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Original Article

Early outcomes of breast cancer patients treated with post-mastectomy uniform scanning proton therapy

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ABSTRACT

Background: Postmastectomy proton radiotherapy improves normal tissue sparing in comparison to photon-based approaches. Several studies have reported dosimetry comparison and tolerable acute toxicity profile with limited follow-up. We report our institutional experience of postmastectomy proton radiation including clinical efficacy and toxicities.

Methods: From December 2013 to February 2015, 42 consecutive patients who received mastectomy for non-metastatic breast cancer were treated with adjuvant chest wall and regional nodal proton therapy at a single proton center. 3D conformal uniform scanning with en face matching fields was used.

Results: The median follow-up among patients was 35 months (range 1–55 months). There was one local failure, zero regional nodal failure, and six distant failures. The 3-year rate of locoregional disease-free survival was 96.3%, metastasis-free survival was 84.1%, and overall survival was 97.2%. The only local failure event occurred on the chest wall within the radiation field, approximately 2.5 years after the completion of radiation. Skin dermatitis, fatigue, and esophagitis were the most common acute toxicity. All patients developed grade 1 or 2 acute skin toxicity and there was no grade 3 or 4 acute skin toxicity. Proton radiation is able to achieve excellent target coverage with median PTV V95 over 95% and heart sparing with median mean heart dose less than 1 Gy (RBE).

Conclusion: With close to three years of median follow-up, post-mastectomy proton radiation has shown excellent locoregional control rates and favorable toxicity profile. Long-term adverse effect of heart-sparing radiation will require longer follow-up time and randomized clinical trials.

Postmastectomy radiation therapy (PMRT) has consistently shown benefits in decreasing the risk of locoregional recurrence and increasing long-term breast cancer-specific survival and overall survival rates for high-risk node positive breast cancer [1–3]. A standard PMRT field includes chest wall and comprehensive coverage of the axillary and supraclavicular lymph nodes. The addition of internal mammary chain in the radiation field has been increasingly adopted and supported by data from randomized clinical trials [4–6].

Delivering PMRT with comprehensive nodal irradiation has been technically challenging especially for patients with left-sided disease and unfavorable chest anatomy. Without compromising target coverage, traditional techniques with three- to five-field can lead to significant radiation exposure to normal tissue such as heart, lung, and contralateral breast. Highly conformal techniques such as intensity modulated radiation therapy (IMRT) can improve target coverage, however it can lead to low dose radiation deposited widely in normal tissue. As the expected lifespan of breast cancer patients continues to rise, the importance of preventing long-term sequelae of radiation becomes more apparent. Several studies have shown increased risk of cardiovascular events associated with incidental radiation of the heart [7–9]. The effect appears to be associated more with radiation to the left breast compared to right breast [8], and positively correlated with mean radiation dose to the heart [10]. Radiation treatment is also associated with a small but significantly increased risk of secondary malignancy in radiation-treated compared to non-treated breast cancer patient [11–14]. Recent meta-analysis of over 40,000 women randomly allocated to breast cancer radiation versus no radiation had shown the risk of contralateral breast cancer, leukemia, lung cancer, esophageal cancer were all significantly elevated in patients who were allocated to the radiation arm [14]. The late toxicities and risk of secondary malignancy negatively influence the quality of life and may offset the benefit of PMRT.

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Postoperative proton therapy has shown dosimetric advantages in normal tissue sparing compared to photon-based approaches. Owing to the physical property of proton particles, proton radiation is able to deposit radiation dose to the target area with minimal to no exit dose. Prior studies have demonstrated the feasibility of postmastectomy proton radiation with well tolerated acute toxicity profile. A Phase I prospective clinical trial of 12 patients at Massachusetts General Hospital showed no grade 3 skin toxicity and average mean heart dose of 0.44 Gy (RBE) [15]. Our institution experience with postoperative proton radiation has similarly shown zero grade 3 skin toxicity and excellent target coverage with V95 > 96% and a mean heart dose of less than 1 Gy [16]. However, due to limited time elapsed since treatment, no clinical efficacy could be reported. In this report, we provide an update of our institutional experience of an expanded cohort of patients who received postmastectomy proton radiation, including clinical outcome, acute and late toxicities.

