Advances in Radiation Oncology (2021) 6, 100710

advances in radiation oncology

www.advancesradonc.org

Scientific Article

Proton Reirradiation for Locoregionally Recurrent Breast Cancer

Michael J. LaRiviere, MD,[a] Alexandra Dreyfuss, MD,[b] Neil K. Taunk, MD, MS,[a] and Gary M. Freedman, MD[a,*]

[a]*Department of Radiation Oncology, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania;* [b]*Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, New York*

Received September 23, 2020; revised March 5, 2021; accepted April 13, 2021

Abstract

Purpose: Local-regional recurrence (LRR) of breast cancer after prior adjuvant radiation (RT) can present a clinical challenge. Proton therapy is recommended by the American Society for Radiation Oncology in cases where reirrradiation is needed; however, data are limited. We present the toxicity and outcomes after reirradiation for local-regional recurrence of breast cancer with proton therapy.

Methods and Materials: A single-institution retrospective review identified patients with the following criteria: LRR of breast cancer, prior photon radiation to the same region, proton beam reirradiation, and definitive intent. Surgery or systemic therapy at the time of recurrence was used when indicated. The log-rank test was used to compare Kaplan-Meier survival estimates. Kruskal-Wallis tests were performed to compare worst reported toxicities with clinical variables.

Results: The population included 27 patients with a history of prior radiation and treated with proton therapy for LRR between 2012 and 2019. The median interval between courses was 9.7 years. Proton reirradiation regimens included whole breast/chest wall (WB/CW) with regional nodal RT (22/27), nodal RT alone (2/27), or WB/CW alone (3/27). The median dose was 51 Gy, and the most common fractionation was 1.5 Gy twice daily. Median follow-up after reirradiation was 16.6 months. Acute grade 3 toxicities included dermatitis in 2 patients and breast pain in 2 patients. Grade 2 or higher late toxicities included 6 G2 rib fractures and 1 G2 brachial plexopathy, 1 G3 dermatitis, 1 G3 breast pain, and 1 G4 dermatitis. Twelve patients had new documented recurrences of which 1 was a second in-field LRR, and there were 7 deaths.

Conclusions: Proton salvage reirradiation to median 51 Gy in 1.5 Gy twice daily appears to be safe with acceptable acute and late toxicity, and effective with >95% local-regional control.

Introduction

Adjuvant radiation therapy (RT) for breast cancer has proven to be highly effective in improving disease-free and overall survival after breast-conserving surgery or mastectomy.[1,2] This has resulted in a high utilization of radiation after breast-conserving surgery and in intermediate- to high-risk women after mastectomy. In addition, contemporary rates of 5- and 10-year local-regional recurrence (LRR) have been decreasing and have become very low (<5% to 10%) due to improvements across disciplines in imaging and tumor/nodal localization, surgery, pathology assessment, and systemic therapy.[3-6] This makes the clinical presentation of LRR in an area of previous adjuvant radiation rare. However, given the

Sources of support: This work had no specific funding.

Disclosures: None.

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

*Corresponding author: Gary M. Freedman, MD; E-mail: gary.freedman@pennmedicine.upenn.edu

https://doi.org/10.1016/j.adro.2021.100710

large number of women treated for primary breast cancer and their relatively long life expectancy, even a small LRR rate of 2% to 5% in the ipsilateral breast, chest wall, or lymph nodes may represent hundreds of women each year. The multidisciplinary management and specific role for reirradiation in local-regionally recurrent breast cancer remains a challenging and clinically relevant question. Goals for reirradiation in managing LRR are the reduction in risk for second LRR, and prevention of resulting symptoms of pain, ulceration, bleeding, edema, or plexopathy from uncontrolled local-regional disease. The effect of radiation on survival in the salvage setting is not known.

