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Intensity Modulated Proton Therapy for Re-Irradiation of Bulky Loco-Regional Recurrent Breast Cancer: A Case Report

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Abstract

Patients with recurrent breast cancer to chest wall, who had previous irradiation, are difficult to manage and have limited options. Several reports described the use of photon therapy, hyperthermia, and brachytherapy. This is a case report of a 72-year-old female with Stage IIIA (pT3N1M0) invasive ductal carcinoma of the right breast status post modified radical mastectomy. The patient developed recurrence to the chest wall and one internal mammary lymph node one year later. She received 3-D conformal photon radiation therapy for this recurrence. Two years later, she had progression of the recurrence at the right chest wall and axillary and internal mammary lymph nodes. She was treated with intensity modulated proton therapy (IMPT) for a total of 6600 cGy in 33 fractions. However, four months later, she was found to have biopsy-proven isolated metastatic disease at her right bicep, which was again treated with IMPT for a dose of 6000 cGy in 20 fractions. Proton beam therapy was used in this case to spare dose to the brachial plexus, heart and lung while optimally irradiating the recurrent tumors. At last follow up, the patient is alive and has been disease free for 39 months. This report describes the technique and dosimetry for this unique case, which also reviewed recent series of re-irradiation using proton beam.

Keywords

Proton Therapy, Breast Cancer, Re-Irradiation, Intensity Modulated Proton Therapy

1. Introduction

Many breast cancer patients receive radiation therapy as part of their initial treatment, either as part of breast conserving therapy or post-mastectomy radiation treatment to the chest wall and regional lymphatics due to high risk features. Despite increased local control rate with post-mastectomy radiation therapy when compared to no adjuvant radiation, some patients do experience loco-regional recurrence in the chest wall [1]. If the local recurrence is the only site of disease status post mastectomy, surgical resection is typically the first option for these patients, followed by systemic therapy. However, some patients are not surgical candidates due to either the tumor size and location or unlikely clear margins of resection. Many patients with loco-regional recurrences receive systemic therapy in order to treat presumed distant microscopic disease. While radiation therapy after resection of a local recurrence is considered a category 2A recommendation, use of radiation in patients who have previously been irradiated to the chest wall is not. Most re-irradiation for recurrent breast cancer has been done with electron or photon therapy in conjunction with hyperthermia as radio-sensitization [2]-[7]. This article describes a case report for a use of Intensity Modulated Proton Therapy (IMPT) for re-irradiation of a bulky loco-regional recurrence. Proton beam therapy (PBT) significantly reduces normal organ dose compared with photon or X-ray radiation therapy (XRT) such as 3-D Conformal Radiation Therapy (3DCRT) and Intensity Modulated (IMRT). Proton beams carry charged particles that deposit relatively low doses in the path proximal to the tumor and deposit most of their energy around the end of its path, called the Bragg peak, the depth of which is determined by the specific energy imparted to the protons, while the organs at risk (OARs) beyond the tumor receive very little dose. On the other hand, the interaction of an x-ray beam within tissue has a relatively superficial dose build-up region and then exponential reduction in dose. As such, PBT has the dosimetric advantage over XRT of reduced or complete lack of dose distal to the target. IMPT is an advanced form of PBT. Pencil beam scanning (PBS), also commonly referred to as intensity-modulated proton therapy (IMPT), is a modern PBT technique in which "spots" of protons are directed by steering magnets across multiple dose layers, achieving excellent conformality including proximal to the target.

2. Case Presentation

The patient is a 72-year-old female who was initially diagnosed with right breast cancer in June 2011 that showed invasive ductal carcinoma, with ER (+) 96%, PR (+) 9%, Her-2/neu borderline, and Ki-67 40%.

She underwent right modified radical mastectomy and ipsilateral lymph node dissection. Final pathology revealed a 6.8 cm invasive ductal carcinoma, Nottingham grade 3. Out of 13 nodes resected, there were two lymph nodes positive for metastatic disease with the largest focus measuring 3.5 cm. Three additional nodes contained scattered foci of cytokeratin positive cells. She was offered adjuvant therapy, but she declined at that time.

