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Reconstructive complications and early toxicity in breast cancer patients treated with proton-based postmastectomy radiation therapy

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Background: Postmastectomy radiation therapy (PMRT) decreases the risk of locoregional recurrence and increases overall survival rates in patients with high-risk node positive breast cancer. While the number of breast cancer patients treated with proton-based PMRT has increased in recent years, there is limited data on the use of proton therapy in the postmastectomy with reconstruction setting. In this study, we compared acute toxicities and reconstructive complications in patients treated with proton-based and photon-based PMRT.

Methods: A retrospective review of our institutional database was performed to identify breast cancer patients treated with mastectomy with implant or autologous reconstruction followed by PMRT from 2015 to 2020. Baseline clinical, disease, and treatment related factors were compared between the photon-based and proton-based PMRT groups. Early toxicity outcomes and reconstructive complications following PMRT were graded by the treating physician.

Results: A total of 11 patients treated with proton-based PMRT and 26 patients treated with photon-based PMRT were included with a median follow-up of 7.4 months (range, 0.7-33 months). Six patients (55%) in the proton group had a history of breast cancer (3 ipsilateral and 3 contralateral) and received previous RT 38 months ago (median, range 7-85). There was no significant difference in mean PMRT ($p = 0.064$) and boost dose ($p = 0.608$) between the two groups. Grade 2 skin toxicity was the most common acute toxicity in both groups (55% and 73% in the proton and photon group, respectively) ($p = 0.077$). Three patients (27%) in the proton group developed grade 3 skin toxicity. No Grade 4 acute toxicity was

reported in either group. Reconstructive complications occurred in 4 patients (36%) in the proton group and 8 patients (31%) in photon group ($p = 0.946$).

Conclusions: Acute skin toxicity remains the most frequent adverse event in both proton- and photon-based PMRT. In our study, reconstructive complications were not significantly higher in patients treated with proton- versus photon-based PMRT. Longer follow-up is warranted to assess late toxicities.

KEYWORDS

carcinoma, mastectomy, proton, radiotherapy, breast

Introduction

The clinical indication for proton-based radiation therapy (RT) continues to grow for treatment of various cancers. This is mainly due to the dosimetric benefits of proton-based RT which includes a low to medium entrance dose and homogenous dose distribution within the target (1–3). In addition, protons have a steep fall-off to zero dose distally to the target, known as Bragg peak, resulting in a significant normal tissue sparing, which may potentially decrease the risk of toxicity. Although these unique characteristics of protons support its use, the clinical significance of proton-based RT has not been clearly demonstrated in breast cancer patients. The RADCOMP trial is currently investigating the efficacy and cardiovascular benefits of proton-based RT in patients with non-metastatic breast cancer.

Adjuvant RT is an important component in the multidisciplinary management of breast cancer patients. In the setting of post-mastectomy, patients with high-risk node positive breast cancer often receive adjuvant RT. Postmastectomy radiation therapy (PMRT) decreases the risk of locoregional recurrence and increases overall survival rates in patients with locally advanced disease as demonstrated in multiple randomized trials, as well as the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis (4–7). More recently, with the increase in number of proton centers, the number of breast cancer patients treated with proton-based PMRT has increased. However, there is limited data on the use of proton therapy in the postmastectomy with reconstruction setting.

Given its significant impact on quality of life, identifying the risk factors for acute toxicities and reconstruction outcomes after PMRT is crucial. In this study, we compared acute toxicities and reconstructive complications in postmastectomy patients with implant or autologous reconstruction treated with proton-based PMRT and photon-based PMRT.

Materials and methods

A retrospective review of our institutional database was performed to identify breast cancer patients treated with adjuvant proton or photon therapy. Patients were eligible for this study if they had mastectomy with implant or autologous reconstruction and underwent radiation therapy. Patients who underwent breast-

conserving surgery and those who had mastectomy without reconstruction were excluded.

Baseline clinical characteristics were collected and included patient age, race, body mass index (BMI), history of smoking, diabetes, history of prior breast cancer and treatment received. Disease-related characteristics including histology, hormone receptor status, AJCC T stage, and AJCC N stage were also recorded. Treatment related factors included type of breast reconstruction (implant vs. autologous), receipt of chemotherapy (neoadjuvant vs. adjuvant chemotherapy), hormonal therapy, and adjuvant radiation therapy (proton- vs. photon-based PMRT).

Early toxicity outcomes (fatigue, dermatitis, pain, and esophagitis) were graded by the treating physician during the treatment course using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. Minor reconstruction complications included infection resolved with oral antibiotics, Baker grade ≤ 2 capsular contracture, or fat necrosis without need for revision. Major reconstruction complications included infection or exposure of implant requiring IV antibiotics and/or operation, Baker grade ≥ 3 capsular contracture or fat necrosis requiring revision.