Standard therapy for LRR has historically been surgical resection with or without systemic therapy.[7] This includes total mastectomy for a LRR after prior lumpectomy and radiation, and surgical excision, if possible, after prior mastectomy. There are relatively few studies reporting toxicity and outcomes of reirradiation in breast cancer.[8-10] This may be due to the small number of patients with isolated LRR and the fear of toxicity of reirradiation among radiation oncologists and their referring physicians. There is also a lack of clear guidelines for the use of reirradiation. The National Comprehensive Cancer Network guidelines allow for additional radiation in treating LRR but only defines this as "if possible," at the physician's discretion, balancing the risks for toxicity with the combined courses of radiation.[7] To better assess the therapeutic ratio, this perceived risk for second LRR needs to be assessed against the toxicities of treatment, and these toxicities are not well known for reirradiation. Several strategies have been proposed to safely reirradiate LRR. Twice daily radiation using external beam or interstitial radiation has been used to reduce the toxicity from reirradiation in the setting of second lumpectomy after local recurrence or radiation-related sarcomas.[11-15] Proton therapy may also provide dosimetric advantages for reirradiation.

The American Society for Radiation Oncology has published a model policy for insurance coverage for proton beam radiation therapy.[16] Reirradiation cases are a group 1 indication for proton beam radiation based on medical necessity requirements and published clinical data. The primary rationale is that protons have unique dose deposition characteristics that can deliver the prescribed target dose while giving a lower dose to normal tissues compared with photon-based forms of external beam radiation therapy. This could be particularly important in minimizing the risk from reirradiation for breast cancer, but there is little published data, and none specifically cited in the American Society for Radiation Oncology model policy statement.[9,16] Here we report a novel use of proton beam and twice-daily fractionation in the management of LRR of breast cancer with reirradiation.

Methods

This single-institution, retrospective study includes 27 patients treated with proton reirradiation between 2012 and 2019 who met the following inclusion criteria: LRR of breast cancer, prior photon radiation to the same region where reirradiation had substantial and direct overlap in the opinion of the treating radiation oncologist, proton beam reirradiation, and definitive intent, defined as treated to a reirradiation dose of at least 42 Gy. Patients with both metastatic and logoregional disease were included. The study was approved by the institutional review board at our institution. Data were abstracted from the electronic medical record and external record chart review. All patients were seen for weekly on-treatment visits, and follow-up visits were generally scheduled 3 months after treatment and then every 6 months for clinician toxicity assessment. Acute and late toxicities were determined from clinician visit notes, including physician or nurse toxicity grading, and other available clinical data. Common Terminology Criteria for Adverse Events version 4.0 toxicity grading was used.

All patients had an initial photon and a second proton course of radiation. All patients had an initial diagnosis of breast cancer and a subsequent local-regional recurrence; 25 of 27 received adjuvant radiation therapy for their initial diagnosis of breast cancer, while 2 of 27 patients did not receive adjuvant radiation in the management of their initial breast cancer diagnosis. These 2 of 27 patients were included, as 1 patient had received prior radiation therapy for Hodgkin lymphoma, and 1 patient had received palliative radiation therapy to the thoracic spine 5.1 years after her initial breast cancer diagnosis. Both patients were included given their prior photon radiation to the thorax. Proton reirradiation was performed using a cyclotron-based multiroom center (IBA, Louvain-La-Neuve, Belgium). Concurrent or sequential cytotoxic chemotherapy was delivered at the discretion of the treating medical oncologist in consultation with the treating radiation oncologist.

An α/β of 3 was used to calculate 2 Gy-equivalent doses (EQD2) for normal tissue toxicity. Kruskal-Wallis tests were performed to compare worst reported toxicities with clinical variables. Kaplan-Meier estimates were used for recurrence and survival analyses. Survival was calculated beginning with the reirradiation treatment completion date. For local recurrence-free survival, events included the earlier of local recurrence or death. For recurrence-free survival, events included the earlier of any recurrence or death. For overall survival, events included death. For all survival analyses, patients were censored at the time of last follow-up. The log-rank test was used to compare survival estimates.

All procedures performed in studies involving human participants were in accordance with the ethical standards

of the institutional or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

Results

Twenty-seven women who had received prior radiation therapy and were retreated with proton radiation were identified for analysis. Median follow-up was 16.6 months after reirradiation (range, 1.0-49.3). Patient characteristics are shown in Table 1. Specific details of the initial and second course of radiation are shown in Table 2.

