The Breast 79 (2025) 103846

Contents lists available at ScienceDirect

The Breast

journal homepage: www.journals.elsevier.com/the-breast

Factors associated with breast lymphedema after adjuvant radiation therapy in women undergoing breast conservation therapy

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A B S T R A C T

Purpose: Breast lymphedema after post-lumpectomy radiation therapy (RT) is poorly defined and difficult to treat. The aim of this study was to define the incidence of breast lymphedema and identify factors associated with the risk of developing breast lymphedema (BL) in women undergoing breast-conserving therapy.
Methods: A retrospective cohort study of patients with early-stage breast cancer who underwent breast-conserving surgery (lumpectomy) followed by RT between January 1, 2014 and July 31, 2019 at a single institution. Women who developed BL, defined as swelling of the breast persisting ≥1 year after RT, were compared with women who did not. Univariate and multivariate regression analyses were used to identify factors associated with risk of BL.
Results: A total of 1052 patients were included in the study: 99 (9.6 %) developed BL and 953 (90.6 %) did not develop BL. The mean ± standard deviation age was 62.9 ± 11.1 years and the mean breast volume was 1352.0 ± 744.9 cm^3. Patients with breast volume ≥1500 cm^3 (adjusted odds ratio [aOR] = 2.34; 95 % CI, 1.40–3.91; $p = 0.001$), Black patients (aOR = 1.78; 95 % CI, 1.12–2.82; $p = 0.015$), those who received neoadjuvant (aOR = 3.05; 95 % CI, 1.28–7.30; $p = 0.012$) or adjuvant chemotherapy (aOR = 2.14; 95 % CI, 1.29–3.55; $p = 0.003$), those with postoperative cellulitis (aOR = 3.94; 95 % CI, 2.20–7.06; $p < 0.001$), and women who developed arm lymphedema (aOR = 2.94; 95 % CI, 1.50–5.77; $p = 0.002$) had significantly higher odds of developing BL.
Conclusion: Patients with larger breast volumes, Black patients, those receiving chemotherapy, and those who develop arm lymphedema or cellulitis may be at higher risk of BL after lumpectomy and RT, suggesting that patients with these risk features may benefit from complementary or alternative surgical approaches and heightened monitoring to avoid BL.

1. Introduction

It is estimated that approximately 180, 000 women diagnosed with new breast cancer in 2023 may undergo breast-conserving therapy (BCT), which comprises breast-conserving surgery (i.e., lumpectomy) followed by postoperative whole-breast radiation therapy (RT) [1,2]. For patients with early-stage breast cancer or ductal carcinoma in situ, BCT is a remarkable evidence-driven development in breast cancer treatment that reduces both local cancer recurrence and breast cancer–specific mortality. Notably, breast-conserving surgery is an acceptable option for patients with a range of comorbidities, and this approach leads to lower rates of postoperative morbidity than mastectomy, providing women with the option of preserving their breast [3–9].

However, both the surgical and RT elements of BCT can cause a range of adverse effects, often through their impact on the lymphatic system [10–18]. Breast lymphedema is a particularly problematic adverse event associated with the lymphatic effects of postoperative RT, and the swelling, discomfort, and physical changes associated with this

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https://doi.org/10.1016/j.breast.2024.103846
Received 22 August 2024; Received in revised form 30 October 2024; Accepted 17 November 2024
Available online 19 November 2024
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condition can substantially affect patients' physical and psychological well-being [2,19,20,22]. Importantly, breast lymphedema is challenging to treat through traditional methods such as manual lymphatic drainage and compression, underscoring a need for effective therapies. But our understanding of BCT-associated breast lymphedema is complicated by the lack of a standard definition, which may be why the reported incidence of breast lymphedema varies widely, ranging from 0 % to 90.4 % [23,24].

The risk of BCT-associated breast lymphedema (BL)—breast swelling lasting beyond the acute phase of post-RT swelling—varies based on treatment and patient factors; however, few studies have examined these factors [2,19–22]. And while some studies have suggested several features that may be associated with a higher risk of developing post-RT BL, such as having axillary lymph node dissection (ALND) or larger breasts [18,25], a definitive understanding of BL risk is still lacking.