In December 2012, she felt a lump on the upper outer portion of her right chest wall. Ultrasound confirmed a 2.7 × 2.4 cm mass. Biopsy confirmed poorly differentiated invasive ductal carcinoma. She declined systemic therapy. Subsequently, she was seen by a surgeon and was told surgery was not an option. Six months later, computed tomography (CT) of her chest, abdomen, and pelvis demonstrated a 1.4 cm nodule in her right pectoralis muscle, a 1.7 cm nodule in the right internal mammary region, and no evidence of distant metastasis. She underwent an incomplete course of photon radiation treatment using three-dimensional conformal technique to the right axilla, right supra-clavicular region using AP/PA 6 MV photon fields. A 12 MeV electron appositional field was matched to the photon field to encompass the right internal mammary nodal metastasis. She received a total of 2340 Gray delivered in 13 fractions. At that time, she decided to stop the radiation treatment.

In late 2014, she started experiencing pain, right arm weakness and numbness, and with growing chest wall mass. She was found to have large recurrence to the right chest wall, axillary and internal mammary lymph node based on the PET/CT scan (Figure 1A and Figure 2A). Of note, there was no malignant disease in her right arm detected on clinical exam or via imaging (Figure 1B). Her CA27-29 was 678.9. She was evaluated by a surgeon, but she was told surgery was not an option. She declined systemic therapy.

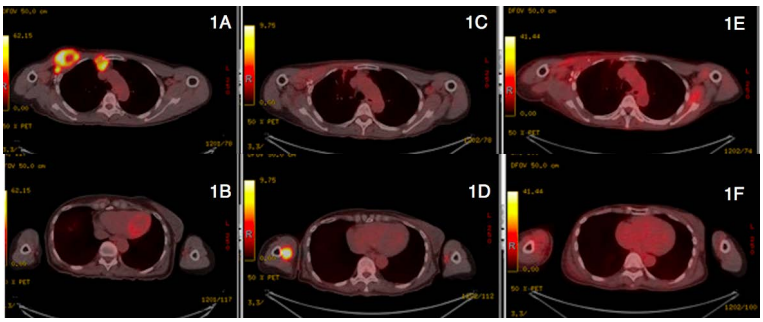


Figure 1. Axial views of the patient's PET/CT imaging before the first course of IMPT in March 2015 (1A & 1B), before the second course of IMPT in September 2015 (1C & 1D), and at most recent follow up in August 2018 (1E & 1F). PET: positron emission tomography. CT: computed tomography. IMPT: intensity modulated proton therapy.

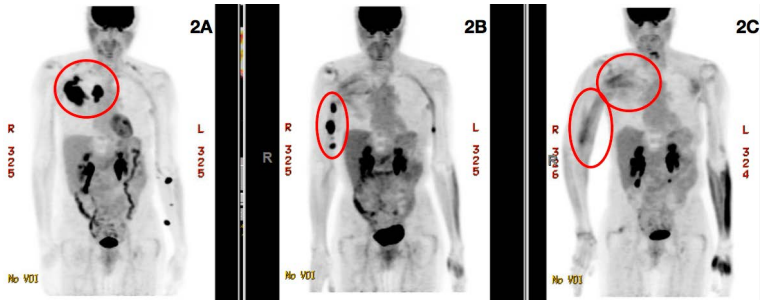


Figure 2. The patient's PET imaging before the first course of IMPT in March 2015 (2A), before the second course of IMPT in September 2015 (2B), and at her six-month follow up in March 2016 (2C). PET: positron emission tomography. IMPT: intensity modulated proton therapy.

Subsequently, she was seen at our center for evaluation of radiation therapy. She concurred the salvage proton therapy. The patient was set up in supine position, and she was immobilized with a Vac-Q-Fix cushion (Qfix, Avondale, PA) as shown in Figure 3. Four radiopaque non-metallic BBs were used on the patient's skin at stable areas, and these 4 areas were tattooed. These 4 BBs were used daily for image-guided radiation therapy (IGRT). A four-dimensional CT scan with Varian RPM system was done to measure chest wall motion with respiration, and it was minimal (less than 3 mm). Thus, no motion management was used. Then, three-dimensional CT imaging with 2.5 mm cuts was done for treatment planning.