Methods and materials

Patient population

From December 2013 to February 2015, 42 consecutive patients with non-metastatic breast cancer and no history of prior radiation to the ipsilateral breast or chest wall were treated with mastectomy followed by adjuvant chest wall and regional nodal proton therapy at a single proton center. Patients were referred by surgeons or radiation oncologists or self-referred for concern over cardiac and pulmonary exposure to radiation. Patients were also eligible if they had prior mastectomy without adjuvant radiation and subsequently developed chest wall recurrence that was resected and treated with chest wall and regional nodal irradiation. Patients included in this study were not part of a randomized clinical trial comparing photon and proton radiation. Patient characteristics, acute and late toxicities, and disease failure rates were obtained from chart review.

Radiation therapy

Patients were simulated with a CT scan in the supine position with ipsilateral arm abducted above the head, immobilized with an alpha cradle. Clinical target volumes (CTV) and normal structures were contoured according to Radiation Therapy Oncology Group (RTOG) and Radiotherapy Comparative Effectiveness (RADCOMP) consortium guidelines [17,18]. Coverage of the internal mammary lymph nodes (IMN) was optional and performed at each physician's discretion. The delineation of IMN stops at the caudal border of third intercostal space, unless there is gross IMN involvement, in which case the delineation stops at the caudal border of the fourth intercostal space. Proton therapy was delivered with 3D conformal uniform scanning with en face matching fields. Deep inspiration breath hold or respiratory gating was not used. The current cohort of patients was treated prior to implementation of pencil beam scanning at our center. Relative biological effectiveness (RBE), the ratio of absorbed doses between two modalities to have the same biological effect, is generally considered to be 1.1 for protons compared to photons [19]. Typically, 50.4 Gy (RBE) was delivered to the chest wall and regional lymph nodes. In certain patients, a conedown off the regional lymph nodes after 45 Gy (RBE) and an additional 5.4 Gy (RBE) boost to the chest wall was given. Any additional boost to the involved lymph nodes, mastectomy scar, and/or tumor bed was used at the physician's discretion. Setup accuracy was confirmed with daily X-ray verification based on bony anatomy. A QA CT scan was done one week after initiating treatment. If there was significant variation in anatomy between simulation and treatment, patients were to be re-simulated and re-planned. Surface anatomy imaging for setup accuracy was not used. Patients were seen weekly while on treatment for symptom assessment.

Follow-up

Patients were seen for follow-up visit at one to two months after radiation therapy completion, and approximately every 6 months thereafter. Follow-up time is counted from the end of the treatment to the last encounter that documents patient's disease status. Acute and late toxicities were assessed using common terminology criteria for adverse events (CTCAE) version 4.0. Acute toxicity was defined by adverse events occurring less than 90 days from the completion of radiation treatment. Chronic toxicity was defined by adverse effects occurring more than 90 days after the completion of radiation. Digital photographs of chest wall were taken at baseline, weekly on treatment visits, and at each follow-up visit to document skin toxicity.

Statistical analysis

Kaplan–Meier actuarial cumulative rates of locoregional recurrence, distant metastasis, and overall survival were calculated. Analyses were performed in Stata software (StataCorp, College Station TX). All *P* values were two sided.

Results

Patient characteristics

Median age of patients included in this study was 47 (range 21–86) years (Table 1). The median follow-up time was 35 months (range 1–55 months). Neoadjuvant chemotherapy was given in 18 out of the 42 patients (43%) prior to surgery. For axillary lymph node staging and management, 33 patients (79%) had axillary

Table 1
Clinical, pathological, and treatment characteristics of the study population.

