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Running title: Clinical lymphedema with proton-based RT

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Abstract

Background: The purpose of this study was to evaluate the incidence of clinical lymphedema following adjuvant proton-based radiotherapy (RT) in breast cancer (BC) patients.

Materials and methods: We performed a retrospective review of our institutional database to identify BC patients treated with adjuvant proton-based RT. Patients receiving re-irradiation for a BC recurrence or those with a history of ipsilateral chest wall radiation were excluded. Clinical lymphedema was determined by documentation in the chart at baseline and during follow-up.

Results: We identified 28 patients treated with adjuvant proton-based RT who met the study criteria. Median age at diagnosis was 45 (range, 24–75). Eleven patients (39%) underwent

mastectomy, and fourteen (50%) underwent axillary lymph node dissection (ALND). Median number of LNs removed was 6 (range, 1–28). Nineteen patients (68%) received neoadjuvant chemotherapy. Median whole breast/chest wall dose delivered was 50 Gy (range, 44–54.0 Gy). Target volumes included the axillary and supraclavicular lymph nodes in all patients and internal mammary lymph nodes in 27 (96%) patients. Mean dose to the axilla was 49.7 Gy, and mean dose to 95% of the axillary volume (D95) was 46.3 Gy (94% of prescription dose). Mean dose to supraclavicular (SCV) volume was 47.7 Gy, and D95 was 44.1 Gy (91% of prescription dose). Grade 3 dermatitis occurred in 14% of patients. Five patients (18%) had clinical lymphedema, 4 from the ALND subset (n = 14).

Conclusions: The incidence of clinical lymphedema after proton-based RT is comparable to rates reported with photon-based RT with comprehensive nodal coverage.

Key words: breast; carcinoma; lymphedema; proton; radiotherapy

Introduction

The clinical application of *proton*-based radiation therapy (RT) for the treatment of various cancers is growing. The dosimetric benefits of proton-based RT includes a low to medium entrance dose, homogeneous dose distribution in the target area, and a steep fall-off to zero dose distally to the target, resulting in a significant normal tissue sparing [1–3]. While these dosimetric findings support the use of proton-based RT, the clinical significance of these theoretical benefits over *photon*-based RT has not been clearly demonstrated in BC patients. Phase I and II studies of proton-based RT for adjuvant treatment of BC have suggested comparable acute toxicity rates and disease control to photon-based RT, but long-term results with regard to late cardiovascular events have not yet been reported [4]. The RADCOMP trial is currently comparing the effectiveness of proton-based RT vs. photon-based RT in reducing major cardiovascular events in non-metastatic BC patients.

Lymphedema is a major complication of BC treatment that occurs in 10–30% of BC survivors and can significantly compromise quality of life [5]. Lymphedema is characterized by protein-rich fluid accumulation in the interstitial spaces of the ipsilateral upper extremity, resulting in swelling, fibrosis, and functional limitation [6]. Prior studies have identified several risk factors for the development of lymphedema, such as axillary surgery, number of lymph nodes removed,

receipt of chemotherapy, receipt of photon-based RT, and elevated BMI [5, 7–9]. However, there is limited data on the incidence of clinical lymphedema following adjuvant proton-based RT.

Given its significant impact on quality of life, it is important to investigate additional risk factors for the development of clinical lymphedema. Higher rates of clinical lymphedema in patients with BC treated with proton-based RT would potentially obviate any cardiovascular toxicity benefit of proton-based RT and would necessitate reconsideration of the utility of further study of proton-based RT vs. photon-based RT in these patients. In this study, we report incidence of clinical lymphedema following adjuvant proton-based RT.

Materials and methods

We performed a retrospective review of our institutional database to identify BC patients treated with adjuvant proton-based RT from 2015 to 2020. Patients receiving re-irradiation for a BC recurrence or those with a history of ipsilateral chest wall radiation were excluded. The treatment was delivered using a Mevion S250™ double-scattering proton accelerator (Mevion, Littleton, MA, USA).

Baseline clinical characteristics were collected and included patient age, smoking history, and body mass index (BMI). Disease-related characteristics included histology, American Joint Committee on Cancer (AJCC) T stage, and AJCC N stage. Treatment-related factors included receipt of chemotherapy (adjuvant or neo-adjuvant), type of surgery, and receipt of adjuvant radiation therapy.