The first radiation course was delivered using photons, with or without electrons, in all patients. The initial radiation course was 15 whole breast (WB), 10 whole breast/chest wall (WB/CW) and regional nodes, 1 involved field treatment for Hodgkin lymphoma (HL), and 1 palliative thoracic spine treatment. In 1 patient with HL, 35 Gy/20 fractions involved field RT was delivered to the cervical nodes and mediastinum, which overlapped with the subsequent reirradiation field. In 1 patient with breast cancer, 20 Gy/5 fractions were delivered to the thoracic spine and ribs for metastatic disease, also overlapping the reirradiation field. The remaining patients were treated to the breast (15/27), breast and regional nodes (6/27), and chest wall and regional nodes (3/27, regional nodal treatment records NA in an additional 1/27). Treatment details are listed in Table 2. Among the 7 of 27 patients with available records (5/7 with acute toxicity records, 2 of 7 with late toxicity records), no grade 3 acute or late toxicities were recorded from the first course of radiation.

At the time of diagnosis of recurrent disease, 10 of 27 patients had local (including local cutaneous metastatic) recurrences, 12 of 27 had LRR, and 5 of 27 had LRR in the setting of metastatic disease. Details regarding tumor histology, receptor status, surgical management, and concurrent chemotherapy are summarized in Table 1. Two of 16 patients with invasive ductal carcinoma also had inflammatory recurrences. Although 3 of 27 patients received chemotherapy concurrent with radiation, 20 of 27 patients also received cytotoxic chemotherapy at some point in the management of their recurrent disease. Among the 8 of 27 patients who underwent either nodal sampling or dissection, 8/8 had positive nodes (range, 1-8 nodes; percent positive 17%-71% among the 7/8 patients with total nodes sampled available).

The second course of radiation used proton therapy in all patients. Median elapsed time between initial and reirradiation courses was 9.7 years (range, 0.9-37.6). Proton techniques included proton double scattering (8), proton pencil beam scanning (18), and combined proton double scattering/pencil beam scanning with double scattering to the supraclavicular and high axillary nodes and pencil beam scanning to the chest wall (1). The second course of radiation targeted the breast/chest wall and axilla/nodes in 22 of 27, breast/chest wall only in 3 of 27 patients, and nodes only in 2 of 27. Nodal target details are listed in Table 2. The supraclavicular fossa was irradiated in both the initial course and the reirradiation course in 4 of 27 patients. The dose delivered was 49.5 to 51 Gy in 1.5 Gy twice-daily (BID) fractions in the majority of patients (19/27). BID fractions were separated by at least 6 hours. Other dose/fractionation regimens included 42 to 65 Gy in 28 to 41 fractions. Three of 27 patients received cytotoxic systemic therapy concurrent with radiation (capecitabine in 3/3). Reirradiation dose in EQD2 (α/β_3) was 44.55 to 45.9 in 19 of 27 patients, and 37.8 in 1 of 27, 50 to 60 in 6 of 27, and 66 in 1 of 27. Cumulative EQD2 (α/β_3) including initial and reirradiation dose was 77.8 to 99.9 in 7 of 27, 100 to 109.9 in 14 of 27, and 110 to 120 in 6 of 27.

At the time of analysis after reirradiation, 1 of 27 patients experienced new in-field LRR and 11 of 27 new distant recurrence. Among 7 of 27 patients who died, at time of death 0 of 7 had local recurrence, 6 of 7 distant recurrence, and 1 of 7 was lost to follow-up and died of an unknown cause. Kaplan-Meier estimates of postreirradiation median loco-regional recurrence-free survival was not reached (95% confidence interval 14.4-not reached [NR]), recurrence-free survival 21.4 months (12.0-NR), and overall survival NR (16.7-NR). Twelve-month loco-regional recurrence-free survival was 78.5% (63.2%-97.4%), 12-month recurrence-free survival was 62.4% (45.3%-85.9%), and 12-month overall survival was 78.5% (63.2%-97.4%). Recurrence-free survival is shown in Fig. 1. Stratifying patients by time elapsed between initial and reirradiation courses, postreirradiation median and 12-month overall survival was significantly improved among patients with an interval of at least 2 years (median NR [16.7-NR] vs 10.3 [7.0.-NR], $P = .04$; 12-month 85.0% [70.4%-100.0%] vs 33.3% [6.7%-100.0%]; Fig. 2).