Patient characteristics	
Number of patients	42
Age (median, range)	46.5 (21–86)
Neoadjuvant chemotherapy	
Yes	18 (43%)
No	24 (57%)
IMN involvement	
Yes	4 (10%)
No	38 (90%)
Side of mastectomy	
Left side	36 (86%)
Right side	6 (14%)
Receptor type	
ER+	32 (76%)
PR+	26 (62%)
HER2+	9 (21%)
Axillary lymph node dissection	
Yes	33 (79%)
No, SLNB only	5 (12%)
No, no LN assessment	4 (10%)
IMN treated	
Yes	32 (76%)
No	10 (24%)
Reconstruction	
Yes	26 (62%)
No	16 (38%)
Type of reconstruction	
Implant	25 (96%)
Autologous	1 (4%)

IMN: internal mammary node; ER: estrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor receptor 2; SLNB: sentinel lymph node biopsy; LN: lymph node.

lymph node dissection, 5 patients (12%) had sentinel lymph node sampling only, and 4 patients (10%) did not receive nodal assessment at time of chest wall recurrence or prior nodal evaluation. All patients received radiation to the chest wall (with or without reconstruction) and regional lymph nodes. Thirty-six patients (86%) received radiation to the left side. The internal mammary chain was included in the radiation field in 32 patients (76%). Twenty-six patients (62%) had immediate reconstructive surgery at the time of mastectomy prior to radiation, with vast majority receiving implant placement (25 patients) and one patient with an autologous reconstruction.

Radiation treatment

Median dose of radiation administered was 50 Gy (RBE) (range 45–61.2 Gy (RBE)). Median PTV V95 was 95.9% (range 79.4–99.6%). The median mean heart dose for all patients was 0.7 Gy (RBE) (range 0–3.2 Gy (RBE)). For left sided breast cancer treatment, median mean heart dose was 0.84 Gy (RBE) (range 0–3.2 Gy) and for right sided breast cancer treatment was 0.07 Gy (RBE) (range 0–0.82 Gy). Median ipsilateral lung V20 was 16.1% (range 2.1%–30.3%) and ipsilateral lung V5 was 34.0% (16.4%–53.8%). Detailed dosimetry parameters are included in Table 2. No patient in this study required re-planning based on the QA CT obtained after initiating treatment.

Efficacy

With median follow-up period of 35 months, there was one local failure, zero regional nodal failure, and six distant failures. The 3-year actuarial rate of locoregional disease-free survival was 96.3%, metastasis-free survival was 84.1%, and overall survival was 97.2% (Fig. 1). The one local failure event occurred on the chest wall within the radiation field, approximately two and half years after the completion of radiation. The chest wall recurrence was subsequently resected with wide local excision, however the patient developed additional chest wall recurrences. In patients who developed distant metastatic disease, the median time interval between the completion of radiation to the development of distant disease was 11.7 months (range 0.6–14.6 months). The most common site of distant metastasis was liver which occurred in 4 patients, followed by brain metastasis in one patient, and spine metastasis in one patient. One patient died of metastatic disease since the completion of treatment.

Acute and chronic toxicities

Skin dermatitis, fatigue, and esophagitis were the most common acute toxicity (Table 3). All patients developed grade 1 or 2 acute skin toxicity. There was no grade 3 or 4 acute skin toxicity. Photos of acute and late skin reactions in patients without breast reconstruction, with implant reconstruction, and with implant reconstruction complicated by capsular contracture and revised with autologous reconstruction, are illustrated in Fig. 2. Nine patients (21%) developed moist desquamation and ten patients (24%) required narcotic medications for skin-related pain. One patient required 2 days of treatment break due to intolerance to dermatitis and skin pain. Another patient did not receive boost treatment due to concern of excessive skin toxicity. Twenty-one patients (50%) developed either grade 1 (33%) or grade 2 (17%) acute esophagitis.

In terms of late toxicity, seventeen patients (40%) developed grade 1 hyperpigmentation and one patient developed grade 1 telangiectasia. There was no grade 2 or above late skin toxicity. Out of the 26 patients who underwent immediate reconstruction, seven patients (27%) developed reconstruction complications. Six patients had capsular contractures and one patient had implant infection. Three patients had implant removed and underwent autologous reconstruction as an unplanned procedure, either due to capsular contracture (two patients), or implant infection (one patient). Two patients had revision surgeries without removal of the implants. Two patients had implants removed and were considering reconstruction options at the time of the last visit.