Baseline characteristics between the two groups were compared using the Chi-squared or Fisher exact test for categorical variables and a t-test for metric variables. Statistical analyses were performed using SPSS statistical software version 25 (IBM Corp., Armonk, NY, USA).

Results

Eleven patients treated with proton therapy and 26 patients treated with photon therapy were included. Baseline patient characteristics are shown in Table 1. Median follow-up was 7.4 months (range, 0.7–33 months). There was no significant difference in age ($p = 0.973$), race ($p = 0.405$), laterality ($p = 0.389$), histology ($p = 0.118$), BMI ≥ 30 ($p = 0.583$), history of smoking ($p = 0.228$) and diabetes ($p = 0.348$) between the two groups. Six patients (55%) in the proton group had a history of breast cancer, of which 3 had ipsilateral and 3 had contralateral disease treated with radiation. For the three patients with a history of prior ipsilateral radiation therapy, all three patients had implant reconstruction in place at the time of proton radiation therapy. Each patient was treated with conventional fractionation in 1.8 Gy per fraction to a total dose of 4,320 to 5,750

TABLE 1 Baseline characteristics.

	Proton	Photon	p
Patient, n	11	26	
Age at diagnosis			
Mean, years	49.3	49.2	0.973
Race, n (%)			0.405
White	10 (91)	19 (73)	
Black or African American	1 (9)	4 (15)	
Asian	0	3 (12)	
Breast laterality, n (%)			0.389
Left	8 (73)	15 (58)	
Right	3 (27)	11 (42)	
Histology, n (%)			0.118
Invasive ductal carcinoma	11 (100)	21 (82)	
Invasive lobular carcinoma	0	5 (18)	
AJCC clinical T stage, n (%)			0.472
T1	2 (18)	4 (15)	
T2	6 (55)	8 (31)	
T3	2 (18)	11 (42)	
T4	1 (9)	3 (12)	
AJCC clinical N stage, n (%)			0.183
N0	3 (27)	2 (8)	
N1	4 (37)	15 (58)	
N2	3 (27)	3 (12)	
N3	1 (9)	6 (22)	
Receptor status, n (%)			
Estrogen receptor-positive	5 (45)	16 (62)	0.367
Progesterone receptor-positive	5 (45)	17 (65)	0.259
HER2/neu-amplified	3 (27)	6 (22)	0.267
History of smoking, n (%)	2 (18)	10 (38)	0.228
Diabetes, n (%)	2 (18)	2 (8)	0.348
BMI \geq 30, n (%)	4 (37)	12 (46)	0.583
History of breast cancer, n (%)	6 (55)	0	<0.001
Ipsilateral, n (%)	3 (27)		
Treated with radiotherapy, n (%)	6 (55)	N/A	
Time since completion of radiotherapy			
Median, months (range)	38 (6.7-85.2)	N/A	
Follow-up			0.342
Median, months (range)	9.1 (2-29)	6.7 (0.7-33)	

BMI, Body mass index.

cGy. The chest wall and axilla were treated in all three patients. The patient treated to 5,750 cGy had mild late contracture; the other two patients had no late toxicity after proton radiation therapy. The median time between previous radiation and second course of RT was 38 months (range 7-85).

There was no difference in reconstruction types between the groups ($p = 0.786$). Treatment-related characteristics are shown in Table 2. The most common reconstruction type was implant (73% in proton and 77% in photon group). There was no significant difference in the mean PMRT dose (4797 cGy and 4986 cGy, $p = 0.064$) and boost dose (948 cGy vs 1033 cGy, $p = 0.608$) in the proton vs photon groups, respectively.

Treatment related toxicities are shown in Table 3. Grade 2 skin toxicity was the most common acute toxicity in both groups (55% in proton and 73% in photon) ($p = 0.077$). Three patients (27%) in the proton group developed Grade 3 skin toxicity. Grade 2-3 pain was reported by 45% of patients in the proton group while only Grade 2 pain was reported by 27% patients in the photon group ($p = 0.077$). Grade 2 fatigue was significantly higher in the proton group (45% vs 12%, $p = 0.035$). No Grade 4 acute toxicity was reported in either group. There was no significant difference in reconstructive complications between the groups (36% in proton vs 31% photon group, $p = 0.946$).

Discussion

Within a cohort of breast cancer patients treated with proton-based PMRT, we noted acceptable rates of acute toxicities and

reconstructive complications that are not significantly higher compared to patients treated with photon-based PMRT.