The treatment plan was done on the Varian Eclipse Treatment Planning System (Varian Medical Systems, Palo Alto, CA). The tumor recurrences in the chest wall, axilla, and internal mammary nodes were contoured with normal structures (Figure 4). The previous treatment area was recreated. A single en-face beam with right anterior oblique direction with pencil beam scanning (PBS) protons was used to treat the disease as seen on PET and CT on the chest wall, as well as the right internal mammary nodes. The clinical target volume (CTV) was defined as the gross tumor volume (GTV) plus a 5 mm margin. Setup uncertainty of 5 mm and 3.5% range uncertainty were added to create the PTV (excluding skin and lung). Normal organs including the right brachial plexus, lung, heart, chest wall, and bone were contoured. A dose of 6600 cGy in 33 fractions was prescribed to the CTV. The dose to the brachial plexus was one of the main dose constraints. We acknowledged her previous radiation of 2340 cGy to her brachial plexus, but we assumed some tissue recovery after three years. However, due to clinical suspicion that her current tumor involved her brachial plexus, a small volume of the brachial plexus at the site of tumor invasion was allowed to reach a maximum cumulative dose of 6529 cGy.

Patient setup was checked daily using orthogonal kV images (Figure 5). The alignment was done using a combination of bony anatomy (right chest wall) and the four skin markers. Patient was seen weekly and had adaptive CT scan done every two weeks. After receiving her twenty-third fraction, tumor shrinkage was demonstrated which required re-planning to accommodate to the new geometry. This is shown in Figure 6.

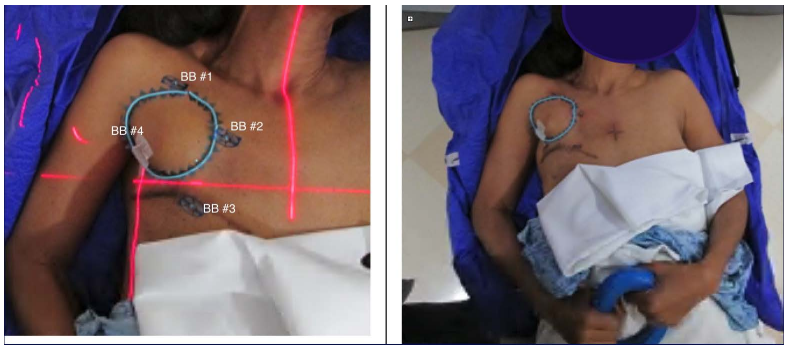


Figure 3. The patient was set up in supine position in a Vac-Q-Fix cushion. 4 radiopaque bb markers were used as "fiducial markers" at the tattooed marks.