There was one case of pneumonitis: what could be a grade 3 radiation pneumonitis was observed in one patient (2%) one year after the radiation treatment. This patient had a history of radiation to the contralateral chest wall/nodes and stem cell transplant, and presented with shortness of breath that required temporary steroids and oxygen supplementation. She was subsequently diagnosed with early pulmonary fibrosis by a pulmonologist. There was no observed cardiac toxicity with no cardiac events or cardiac deaths. Late grade 1 lymphedema was observed in 12 patients, all of whom have had axillary lymph node dissection. Nine patients had pre-existing lymphedema either prior to radiation or within

Table 2
Dosimetry values of target and normal tissue.

	Dosimetry	Median	Max	Min
PTV	PTV V100	87.9%	97.2%	68.6%
	PTV V95	95.9%	99.6%	79.4%
	Max point dose (Gy (RBE))	58.8	70.5	51.0
	Max point dose (%)	115.2%	129.5%	95.1%
	PTV V110	11.0%	24%	1.4%
	IMN D95% (Gy (RBE))	46.0	40.7	53.8
Heart	Heart Mean dose (Gy (RBE))	0.7	3.2	0.0
	Heart V20	0.5%	6.0%	0.0%
	Heart V5	4.3%	16.2%	0.0%
	Heart Max point dose (Gy (RBE))	16.3	51.9	0.1
Lung	Lung V20	7.1%	19.1%	0.1%
	Ipsilateral Lung V20	16.1%	30.3%	2.1%
	Ipsilateral Lung V5	34.0%	53.8%	16.4%
	Contralateral Lung V5	0.3%	42.4%	0.0%
Contra breast	Contralateral Breast V5	1.8%	9.9%	0.0%
	Contralateral Breast Mean Dose (Gy (RBE))	0.3	3.5	0.0
Spinal cord	Spinal Cord Max point dose (Gy (RBE))	0.8	18.2	0.0
Esophagus	Esophagus Mean Dose (Gy (RBE))	7.5	26.9	0.0

PTV, planning target volume; MPD, maximum point dose; RBE: relative biologic effectiveness.