Toxicity of reirradiation is shown in Table 3, with examples of late skin appearance shown in Fig. 3. Grade (G) 3 or higher toxicities include acute G3 dermatitis in 2 of 27, acute G3 breast pain in 2 of 27, late G3 dermatitis in 1 of 27 and G4 dermatitis in 1 of 27, and late G3 breast pain in 1 of 27. Other important late toxicities include 6 G2 rib fractures and 1 G2 brachial plexopathy. No pneumonitis was reported. Among 4 patients treated to the supraclavicular fossa both at the time of initial RT and reirradiation, notable toxicities included late G4 dermatitis in 1 of 4 (patient 24) and late G1 lymphedema in 1 of 4 (patient 26).

Grade 2 late brachial plexopathy was seen in 1 of 4 (patient 25). The patient first noted numbness and tingling of the first 3 digits of the ipsilateral hand approximately 2.5 months after completing radiation therapy. Of note, the site of this patient's recurrent

Table 1

First diagnosis		Recurrence	
Variable	Value (range)	Variable	Value (range)
Age at diagnosis, y	49* (11-73)	Age at recurrence, y	58* (39-80)
Tumor histology		Tumor histology	
IDC	19	IDC	16
ILC	0	ILC	4
DCIS	3	Other/NA	7
Hodgkin Lymphoma	1		
Other/NA	4		
		Receptor status	
		ER+/PR+/Her2−	8
		ER+/PR+/Her2 eq.	1
		ER+/PR−/Her2−	5
		ER+/PR−/Her2 eq.	1
		ER−/PR−/Her2+	3
		ER−/PR−/Her2−	5
		Other/NA	4
Surgery		Surgery	
Lumpectomy	8	Lumpectomy	2
Lumpectomy + SLNB	7	Mastectomy +/− ALND	11
Lumpectomy + ALND	7	Other	8
Mastectomy +/− SLNB	4	NA/none	6
Other/NA	1		
		Surgical final margins	
		(−)	8
		<1 mm	1
		Focally (+)/gross residual	10
		NA	2
		No surgery	6
Chemotherapy		Concurrent Chemotherapy	
Yes	20	Yes	3
No	7	No	24
Age at RT	51* (11-74)	Age at reirradiation	59* (40-80)
		Time between RT (y)	9.7* (0.9-37.6)
RT location		RT location	
Breast	15	B/CW	3
Breast + nodes	6	B/CW + axilla/nodes	22
CW +/− nodes	4	Nodes only	2
Other	2		
RT initial dose (cGy)	4680* (2000-6100)	RT initial dose (cGy)	5100* (4202-5400)
Initial fraction size (cGy)	180* (175-500)	Fraction size (cGy)	150* (150-250)
Boost dose (cGy)	1000* (0-2000)	Boost dose (cGy)	0* (0-1400)
Boost fraction size (cGy)	200* (180-200)	Boost fraction size (cGy)	165* (150-250)
RT technique		RT technique	
Photons	12	Protons BID	26
+ Electron boost	4	Protons QD	1
NA	11		

* Median.

Abbreviations: ALND = axillary lymph node dissection; BID = twice-daily; DCIS = ductal carcinoma in situ; Eq. = equivocal; IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma; NA = not available; RT = radiation therapy; SLNB = sentinel lymph node biopsy; QD = daily.

disease was located superior to the brachial plexus. At her last follow-up 22 months after reirradiation, she reported episodes of right arm and hand numbness and paresthesia, but no motor weakness was noted. For her reirradiation course, the maximum dose to the brachial plexus was 57.3 Gy over 40 twice-daily 1.5 Gy fractions. Although only paper records were available for her prior treatment course, the supraclavicular fossa was treated to 45 Gy in 25 daily 1.8 Gy fractions 16.1 years earlier; it is therefore possible that a