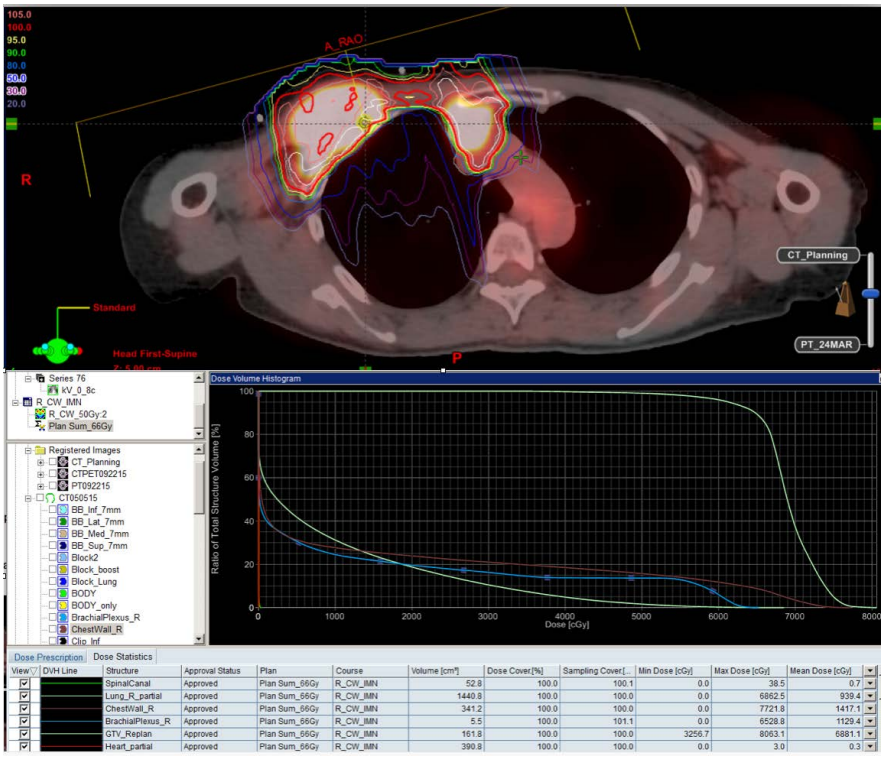


Figure 4. The treatment plan, dose volume histogram, and isodose for 66 Gy in 33 treatments to the recurrence to the chest wall.

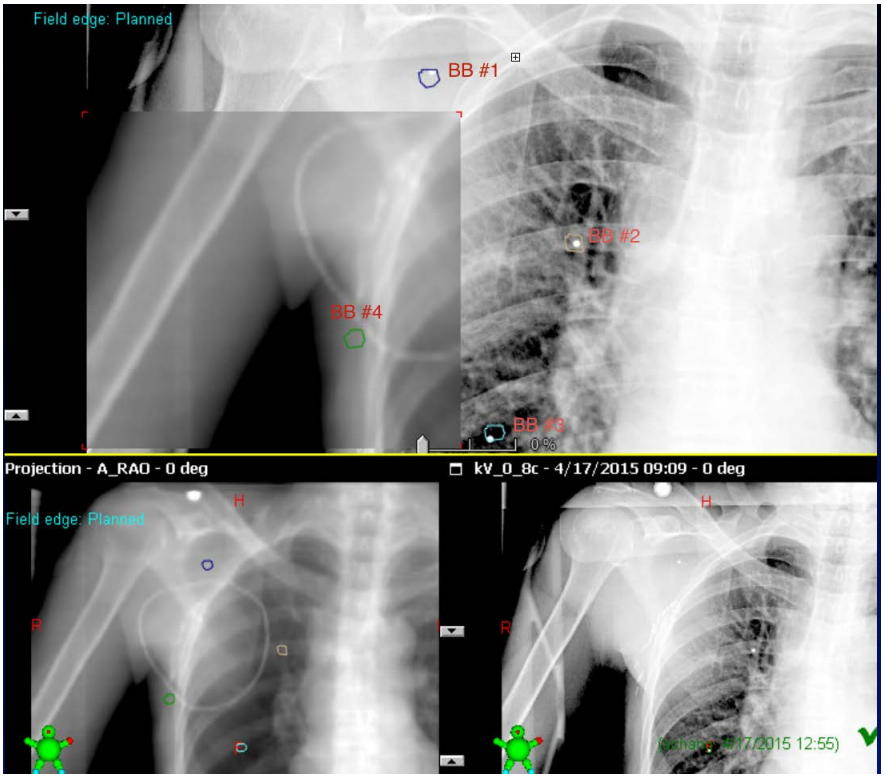


Figure 5. The patient setup was checked daily using orthogonal kV images. The alignment was done using a combination of bony anatomy (right chest wall) and 4 skin bb markers.