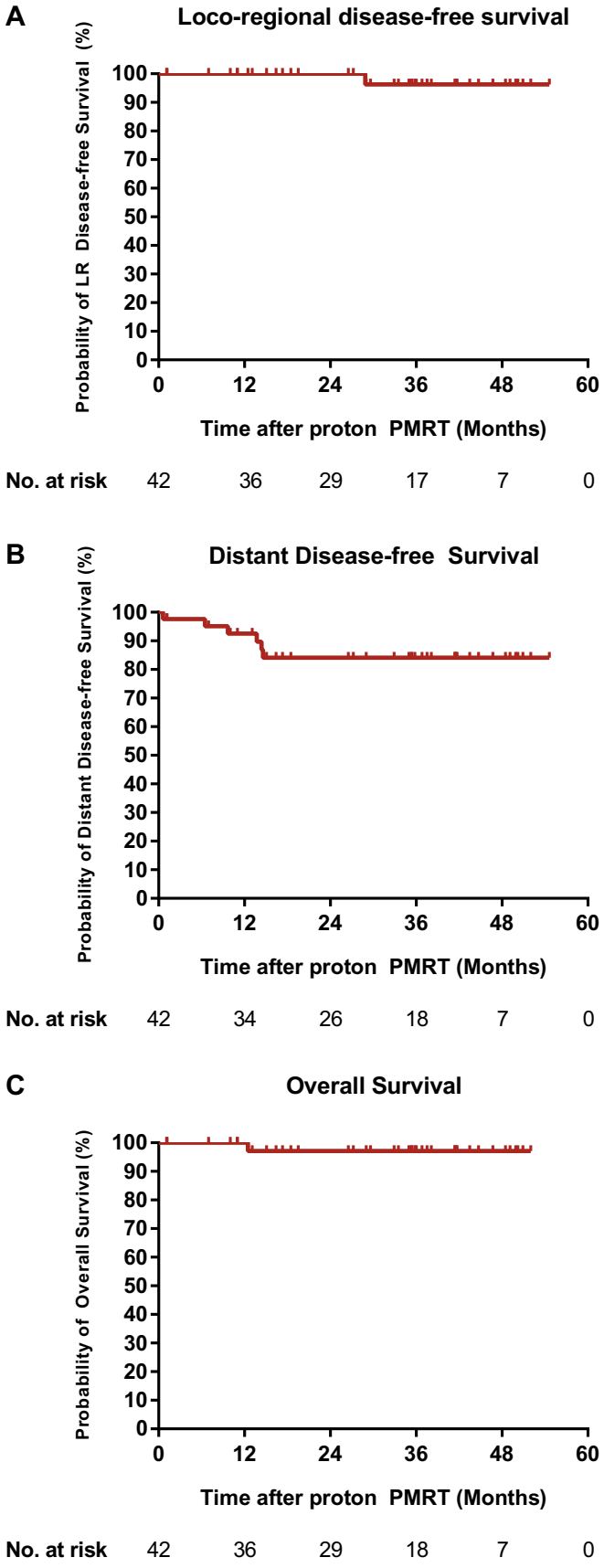

Fig. 1. Kaplan–Meier estimates of survival rates after postmatectomy proton radiation. (A) Locoregional disease-free survival. (B) Distant disease-free survival. (C) Overall survival.

3 months after completing radiation. No rib fracture or brachial plexus injury was observed.

Discussion

This study represents the longest follow-up of patients who received post-mastectomy proton radiation. Prior to this report, evidence for postoperative proton radiation is limited to small groups of patients with short follow-up times, published with the goal of demonstrating dosimetry, feasibility, and safety. Verma et al. recently reported on a combined 91 patients who received postoperative proton therapy after either lumpectomy or mastectomy with a median follow-up of 15.5 months [20]. Here we report the early clinical outcome of 42 patients treated with postmastectomy proton radiation to the chest wall and regional lymph nodes with a median follow-up time of 35 months, with >45% of patients having more than 3 years of follow-up. Reflecting the current trend in lymph node management, the majority of patients (76%) received treatment to the internal mammary chain. Despite this being a high risk group of patients, the 3-year locoregional control was excellent with <5% failure rate and 97% overall survival rate.

While proton therapy reduces organs at risk (OAR) exposure, there is still limited data that proton therapy results in equivalent disease control. Our study and Verma et al. both demonstrate local control rates of >95% in groups of patients with relative high risk for locoregional recurrence, which is comparable to historical controls. Results from the proton partial breast irradiation (PBI) trials with longer follow-up have also shown excellent local control rates [21,22]. Thus, the published literature suggests that disease control with proton radiation is similar to what is achieved with photon radiation, with no suggestion of increased marginal misses or underdosing as a result of uncertainties associated with proton therapy.

Proton radiation in this postmastectomy population was well tolerated. There were no grade 3 or 4 acute toxicities reported in this cohort. A third to one-half of the patients developed grade 1 late toxicity in the form of hyperpigmentation, telangiectasia, or fibrosis. There was no grade 2 or above late skin toxicity. Notably seven patients suffered from breast reconstruction complications requiring implant removal or under consideration for revision surgery. The risk of postoperative complication is known to be higher in post-reconstruction irradiated breast compared to non-irradiated breast or pre-reconstruction irradiated breast [23,24]. A "reconstruction failure" has been defined in the plastics surgery literature as removal of the implant followed by either flap reconstruction or no implant replacement [25]. Five patients in this study (19%) were considered to have reconstruction failures, three of whom had flap reconstruction and two others were deciding on reconstructive options. There has been an increasing trend in the use of autologous reconstruction as more plastic surgeons receive further training in microsurgery and express a preference for autologous reconstruction. With the recognition of evolving practice pattern and temporal biases, the failure rate of 19% in this study is similar to previously reported implant failure rate of 20% in a systemic review 977 breasts exposed to post-reconstruction irradiation [25]. When comparing across studies, institutions, providers, geography, and treatment era, it is important to remember that even something as seemingly objective as implant failure is not truly objective. Our reported failure rate also captures patients who electively had implant removal or replacement due to cosmetic preference unrelated to changes after radiation. Taking this all into consideration, it seems that reconstructive outcomes are comparable to other historical PMRT studies with photon radiation.

Table 3
Acute and chronic toxicities associated with post-mastectomy proton radiation.