Table 2

Patient ID	First RT targets	First RT dose (cGy) initial + boost total/fx size	Re-RT targets	Re-RT nodal target details	Re-RT dose (cGy)	Grade 3+ toxicities	Rib fracture, edema
No supraclavicular nodal reirradiation							
1	Breast	4500/180 + 2000/200	CW + regional nodes	S'clav, i'clav	5100		
2	Spine/ribs metastases	2000/500	CW + regional nodes	S'clav	6000	Acute and late grade 3 dermatitis and breast pain	
3	Breast	4600/200 + 2000/200	CW	-	5100		Acute G1 lymphedema
4	Cervical nodes + Mediastinum*	3500	CW + axilla II-III	Axilla II-III	4950		Acute G1 lymphedema
5	Breast	6440	CW**	-	5100	Acute grade 3 breast pain	
6	Breast + regional nodes	6000	CW + full axilla	Full axilla	5100		Late G1 lymphedema
7	Breast	6500	CW + regional nodes	S'clav, high axilla	4950		Rib fracture, late G1 lymphedema
8	Breast	6000	CW + regional nodes	S'clav	5100		
9	Breast	6040	CW + regional nodes	S'clav, axilla	5100		
10	Breast	6080	CW + regional nodes	S'clav	5100		Rib fracture
11	Breast	6040	CW + regional nodes	S'clav	5100		
12	Breast	6040	CW + regional nodes	S'clav	5100		Rib fracture
13	Breast	6100	CW + regional nodes	IMN, s'clav, axilla	5100		
14	Breast	6000	CW + regional nodes	IMN, s'clav, axilla	5100		Rib fracture
15	Breast	5500	CW + regional nodes	IMN, s'clav, axilla	5100		
16	CW + regional nodes	5040	CW	-	5100		Rib fracture
17	Breast	5040/180 + 1600/200	CW + regional nodes	IMN, s'clav, axilla	5100		
18	Breast	6000	CW + regional nodes	IMN, s'clav, axilla	5100/150 + 900/180	Acute grade 3 dermatitis	
19	Breast	5256	CW + regional nodes	IMN, s'clav, axilla	5100/150 + 600/150		Acute G1 lymphedema
20	Breast + regional nodes	6100	CW + regional nodes	IMN, axilla I-II	5040/180 + 1000/200		
21	CW + regional nodes	5040	CW + regional nodes	IMN, axilla I-III	5100		Rib fracture, late G2 lymphedema
22	Breast + regional nodes	6000	CW + regional nodes	IMN, axilla I-III	5100/150+1400/200		
23	CW +/− regional nodes	5040/180 + 1000/200	CW + regional nodes	IMN, axilla I-III	4200		
Supraclavicular nodal reirradiation							
24	Breast + regional nodes	6000	CW + regional nodes	S'clav	4950	Late grade 4 dermatitis	
25	CW + regional nodes	5040	Axilla and med/lat s'clav	Axilla and med/lat s'clav	6000		Late G1 brachial plexopathy
26	Breast + regional nodes	6000	CW + regional nodes	S'clav	5100		Late G1 lymphedema
27	Breast + regional nodes	4500/180 + 1600/200	Regional nodes	S'clav, axilla	5400/150 + 600/150		

Abbreviations: CW = chest wall; IMN = internal mammary nodes; RT = radiation therapy; S'clav = supraclavicular; I'clav = infraclavicular.