Therefore, because more women with breast cancer are being successfully treated with BCT, a clearer understanding of the risk factors involved in RT-associated BL is needed so that risk stratification procedures and preventive strategies can be developed. To address this gap, we performed a retrospective cohort study to determine the incidence of BL at our institution, delineate the clinical and patient characteristics associated with risk of BL, and uncover which clinical outcomes women with BL may be more likely to develop. Importantly, we performed a detailed analysis to determine the relationship between BL and quantitatively measured breast volume. Our comprehensive and nuanced study provides a range of details for clinicians to consider when deciding on best treatment strategies for women undergoing BCT so that BL may be avoided.

2. Methods

2.1. Study design and population

This was a retrospective cohort study of female patients with a new diagnosis of breast cancer who underwent lumpectomy or oncoplastic reduction mammoplasty and received adjuvant whole breast RT between January 1, 2014, and July 31, 2019, at a quaternary care cancer institute. Women with stage IV breast cancer and those who underwent RT at an outside institution were excluded. Women who underwent lymphatic microsurgical preventive healing approach (LyMPHA) were also excluded. Breast surgeons who performed the lumpectomies were breast fellowship trained or trained in surgical oncology. Patients were stratified into 2 groups: those who developed BL, defined as visible breast swelling persisting for 1 year or longer after completion of RT, or at least equivalent to stage 2 on the International Society for Lymphology lymphedema staging, to differentiate from the transient swelling that is unlikely to last one year or more; and those who did not develop BL. Patients were identified as having breast lymphedema by documentation of physical exam, physical therapy notes, or as shown by imaging.

2.2. Radiotherapy technique

All patients underwent simulation in the supine position on an inclined breast board for immobilization with a computed tomography scanner for radiation treatment planning. Wires were then placed along the borders of the breast and around the palpable breast tissue. For left-sided breast scans, both active breathing coordinator-assisted deep inspiration breath hold and 4-dimensional imaging were used to protect the heart.

All patients underwent postoperative whole breast RT, including the regional lymphatics if indicated, with a photon beam instrument either with a conventional fractionation of 50 Gy in 25 fractions or a hypofractionated regimen of 42–43 Gy in 15–16 fractions. A sequential boost, (e.g., 10 Gy in 5 fractions) was delivered to the lumpectomy cavity when clinically indicated. Three-dimensional conformal RT was the predominant technique used.

2.3. Data collection

This study was approved by the Henry Ford Health Institutional Review Board. Patient records were accessed through the Henry Ford Health cancer registry and Epic electronic medical record (Epic Systems Corporation, Verona, WI). Preoperative, operative, and postoperative notes were manually reviewed by researchers. Radiation-specific data per patient were provided by the radiation oncology department.

Demographic and clinical characteristics (age, race/ethnicity, body mass index, and smoking status), comorbidities, perioperative data, treatment history, RT data, and postoperative complications were collected. Preoperative breast volumes were estimated using 3-dimensional contour analysis, which was added to the weight of the lumpectomy specimen. If breast contour analysis could not be performed, breast volumes were estimated by the 95 % isodose volumes from the Eclipse RT treatment planning system (Varian, Palo Alto, CA).

Primary postoperative outcomes were radiation dermatitis (grades 1–4), cellulitis, hematoma, seroma, wound dehiscence, and reoperation. The incidence of BL and breast cancer-related arm lymphedema (BCRaL) were also assessed. BCRaL was defined as the combination of persistent visible arm swelling requiring complete decongestive therapy and complains of symptoms of heaviness, numbness and pain lasting one year or more post-RT (or, at least equivalent to stage 2 on the International Society for Lymphology lymphedema staging). Although bioimpedance spectroscopy is the preferred tool for arm measurements, it is not available at our institution. Consequently, arm measurements were documented during the physical therapists' evaluations utilizing tape measure. All women who developed cellulitis received antibiotic therapy.

2.4. Statistical analysis

Density curve analysis was done to determine the optimal volume cut-off for defining macromastia. The distribution of breast volumes for patients with and without BL was plotted on a Kernel density plot. To estimate the cutoff in breast volume resulting in the largest difference in breast lymphedema risk, overlapping breast volume distributions for the 2 groups were plotted.