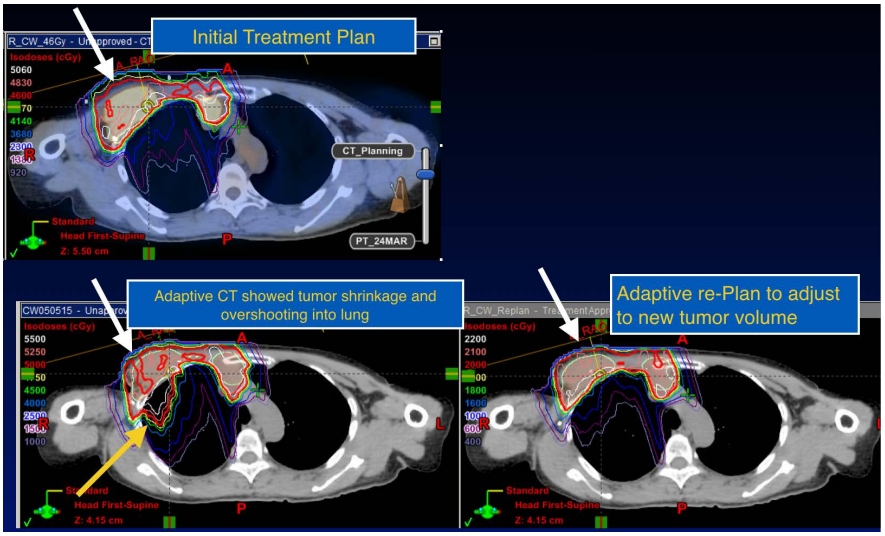


Figure 6. An adaptive CT scan at 4 weeks showed tumor shrinkage, which caused the dose to spill into the lung (yellow arrow). This was corrected with the replan to accommodate the new geometry. CT: computed tomography.

She completed her planned course of proton therapy in May 2015 for 6600 cGy in 33 treatments. She tolerated the treatment well, and she had relief of her chest wall pain and improvement in her right arm weakness. The main symptoms she experienced were mild fatigue and skin reaction (grade 2). A picture of her skin on the last day of treatment is shown in **Figure 7**.

She was subsequently monitored with clinical examination, blood work, and PET/CT. Approximately four months after her treatment, her CA27-29 decreased to 84.9. PET/CT imaging showed resolution of the right chest wall mass and internal mammary lymph nodes (**Figure 1C**). However, it revealed three new FDG-avid masses near her right bicep area or along the right forearm lymphatic channel as shown on **Figure 1D** and **Figure 2B**. These corresponded to new lumps on her medial right bicep area palpated on examination. This was biopsied and confirmed metastatic nodal disease with histology similar to her previous breast cancer recurrence.

Upon radiotherapeutic evaluation, several factors of her metastasis were considered, including that this was the only site of her disease and that there were no critical organs nearby except for the humerus. She received proton therapy to the right bicep area for a total dose of 6000 cGy delivered in 20 fractions from October 2015 to November 2015. The rationale to for hypo-fractionated treatment included consideration of her commute to treatment (she lived one hour away from the center), outside previous treatment field, as well as intent to provide higher radiobiological effect to the tumor. Her treatment plan and dose volume histogram are shown in **Figure 8** and **Figure 9**. She was treated using a single oblique field. Dose matching was done to avoid overlapping the previous proton therapy nearby at the axilla. The goals of the treatment were to minimize dose to the humerus, avoid the previous radiation area near the axilla, and avoid

treating the whole circumference of the right arm. She was set-up similarly to her previous proton treatment, except that the right arm was placed further away from her chest.

She tolerated the second course of proton therapy well with relief of her pain and resolution of the tumor as detected on PET/CT. At the end of treatment, she developed grade 2 right arm lymphedema, for which she received physical therapy and used compression stockings. She also experienced grade 2 skin reaction with 2 cm^2 skin breakdown at the axilla (field junction) that required topical and empirical antibiotics for a week.

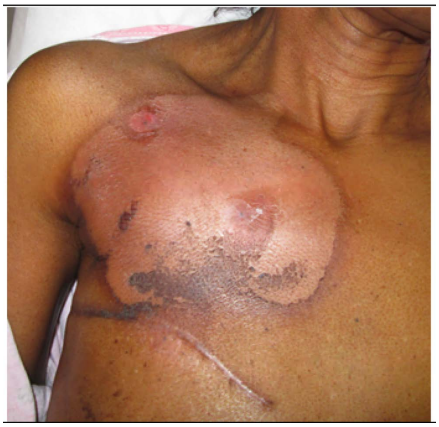


Figure 7. The patient's skin reaction on the last day of her treatment (Grade 2 toxicity).