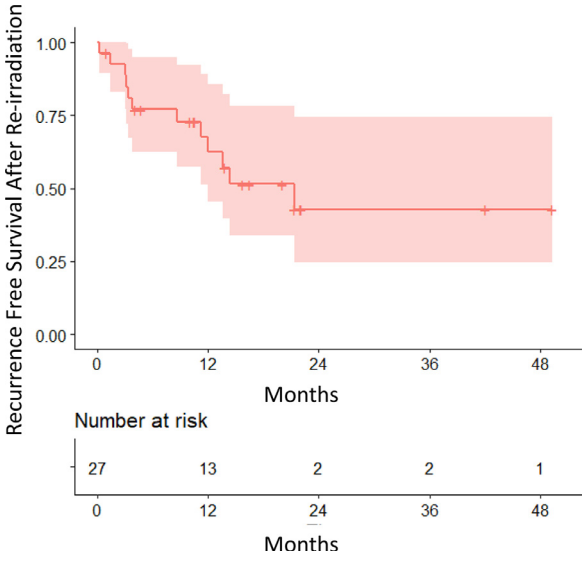

Figure 1 Recurrence-free survival after reirradiation.

portion of the brachial plexus saw a total dose of 102.3 Gy. Due to the proximity of the recurrence to the brachial plexus, this organ-at-risk was contoured but not specifically constrained.

The patient with grade 4 toxicity had reirradiation concurrent with capecitabine for gross residual disease after systemic therapy. Double scatter protons were delivered BID to the chest wall, flap, regional infraclavicular nodes, axillary nodes, and internal mammary nodes to a dose of 49.5 Gy in 33 fractions. The maximum dose was 61.6 Gy and the plan sum maximum dose was 117.6 Gy, with

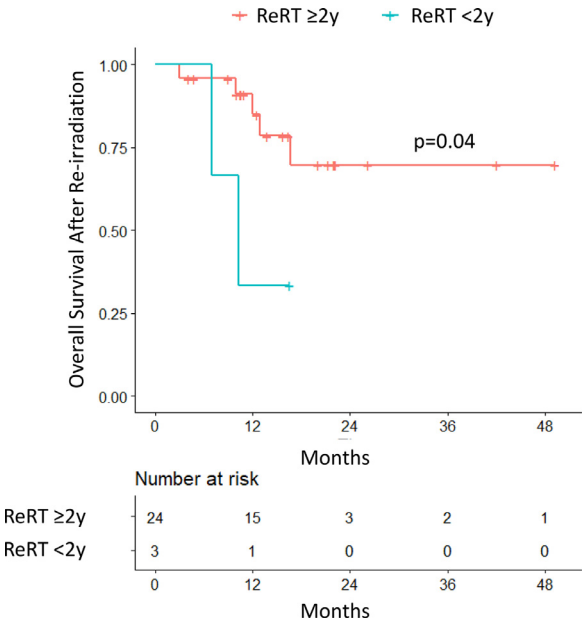

Figure 2 Overall survival after reirradiation. Patients are stratified by interval between initial and reirradiation courses, ≥2 years versus <2 years between radiation courses.

portions of the chest wall and axilla receiving a total dose of over 90 Gy. Her worst acute toxicity was grade 2 breast pain, but she went on to develop a left chest wall necrotizing soft tissue infection 10 months after completing RT. This required multiple debridements and was subsequently managed with hyperbaric oxygen therapy.

On univariate analysis, worst any (acute or late) toxicity was not associated with age at the time of first or recurrent RT course, extent of disease at initial diagnosis (local vs regional) or recurrence (local vs regional vs distant), initial RT EQD2, recurrent RT EQD2, total EQD2, elapsed time between RT courses, supraclavicular reirradiation (both initial and reirradiation course), concurrent systemic therapy, daily versus BID fractionation, and double scattering versus pencil beam scanning proton technique.