Univariate analysis was done to evaluate the patient characteristics, treatment factors, and complications associated with development of BL. Continuous variables following a normal distribution were described with mean ± standard deviation, and those following non-normal distributions were described with median and interquartile range. Categorical variables were described with counts and frequencies. Normality was assessed with the Shapiro-Wilk test ($p > 0.05$). This dataset did not follow a normal distribution; therefore, nonparametric tests were used. Fisher exact test was used to analyze categorical data and Wilcoxon rank sum test was used to analyze continuous data. The assumption of equal variances between the case and control groups was tested with Levene's F test, and Satterthwaite's approximation was used when groups had unequal variances.

Multivariate regression analysis was done to determine factors associated with BL. Independent variables significantly associated with BL in univariate analysis were included in the multivariate regression model, and adjusted odds ratios (aOR) were determined. All statistical analysis was carried out in R version 3.6.1 (R Foundation, Vienna, Austria). Statistical significance was defined as $p < 0.05$ (two-tailed) with 95 % CIs that did not include 0.

3. Results

3.1. Patient descriptions and main outcomes

A total of 1052 patients underwent BCT (lumpectomy and RT) during

the study period, the mean ± standard deviation follow-up time 1 year after RT completion was 50.9 ± 20.2 months, and the median Interquartile range (IQR) follow-up time 1 year after RT completion was 52 (39–61) months. The mean age for the entire population was 62.9 ± 11.1 years, the mean body mass index was 31.2 ± 7.0 kg/m^2, and the mean preoperative breast volume was 1352.0 ± 744.9 cm^3. There were 689 women (65.5 %) who had preoperative breast volumes <1500 cm^3, 363 (34.5 %) with breast volume ≥1500 cm^3, and 118 (11.2 %) who underwent ALND. Mean total radiation dose was 58.9 ± 16.0 Gy, and mean radiation boost dose was 10.7 ± 2.7 Gy. Most patients underwent whole breast radiation (n = 1023; 97.1 %), and 31 (2.9 %) underwent whole breast and axillary radiation (Table 1).

Of the 1052 women, 99 developed BL, an incidence of 9.4 %, and 953 women (90.6 %) did not develop BL. The incidence of BCRaL was 6.2 % (n = 65). Most women (n = 858; 81.6 %) had grade 2 radiation dermatitis skin changes, whereas 389 developed seroma (37.0 %), 92 had cellulitis treated with antibiotics (8.7 %), 62 had hematoma (5.9 %), 21 experienced surgical wound dehiscence (2.0 %), and 6 required reoperation (0.6 %) (Table 2).

3.2. Factors associated with development of breast lymphedema

Estimating a breast volume cutoff with a Kernel density plot to define macromastia showed that the shapes of the breast volume distributions were similar for both groups, but the distribution for the no BL group was shifted toward smaller volumes. The intersection between the 2 curves was at 1462 cm^3, which we rounded to 1500 cm^3 as the differentiating point between low and high breast volume (Fig. 1).

Univariate analysis showed that the women with BL had a significantly higher mean body mass index (33.8 vs. 30.9 kg/m^2; $p < 0.001$) and had larger mean breast volume (1684.8 vs. 1317.4 cm^3; $p < 0.001$) than women in the no BL group. Also, relative to the no BL group, the BL group had a larger proportion of Black patients (55.6 % vs 37.6 %) and a lower proportion of White patients (42.4 % vs 59.2 %) ($p = 0.002$). A larger proportion of the BL group compared to no BL group had ALND (25.3 % vs. 9.8 %; $p < 0.001$), received higher radiation doses (62.8 vs. 58.5 Gy; $p = 0.010$), endured grade 2 radiation dermatitis post-RT (82.7 % vs 82.4 %; $p = 0.268$), and experienced the postoperative complications of cellulitis (24.2 % vs. 7.1 %; $p < 0.001$), hematoma (11.1 % vs. 5.4 %; $p = 0.036$), seroma (48.5 % vs. 38.8 %; $p = 0.017$), and BCRaL (20.2 % vs. 4.7 %; $p < 0.001$) (Table 3).