Acute toxicity (<90 days)	Grade 1	Grade 2	Grade 3	Grade 4
Dermatitis	11(26%)	31 (74%)	0	0
Skin pain	5 (12%)	10 (24%)	0	0
Fatigue	12 (29%)	1 (2%)	0	0
Pneumonitis	0	0	0	0
Cardiac toxicity	0	0	0	0
Esophagitis	15 (36%)	7 (17%)	0	0
Lymphedema	8 (19%)	0	0	0
Chronic toxicity (>=90 days)	Grade 1	Grade 2	Grade 3	Grade 4
Dermatitis	14 (33%)	0	0	0
Skin pain	1 (2%)	0	0	0
Fatigue	0	0	0	0
Pneumonitis	0	0	1 (2%)	0
Cardiac toxicity	0	0	0	0
Esophagitis	1 (2%)	0	0	0
Lymphedema	12 (29%)	0	0	0

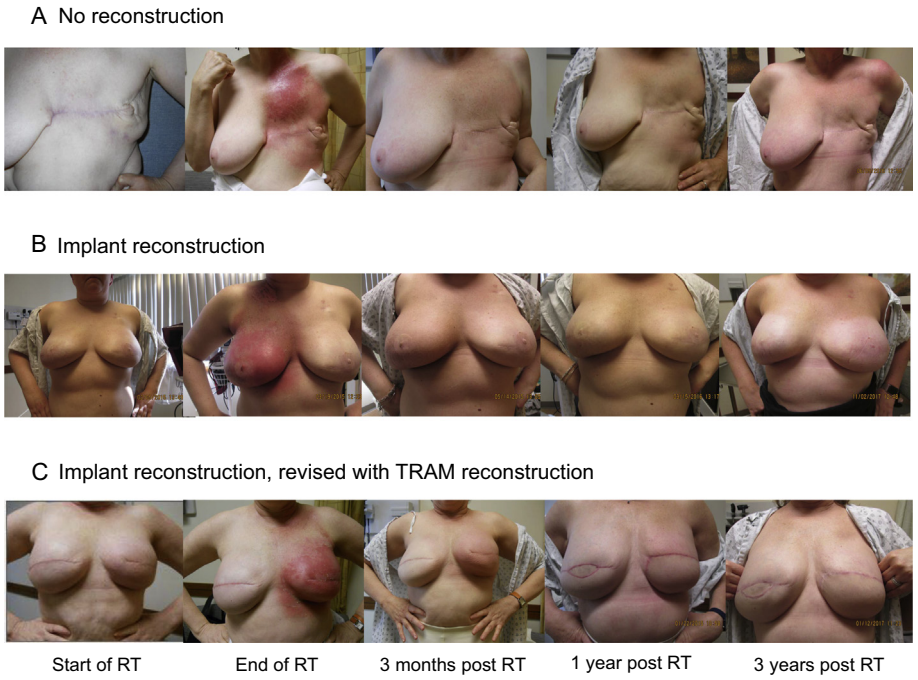

Fig. 2. Skin condition before, and reactions during and after postmastectomy proton radiation. (A) Patient with left chest wall radiation without reconstruction. (B) Patient with right mastectomy with implant reconstruction. (C) Patient with left mastectomy and implant reconstruction initially, developed capsular contracture and underwent bilateral autologous (TRAM) reconstruction 7 months after radiation.

Proton radiation planning is able to achieve excellent normal tissue sparing without compromising target coverage. In comparison with intensity-modulated radiation therapy plans, the dosimetry from this series significantly reduced the heart and lung exposure with median mean heart dose of 0.7 Gy. The reported mean heart dose from various breast IMRT techniques ranges from 2.6 Gy to 8.7 Gy [26–28]. Jagsi et al. compared four IMRT techniques and found the heart-blocked segmental technique produced the lowest average mean heart dose of 1.9 Gy [29]. The median cardiac exposure in this cohort is consistent with previously reported breast proton radiation dosimetry of mean heart dose less than 1 Gy (RBE) [15,30]. Photon radiation dose to the heart and lung has been reduced by modern techniques such as deep inspiratory breath hold (DIBH), where patients hold their breath during peak inspiration and create an anatomical separation of breast/chest wall and heart. Recent publication by Patel et al. from Massachusetts General Hospital showed that for left-sided PMRT, the benefit of cardiopulmonary sparing with protons with free-breathing remains significant when compared with photon treatment with DIBH technique [31].

