxicity management would be exclusive medical management, an assumption that might severely underestimate the true cost of heart disease. Nevertheless, PT favorability mean heart dose thresholds approximating 7

to 9 Gy (RBE) for women without cardiac risk factors and 4 to 5 Gy (RBE) for women with at least 1 cardiac risk factor were calculated. Considering a systematic review of mean heart doses for photon-based regional nodal radiation,¹⁸ the authors noted that PT might be cost-effective for more than 95% of women with ≥ 1 cardiac risk factor and undergoing RNI for left breast cancer.

As an alternative to randomized controlled clinical trials comparing photons and protons, which the authors note might be impractical in many scenarios given the rapidly evolving technology and prolonged latency of radiation-associated late effects, Langendijk et al⁹ have proposed and implemented a 2-phase model-based approach for patient selection for PT in the Netherlands.⁹ The first phase aims to select patients who might benefit most from PT by integrating comparative planning studies with normal tissue complication probability 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.¹² 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. Although no CEAs with effectiveness endpoints have been captured, a cost analysis noted comparable cost of proton APBI versus other APBI techniques.¹⁷² Hypofractionated and ultra-hypofractionated regimens have emerged as new standards in early-stage breast cancer treated with photon therapy.^{173–175} If also proven acceptable for PT, or if the improved normal tissue sparing of PT facilitates further treatment acceleration, the reduction in costs could further improve the cost acceptability of PT.^{93,176}

Conclusion

PT is being investigated as an adjuvant radiation therapy 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 improve treatment delivery. These advances and potential variability in techniques across institutions also present challenges for evidence development. Close attention to the PT techniques being used is vital in evaluating available and burgeoning PT outcomes. Additional research is needed to explore the distinct physical and biological characteristics of PT,¹⁷⁷ including optimizing dose-fractionation schedules, to improve cure rates and optimize quality of life.

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