Discussion

The present study is one of few in the literature to report on reirradiation for management of local-regionally recurrent breast cancer. Multidisciplinary guidelines generally recommend surgical salvage with or without systemic therapy to the extent possible for local-regional recurrence of breast cancer.[7,17] There is consensus that a local recurrence after mastectomy without initial radiation therapy should be managed by surgery and radiation at time of recurrence. Otherwise, there is no routine role for reirradiation. The National Comprehensive Cancer Network guidelines recommend that the decision "... must factor in any prior radiation to the area and the risk of late normal tissue toxicity from the sum of the prior and planned radiation courses."[7] Patients in this series were generally selected for reirradiation for reasons of adverse clinical or pathologic features. Patients had LRR that generally would have required postmastectomy radiation if presenting in the up-front setting (T4/inflammatory, positive margins, or regional node disease). The risks of reirradiation were felt justified in these patients due to a possible 30% to 50% risk of second local recurrence. By institutional practice, these were not cases of isolated T1N0 lesions that may have been eligible for second lumpectomy and partial breast radiation per the RTOG 1014 protocol.[18] For that reason, the default goals were to treat a usual postmastectomy volume of the involved chest wall/breast and regional nodes. This included elective treatment of nodal groups not previously irradiated, and in some cases a boost to grossly involved sites of recurrence. But in the present series, 4 patients were treated to the chest wall only, without elective regional supraclavicular reirradiation, due to risk of brachial plexopathy. Yet only 1 of 4 patients, with a LRR near the brachial plexus who was treated both initially and with reirradiation to the supraclavicular fossa,

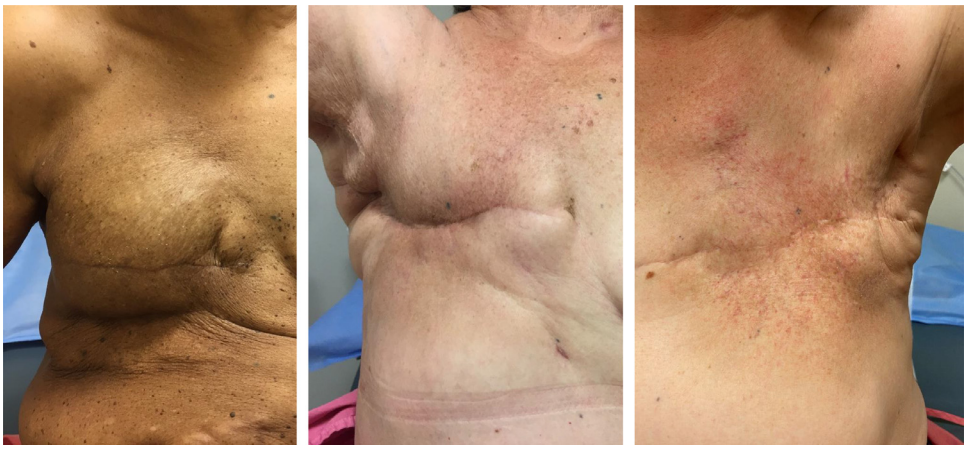

Figure 3 The chest wall appearance for 3 women treated with proton reirradiation at 1.5 Gy twice daily. (A) One year after 57 Gy, (B) 1.5 years after 51 Gy, and (C) 2 years after 51 Gy reirradiation.

experienced a low-grade brachial plexopathy. Ultimately, clinical judgment on a patient-by-patient basis is needed.

Proton therapy was employed for its ability to minimize the volume of overlap with prior radiation. Thus, highly conformal volumes were retreated without the moderate- and low-dose bath that conformal photon intensity modulated radiation therapy would otherwise produce. The disadvantages of proton therapy include distal range uncertainty coupled with the question of whether there is a higher relative biological effective dose at the distal edge of the Bragg peak.[19] These issues are particularly salient in light of the 6 (22%) patients with rib fracture. Although it is unknown if this is unique to proton reirradiation or of higher incidence than photon reirradiation, a recent phase II trial found that proton therapy in the adjuvant (nonreirradiation) setting for breast cancer was associated with a modestly higher rate of rib fracture compared with reports using photon radiation therapy.[20] We treated the majority of women with twice-daily proton reirradiation to 49.5 to 51 Gy in 1.5 Gy BID fractions. The use of smaller dose per fraction twice daily has been thought to be associated with a lower risk of late tissue toxicity, namely late fibrosis. This could be particularly important in the setting of reirradiation. From a radiobiology perspective, hyperfractionation has been used to address the rapid tumor growth rate in the setting of angiosarcoma and reirradiation after breast cancer.[15] We hypothesized that locally recurrent breast cancers may also harbor a more aggressive tumor biology and benefit from hyperfractionation, and delivery of dose in a shorter "dose-dense" time frame than a conventional 1.8 Gy per day over 7 weeks allows for a shorter time off of systemic therapy. However, this series is limited in size to determine whether hyperfractionation has superior outcomes vs conventional fractionation.