There are several limitations of this study. Patients in our study were treated with en face uniform scanning (US) proton beams. Although US beam achieves the goal of adequate target coverage with minimal dose to the normal tissue, several aspects of the technique are less ideal. Compared to intensity modulated beams, US beams result in higher skin dose. Pencil beam scanning (PBS) technique allows modulation of the entrance dose and the dose proximal to the target, which results in lower skin dose and less skin toxicity. However, in the PMRT setting, where a high skin dose over the chest wall is necessary, the effect of the difference in skin dose achieved by US versus PBS is likely minimal. The majority of the proton centers being built today are almost exclusively using PBS, implying that US proton treatments will likely be phased out in the next few years.

The skin toxicity in our study was not significantly different than historical photon series and there was no grade 3 skin toxic-

ity. The cohort from Patel et al. had a higher incidence of acute dermatitis of US patients, which may be related to a different skin constraint or other differences in the treatment planning process [31]. It may also be explained by the retrospective nature of the study and toxicity may be underreported based on limited information available through chart review. Prospective studies have shown that even a small portion of postlumpetomy photon patients have grade 3 dermatitis and a significant portion of PMRT photon patients in a recent clinical trial at Memorial Sloan Kettering Cancer Center, suggesting that there is likely some degree of underreporting [32].

Our cohort excluded patients who underwent immediate reconstruction after mastectomy with tissue expanders containing metallic ports. Historically these patients are not candidates for proton radiation due to the uncertainty in delivered dose within the vicinity of high-density materials such as those contained in the filling port [33]. Recent reports have demonstrated the feasibility of using intensity modulated proton therapy (IMPT) to overcome this challenge [34,35]. Mutter et al. used 2-field IMPT in 12 patients who had tissue expander reconstruction and showed small and acceptable dose uncertainties to target and organ at risk [34]. This technique has been adopted at our treatment facility.

Lastly, the study has limited follow-up period particularly for the purpose of observing any late side effects of postmastectomy radiation. Clinical manifestations of long-term adverse effects such as major cardiovascular events, brachial plexus injury, and secondary malignancy take many years to decades to occur [10]. Currently there has not been any clinical report of reduced cardiac toxicity observed with proton radiation and the documented advantages of proton radiation remain dosimetric. Therefore, long-term follow-up is needed to reveal whether dosimetric advantage of proton radiation in heart sparing can translate to a lower risk of heart disease and thereby improve the therapeutic ratio. A prospective randomized trial comparing the effectiveness of proton versus photon therapy, RTOG 3510 (RADCOMP trial), is underway and will provide high quality evidence on the effect of proton radiation in reducing major cardiovascular events. The study will need to accrue approximately 1700 patients over five years to detect a 40% reduction in cardiovascular events. Secondary endpoints of the trial include disease control, cosmetic outcomes, skin toxicity, and other late effects.

In conclusion, the study represents the longest known follow-up of patients who received postmastectomy proton radiation to the chest wall and regional lymph nodes. Proton radiation achieved a 3-year locoregional control rate of 96% and overall survival rate of 97%. Toxicity with a median follow-up of 3 years was minimal and compared favorably to historical controls. Compared to a photon-based approach, proton radiation is able to significantly reduce the radiation dose to heart and lung without compromising target coverage, especially in patients with challenging chest anatomy and in the era of increasing internal mammary node treatment. The cardiopulmonary sparing achieved with proton therapy in this paper is superior to what has been reported with photons. The study cohort is limited to patients treated with traditional uniform scanning proton beams and patients without tissue expanders with metallic ports. Long-term adverse effect of heart-sparing radiation will require longer follow-up time and randomized clinical trials such as the ongoing RTOG 3510 (RADCOMP trial).

Conflict of interest statement

We confirm that all named authors have no conflicts of interest to disclose and have all contributed to and reviewed the manuscript with agreement on the content.

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