Evaluation of the success of the breast reconstruction following PMRT is an important aspect of the treatment outcome. Photon-based PMRT to the reconstructed breast has a complication rate of 35%, including a Baker III or IV contracture rate of 38% in implant-based reconstructions (8, 9). Consensus guidelines regarding radiation therapy in the context of breast reconstruction provide important guidance for radiation oncologists (10). However, the data on reconstructive complications following proton-based PMRT, the subject of the present study, remains limited. Several prior small studies have investigated this topic. In a small study by Luo et al. including 27 patients treated with proton-based PMRT, reconstructive complications occurred in 27% including six patients with capsular contractures and one patient with implant infection (11). Similarly, Smith et al. reported a 39% reconstruction complication rate in 42 patients following proton-based PMRT (12). In a recent study by Naoum et al. proton-based PMRT significantly increased overall reconstruction failure when compared photon-based PMRT (53% vs 43%, p -value = 0.004) (13). In our study, the reconstruction complication rate was 36% following proton-based PMRT, which is comparable to the rates reported in prior studies, and not significantly different when compared to patients treated with photon-based PMRT.

A better understanding of the risk of complications might impact the decision on when to use proton-based therapy. Similar to the incidence of reconstruction complications, no significant difference in acute skin toxicity and pain was noted between the treatment groups. However, grade 3 skin toxicity was only reported in patients treated with proton-based PMRT. This is likely due to the increased skin

TABLE 2 Treatment-related characteristics.

	Proton (n:11)	Photon (n:26)	<i>p</i>
Type of breast reconstruction, n (%)			0.786
Implant	8 (73)	20 (77)	
Autologous	3 (27)	6 (23)	
Systemic therapy			
Chemotherapy ^a			0.033
Neoadjuvant	3 (27)	18 (69)	
Adjuvant	8 (73)	7 (27)	
Trastuzumab	4 (36)	5 (19)	0.226
Endocrine therapy	4 (36)	18 (69)	0.063
Radiation therapy parameters			
Mean dose (cGy)	4797	4986	0.064
Fraction number, mean	25	25	0.668
Boost, n (%)	4 (36)	18 (69)	0.063
Mean dose (cGy)	947.5	1033.3	0.608
Radiation Field Design			0.005
3-4 fields ^b	7 (64)	26 (100)	

^aOne patient in photon group did not receive chemotherapy.

^bSupraclavicular field with or without a posterior axillary boost.

TABLE 3 Treatment related toxicities.

	Proton (n:11)	Photon (n:26)	p
Dermatitis, n (%)			0.077
Grade 2	6 (55)	19 (73)	
Grade 3	3 (27)	0	
Pain, n (%)			
Grade 2	3 (27)	7 (27)	0.077
Grade 3	2 (18)	0	
Fatigue, n (%)			
Grade 2	5 (45)	3 (12)	0.035
Esophagitis, n (%)			
Grade 2	1 (9)	0	
Reconstructive complication, n (%)			0.946
Minor ^a	1 (9)	2 (8)	
Major ^b	3 (27)	6 (23)	

^aMinor = infection resolved with po antibiotic, Baker grade ≤ 2 capsular contracture, or fat necrosis without need for revision.

^bMajor = infection or exposure of implant requiring IV antibiotic and/or operation, Baker grade ≥ 3 capsular contracture or fat necrosis require revision.

surface dose with proton therapy. Better understanding the proton treatment planning and improvement in treatment delivery techniques such as pencil beam versus scattered beams can help improve the acute toxicity outcomes.

Limitations of our study include its small sample size, retrospective design, and inherent confounding factors that cannot be completely accounted for in a non-randomized study. In addition, another limitation is the lack of assessment of the cosmetic outcome which is an important part of the treatment success. An additional limitation is that the small sample size of the present study limited any meaningful analysis of the impact of implant size on toxicity. Furthermore, the definition of reconstruction complication and assessment is not universally agreed upon which limits the external validity when results are compared with published studies.

In patients with a history of thoracic irradiation, challenging anatomies, or left-sided disease requiring nodal irradiation, proton therapy can provide significant advantages. However, the benefits of proton-based PMRT must be weighed against its potential complications.

Conclusions

Our study reported similar rates of reconstructive complications and physician-reported toxicity in patients treated with proton-based and photon-based PMRT. Grade 3 skin toxicity was higher in the proton-based PMRT group. Despite being well tolerated, the benefit of proton-based PMRT is still investigational. For patients with left-side breast disease, challenging anatomies or history of previous radiation, proton-based PMRT is beneficial based on small retrospective studies while awaiting the results of the RADCOMP trial which will provide a better insight into the clinical benefits of proton therapy.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Rutgers Cancer Institute of New Jersey. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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