Reirradiation was reported by Wahl et al to be associated with very low grade 3 and 4 toxicity rates, <5% to 10%, as well.[8] Dose of reirradiation ≥45 Gy and interval between treatments ≥3 years was associated with improved disease-free survival. However, that study was unable to show a toxicity or disease-free survival benefit to hyperfractionation. In the present study, acute and late grade 3 or higher toxicities of 15% and 11%, respectively, are somewhat higher than those in Thorpe and colleagues' report of proton reirradiation.[9] Thorpe et al found that grade 3 or higher toxicities occurred only among patients receiving reirradiation to volumes including the internal mammary nodes,[9] in contrast to our finding that only 1 of 10 patients who received reirradiation to the internal mammary nodes experienced a grade 3 toxicity (acute dermatitis). Moreover, 2 of 4 acute and 2 of 3 late grade 3+ toxicities occurred in the same patient. This patient's clinical features differ from those of most patients in our series, as her first radiation course comprised a hypofractionated palliative regimen of 20 Gy in 4 Gy fractions to the spine and rib metastases, rather than initial breast or chest wall radiation. For her reirradiation course, she was 1 of 2 patients treated to a total dose of 60 Gy using 2.5 Gy daily hypofractionated protons, rather than 1.5 Gy BID protons. The acute and late toxicity rates among the remaining patients, as well as loco-regional recurrence rates, were comparable to those previously reported.[9]

Limitations of this study include its relatively small patient cohort that may be underpowered to find associations between treatment characteristics and observed toxicities. The patients comprising this cohort have heterogeneous initial disease characteristics, as well as varied initial surgical, systemic, and radiation treatment parameters. These patients, moreover, have heterogeneous recurrent disease characteristics, including patients with both isolated locoregional recurrence and locoregional recurrence in the setting of distant metastatic disease at the time of reirradiation. Due to this heterogeneity, survival outcomes should be interpreted with caution. Nonetheless, a strength of this study is the

Table 3

	Acute								Late							
	grade 1		Grade 2		Grade 3		Grade 4		grade 1		Grade 2		Grade 3		Grade 4	
Dermatitis	14	52%	8	30%	2	7%	-	-	5	19%	1	4%	1	4%	1	4%
Breast pain	9	33%	3	11%	2	7%	-	-	3	11%	1	4%	1	4%	-	-
Lymphedema	7	26%	-	-	-		-	-	8	30%	2	7%	-	-	-	-
Restricted motion	6	22%	1	4%	-		-	-	3	11%	-	-	-	-	-	-
Dysphagia/odynophagia/esophagitis	-	-	1	4%	-		-	-	-	-	1	4%	-	-	-	-
Fibrosis	2	7%	-	-	-		-	-	2	7%	1	4%	-	-	-	-
Brachial plexopathy	-	-	-	-	-		-	-	-	-	1	4%	-	-	-	-
Rib fracture	-	-	-	-	-		-	-	6	22%	-	-	-	-	-	-

relatively homogeneous reirradiation approach used. Moreover, this retrospective analysis relies on documented nurse- and physician-reported toxicities, as well as physician-recorded history and physical examination findings. Future work would be strengthened by a prospective study using a homogeneous dose for reirradiation, and relatively uniform eligibility criteria to receive reirradiation.

Conclusions

The present study results suggest that proton reirradiation to a median dose of 51 Gy in 1.5 Gy BID fractions confers acceptable risks of toxicity and excellent local-regional control. The primary mode of failure in this population was distant, suggesting improved systemic therapy is still needed. The low rate of grade 3 to 4 toxicity with the doses used in this experience suggests there may be a role for further dose escalation to 54 to 60 Gy in some patients with high-risk features or gross disease. Future work may further investigate reirradiation combined with targeted therapy or immunotherapy on a prospective clinical trial, a more homogeneous dose regimen, and longer follow-up of cosmetic (namely fibrosis) and brachial plexus toxicity.

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