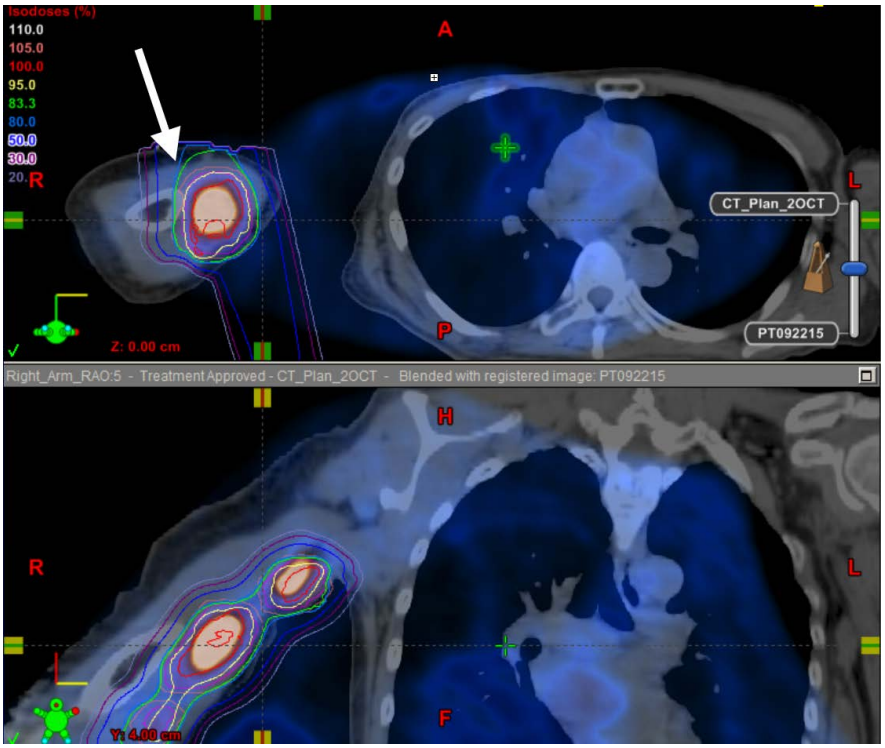
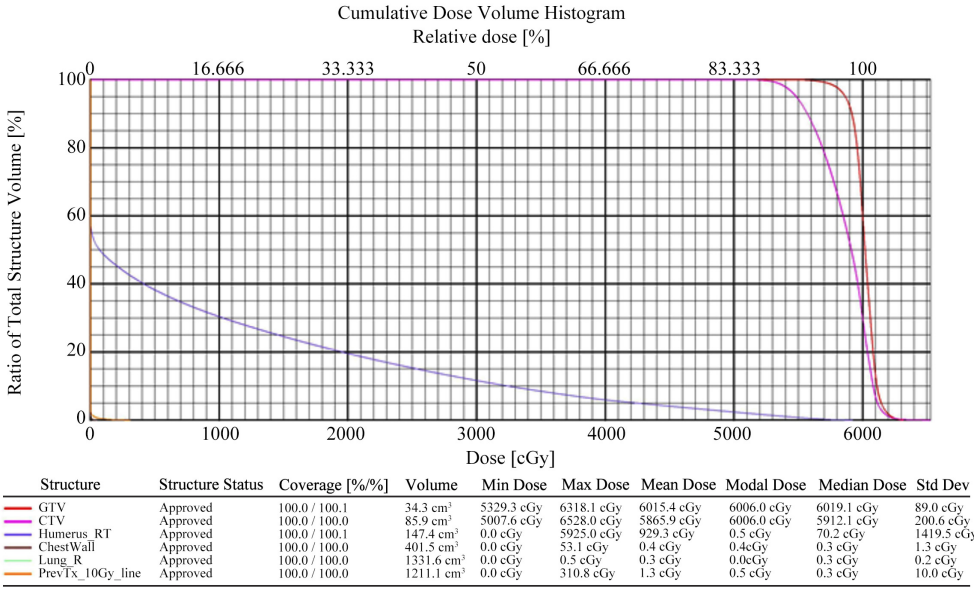


Figure 8. The white arrow points to the treatment plan isodose for the right arm/bicep area.