The primary outcome of this study was incidence of clinical lymphedema. Secondary outcomes were other non-lymphedema acute RT toxicities.

Early toxicity outcomes 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. Clinical lymphedema was determined by documentation in the chart at baseline and during follow-up. Dose-volume histograms (DVHs) were reviewed to obtain dosimetry data. Patient, disease, and treatment related factors were compared using the Chi-squared, Fisher’s exact, and independent t-tests. Statistical analyses were performed using SPSS statistical software version 25 (IBM Corp., Armonk, NY, USA).

Results

We identified 28 patients treated with adjuvant proton-based RT who met the study criteria. Baseline patient characteristics are shown in Table 1. Median age at diagnosis was 45 (range, 24–75). Median body mass index (BMI) was 27 (range, 20–38). Five patients (18%) had a history of diabetes and six patients (21%) smoking. Twenty-four patients had T1-2 primary tumors (86%), twenty-five (89%) were node-positive, and nineteen (68%) had left-sided tumors. Eleven patients (39%) underwent mastectomy, and fourteen (50%) underwent axillary lymph node dissection (ALND). Median number of LNs removed was 6 (range, 1–28). Nineteen patients (68%) received neoadjuvant chemotherapy (Tab. 2).

Five patients (18%) had clinical lymphedema, 4 from the ALND subset (n = 14). Median whole breast/chest wall dose delivered was 50 Gy (range, 44–54.0 Gy). Target volumes included the axillary and supraclavicular lymph nodes in all patients and internal mammary lymph nodes in 27 (96%) patients. Twenty-two patients (79%) received a lumpectomy/scar boost with a median dose of 10Gy (range, 6–14 Gy). Mean dose to the axilla was 49.7 Gy, and mean dose to 95% of the axillary volume (D95) was 46.3Gy (94% of prescription dose). Mean dose to the supraclavicular (SCV) volume was 47.7 Gy, and D95 was 44.1 Gy (91% of prescription dose).

CTCAE grade 2 dermatitis occurred in nineteen patients (68%) and grade 3 in four patients (14%) (Tab. 3). One patient developed acute esophagitis. Median follow-up was 24 months (range, 5-48 months). There were no significant differences in age, BMI, primary breast surgery, axillary surgery, dose to the axilla, or dose to the supraclavicular region between patients with and without clinical lymphedema (Tab. 4).

Discussion

Within a cohort of BC patients treated with adjuvant proton-based RT, we noted acceptable rates of clinical lymphedema.

Long-term effects of treatment have become increasingly important for BC patients as there is a growing population of BC survivors. BC related-lymphedema (BCRL) is a major complication of breast cancer treatment that can significantly compromise quality of life. There is a wide variation in the incidence rates of clinical lymphedema reported in current literature. Prior studies have identified several risk factors for the development of BCRL, such as axillary surgery, number of lymph nodes removed, receipt of chemotherapy, receipt of radiation therapy,

and elevated BMI [5, 7–9]. Depending on these risk factors, incidence of clinical lymphedema is approximately 10–30% [7, 10, 11]. While prior studies reported extensively on lymphedema, this data is largely limited to photon-based RT. While our current study was not able to identify risk factors associated with development of clinical lymphedema, likely due to limitations in sample size, the rates of clinical lymphedema were comparable to rates reported with photon-based RT in prior studies.

The clinical application of proton-based RT has been growing in recent years. The dosimetric benefits of proton-based RT are well documented, including a low to medium entrance dose, homogeneous dose distribution in the target area, and sharp dose falloff known as the Bragg peak, result in a significantly reduced whole-body integral dose [1–3]. These advantages may offer an advantage over photon-based RT for all patients in terms of minimization of late cardiovascular toxicity, as well as benefit for patients with a history of prior thoracic RT, patients with connective tissue disease or other comorbidities that increase the risk of acute and late toxicity, and very young patients. Currently, the RADCOMP trial is assessing the efficacy and cardiovascular benefits of proton-based RT compared to photon-based RT in the treatment of BC. Despite the increasing use of proton-based RT, the data on incidence of clinical lymphedema following proton-based RT remains limited to small retrospective studies [12, 13]. Cuaron et al. reported favorable outcomes in thirty patients with BC treated with proton-based RT [12]. Rate of clinical lymphedema was 29% at a median follow-up of 9 months. Luo et al. reported 19% clinical lymphedema in forty-two BC patients treated with proton-based RT [13]. We observed similarly low rates of clinical lymphedema (18%).