Structure	Structure Status	Coverage [%/%]	Volume	Min Dose	Max Dose	Mean Dose	Modal Dose	Median Dose	Std Dev
GTV	Approved	100.0 / 100.1	34.3 cm^3	5329.3 cGy	6318.1 cGy	6015.4 cGy	6006.0 cGy	6019.1 cGy	89.0 cGy
CTV	Approved	100.0 / 100.0	85.9 cm^3	5007.6 cGy	6528.0 cGy	5865.9 cGy	6006.0 cGy	5912.1 cGy	200.6 cGy
Humerus_RT	Approved	100.0 / 100.1	147.4 cm^3	0.0 cGy	5925.0 cGy	929.3 cGy	0.5 cGy	70.2 cGy	1419.5 cGy
ChestWall	Approved	100.0 / 100.0	401.5 cm^3	0.0 cGy	53.1 cGy	0.4 cGy	0.4cGy	0.3 cGy	1.3 cGy
Lung_R	Approved	100.0 / 100.0	1331.6 cm^3	0.0 cGy	0.5 cGy	0.3 cGy	0.0cGy	0.3 cGy	0.2 cGy
PrevTx_10Gy_line	Approved	100.0 / 100.0	1211.1 cm^3	0.0 cGy	310.8 cGy	1.3 cGy	0.5 cGy	0.3 cGy	10.0 cGy

Figure 9. The dose volume histogram for the treatment plan for the right arm/bicep area.

At her most recent follow-up in August 2018, which was about 39 months from completion of her first course of proton therapy treatment, patient is still alive without evidence of disease based on her PET/CT scan (**Figure 1E**, **Figure 1F**, and **Figure 2C**). Her CA27-29 as of August 2018 was 27.3, which decreased from 72.6 in August 2016. She still experienced grade 2 lymphedema for which she had occasional physical therapy and used compression stocking. Her right arm strength was 4/5. Her numbness was mild. She was able to complete her activities of daily living and other activities including as use of computer and writing. She had intermittently been taking hormonal therapy due to experienced side effects.

3. Discussion

Most patients who receive re-irradiation for recurrent breast cancer were treated with electrons or photons, mostly in conjunction with hyperthermia (HT) as radio-sensitization as shown in **Table 1** [2] [3] [4] [5] [6]. The largest series was reported by Linthorst *et al.* from the Netherlands for 248 patients treated with external beam radiation therapy (photon, electron, or combination) in conjunction with hyperthermia [4]. Patients were treated with 8 fractions of 4 Gy with 2 treatments per week for total of 32 Gy, given in conjunction with hyperthermia. With median follow-up of 32 months, they reported a complete response rate of 70%. The local control rate was 40% at 5 years. Median overall survival was 19 months, and overall survival rate of 32% at 3 years, 18% at 5 years, 10% at 10 years [4]. A recent meta-analysis of hyperthermia with radiation therapy for locoregional breast cancer recurrence showed that for a mean total radiation dose of 38.2 Gy, the addition of hyperthermia increased complete response by 22% (60% for radiation plus hyperthermia versus 38% for radiation alone) [7].

Table 1. Re-irradiation for recurrent breast with electron or photon, most in conjunction with hyperthermia as radio-sensitization (HT = Hyperthermia; EBRT = External Beam Radiation Therapy).

	Number of patients	Follow-up	Initial RT Dose (Gy)	Re-RT Dose (Gy)	Technique	Complete Response (%)	Grade 3 Toxicity (%)
Laramore *et al.* [2]	13	9 mo - 5 yr	40 - 50	40 - 50	Electron	61.5	0
Phromratanaponge *et al.* [3]	44	1 mo	35 - 66	16 - 56	EBRT + HT	40.9	25
Linthorst *et al.* [4]	248	32 mo	49	32	EBRT + HT	40 (5 yr)	1 (5 yr)
Oldenborg *et al.* [5]	78	64.2 mo	>50	32	EBRT + HT	78 (3 yr), 65 (5 yr)	32
Jones *et al.* [6]	52	2 - 9 yr		60 - 70	EBRT	42	2
Jones *et al.* [6]	56	2 - 9 yr		30 - 66	EBRT + HT	66	3

RT: Radiation therapy. HT: hyperthermia.

There are a couple of studies that support proton beam reirradiation for recurrent breast cancer. Gabani *et al.* reported the series of 16 patients at Washington University who underwent re-irradiation of local recurrent breast cancer with proton beam radiation therapy from 2013 to 2018 [8]. The median dose was 50.4 Gy in 28 treatments. The median number of years since previous radiation was 10.2 years. After a mean follow-up time of 19 months, 15/16 patients were still alive, no local failures and one distant metastasis. In terms of acute toxicities, 25% developed infection, 75% developed hyperpigmentation, Skin toxicity Grade 3 & 4 were about 30%. Late toxicities include Grade 3 & 4 fibrosis of 20%, pneumonitis of 12.5%, rib fracture, brachial plexopathy in 6%, lymphedema in 6%, and telangiectasia in 25%. The conclusion of the study was that re-irradiation with proton beam for recurrent breast cancer had acceptable toxicities with the given data, and future studies with larger sample sizes and longer follow-up times are needed.

Thorpe *et al.* reported a series of 50 patients from Proton Collaborative Group registry who had re-irradiation for recurrent breast cancer from 6 centers from 2011 to 2016. Median follow-up was 12.7 months with a median prior RT dose of 60 Gy and median time from previous radiation was 8.5 years. The median re-irradiation dose was 55.1 Gy (range 45 - 76). The cumulative total dose was 110 Gy. 30% of patients had gross disease. 84% of patients needed nodal re-treatment, of which 66% had internal mammary nodes (IMN) treated. The one year LRFS was 93% and overall survival was 97%. Grade 3 adverse effects were experienced by 16%, of which 10% early and 6% late. Grade 3 side effects were more in patients associated with a BMI > 30 kg/m^2 ($p = 0.04$), bilateral recurrence ($p = 0.02$), and bilateral retreatment ($p = 0.004$). There was no grade 4 or 5 toxicity. The conclusions of the study were that PBT was well tolerated with favorable local control, and grade 3 AEs were associated with BMI > 30, bilateral disease, and IMN retreatment. The authors concluded that re-irradiation with proton is feasible even with cumulative dose > 110 Gy, rate of severe toxicity is comparable to re-irradiation with non-proton technique, and good local control seen in patient without gross disease.

Over the last 3.5 years, we have re-irradiated over ten breast cancer patients who have had previous radiation therapy in or nearby the area [9]. The chest wall has the advantage of minimal motion, so there is less uncertainty with Intensity Modulated Proton Therapy (IMPT). For re-irradiation in breast and chest wall area, IMPT has the potential advantage of sparing low and intermediate dose to surrounding structures such as lung, heart, soft tissue, bone, and nerves. Another advantage of IMPT is the ability to deliver different doses to different regions within the target at the same time (simultaneous integrated boost). With IMPT, one can use one or two beams, which can minimize collateral low dose bath that is seen with intensity modulated radiation therapy and passive scatter proton therapy.

4. Conclusion

With careful planning and patient selection, intensity modulated proton therapy (IMPT) can be a useful modality for retreatment of the recurrent breast cancer. There is still a limited amount of data on the use of IMPT for re-irradiation for breast cancer. Hopefully, with more treatment centers opening with IMPT capability, a prospective clinical trial should be conducted to gain more experience and create guidelines for this new modality for re-treatment of recurrent breast cancer, perhaps exploring whether IMPT can be done in conjunction with hyperthermia and/or other radio-sensitizing or radio-protector agents.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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