In the present study, the rate of grade 3 dermatitis was 14%. This compares similarly to rates observed with prior proton-based RT studies, which is not unexpected given the higher skin dose with a proton beam compared with a photon beam [14–16]. 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 conclusion, the incidence of clinical lymphedema after proton-based RT is comparable to rates reported with photon-based RT with comprehensive nodal coverage that can be difficult to achieve using conventional planning techniques.

Conflicts of interest

None declared.

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Table 1. Baseline characteristics

Patient, n	28
Age	
Median, years (range)	45 (24-75)
Breast laterality, n (%)	
Left	19 (68)
Right	9 (32)
Histology, n (%)	
Invasive ductal carcinoma	27 (96)
Ductal carcinoma in situ	1 (4)
AJCC clinical T stage, n (%)	
T1	11 (40)
T2	13 (46)
T3	4 (14)
AJCC clinical N stage, n (%)	
N0	3 (11)

N1	19 (67)
N2	3 (11)
N3	3 (11)
History of smoking, n (%)	6 (21)
Diabetes, n (%)	5 (18)
Median BMI, (range)	27 (20–38)
Follow-up	
Median, months (range)	24 (5–48)

AJCC — American Joint Committee on Cancer; BMI — body mass index

Table 2. Treatment-related characteristics

Systemic therapy	
Chemotherapy	
Neoadjuvant, n (%)	19 (68)
Adjuvant, n (%)	12 (43)
Type of breast surgery	
Breast conserving surgery	17 (61)
Mastectomy	11 (39)
Management of the axilla	
SLNB only	14 (50)
SLNB + ALND	6 (21)
ALND only	8 (29)
Total number of LN removed	
Median, range	6 (1-28)
Radiation therapy parameters	
Median dose [Gy] (range)	50 (44-54)
Median fraction number, (range)	25 (16-30)
Boost, n (%)	22 (79)
Median dose [Gy] (range)	10 (6-14)
Radiation field design	
3–4 fields[a]	28 (100)
Mean dose to axilla [Gy] (SD)	49.7 (2.78)
D95 axilla, mean [Gy] (SD)	46.3 (3.71)
Mean dose to SCV [Gy] (SD)	47.7 (2.76)
D95 SCV, mean [Gy] (SD)	44.1 (3.97)

SLNB — sentinel lymph node biopsy; ALND — axillary lymph node dissection; D95 — mean dose to 95% of the X volume; LN — lymph node; [a]Supraclavicular (SVC) field with or without a posterior axillary boost

Table 3. Treatment related toxicities

Dermatitis, n (%)	
Grade 2	19 (68)
Grade 3	4 (14)
Pain, n (%)	
Grade 2	9 (32)
Fatigue, n (%)	
Grade 2	7 (25)
Esophagitis, n (%)	
Grade 2	1 (4)
Lymphedema	5 (18)

Table 4. Comparison of baseline characteristics between patients with and without lymphedema

	No lymphedema	**Lymphedema**
Patient, n	23	5
History of smoking (%)	3 (13)	2 (40)
Diabetes (%)	2 (9)	2 (40)
BMI, mean (SD)	27.6 (5.8)	26.1 (4.8)
Surgery		
Lumpectomy	15 (65)	3 (60)
Mastectomy	8 (35)	2 (40)
ALND	10 (43)	4 (80)
Number of LN removed, mean (SD)	9 (8)	13 (9)
Total RT dose, mean, Gy (SD)	49.4 (2.2)	48.3 (2.6)
RT dose to axilla, mean, Gy (SD)	50.3 (2.7)	48.3 (2.1)
D95 axilla, mean, Gy (SD)	46.9 (3.4)	44.5 (4.5)
RT dose to SCV, mean, Gy (SD)	48.2 (2.7)	46.6 (2.1)
D95 SCV, mean, Gy (SD)	44.4 (4.1)	43.7 (2.9)

BMI — body mass index; ALND — axillary lymph node dissection; D95 — mean dose to 95% of the X volume; SVC — supraclavicular; SD — standard deviation