Multivariate regression analysis showed that patients with preoperative breast volume ≥1500 cm^3 had approximately 2.34 times higher odds of developing BL than those with breast volume of <1500 cm^3 (95 % CI, 1.40–3.91; $p = 0.001$). Also, Black patients had about 1.78 higher odds of developing BL than White patients (95 % CI, 1.12–2.82; $p = 0.015$). Patients who received neoadjuvant chemotherapy (aOR, 3.05; 95 % CI, 1.28–7.30; $p = 0.012$) and those who received adjuvant chemotherapy (aOR, 2.14; 95 % CI, 1.29–3.55; $p = 0.003$) had significantly higher odds of developing BL. Patients who developed cellulitis (aOR, 3.94; 95 % CI, 2.20–7.06; $p < 0.001$) and postoperative BCRaL (aOR, 2.94; 95 % CI, 1.50–5.77; $p = 0.002$) also had significantly higher odds of developing BL (Table 4).

Table 1
Demographic and clinical characteristics.

Characteristic	All patients (N = 1052)
Age, years	62.9 ± 11.1
Race/Ethnicity	
Black	413 (39.3)
White	606 (57.6)
Other	33 (3.1)
BMI, kg/m^2	31.2 ± 7.0
Smoking status	
Current	97 (9.2)
Former	339 (32.2)
Never	616 (58.6)
ALND at time of surgery	118 (11.2)
Follow-up time after RT, months	50.9 ± 20.2
Follow-up time after RT, (IQR), months	52.0 (39–61)
Oncoplastic reduction mammoplasty	44 (4.2)
Chemotherapy	
Neoadjuvant	81 (7.7)
Adjuvant	250 (23.8)
Re-excision lumpectomy	134 (12.7)
Conversion to mastectomy	6 (0.6)
AJCC stage	
0	204 (19.4)
1	645 (61.3)
2	168 (16.0)
3	28 (2.7)
Unknown	7 (0.7)
Preoperative breast volume, cm^3	1352.0 ± 744.9
Preoperative breast volume category	
≥1500 cm^3	363 (34.5)
<1500 cm^3	689 (65.5)
Lumpectomy specimen volume, cm^3	145.31 ± 274.9
Radiation category	
Whole breast	1023 (97.1)
Whole breast and axillary	31 (2.9)
Radiation dose characteristics, Gy	
Tumor dose	45.0 ± 3.6
Boost dose	10.7 ± 2.7
Total dose	58.9 ± 16.0
Supraclavicular dose	46.9 ± 6.6
Posterior axillary boost dose	11.7 ± 3.7

Data are presented as number (%) and mean ± standard deviation.
AJCC, American Joint Committee on Cancer; ALND, axillary lymph node dissection; BMI, body mass index; Gy, Grey; RT, radiation therapy.

Table 2
Presence of lymphedema, treatment outcomes, and post-operative complications.

	All patients (N = 1052) n (%)
Lymphedema	
Breast	99 (9.4)
Arm	65 (6.2)
Total lymphedema	164 (15.6)
Outcomes	
Radiation dermatitis	
Grade 1	89 (8.5)
Grade 2	858 (81.6)
Grade 3	92 (8.7)
Grade 4	2 (0.2)
Unknown	11 (1.0)
Cellulitis	92 (8.7)
Surgical site dehiscence	21 (2.0)
Hematoma	62 (5.9)
Seroma	389 (37.0)
Reoperation	6 (0.6)

4. Discussion

In this cohort study, we observed that women undergoing BCT with larger breast volume were at higher risk of developing BL than women with smaller breast volume, and women who received either neoadjuvant or adjuvant chemotherapy and those who developed postoperative cellulitis also had higher odds of developing BL after RT. While uncommon, BL is a daunting potential side effect of BCT that should be mitigated as much as possible, especially because it is challenging to treat. Our study highlights several factors that may indicate higher risk for post-RT BL, and patients with these risks may benefit from discussions about alternative routes for their breast surgery.

The 10 % incidence of BL in our study may seem intuitively low, but considering that approximately 180, 000 women undergo BCT each year in the United States, this would mean that around 18,000 patients per year could theoretically develop this disabling long-term complication

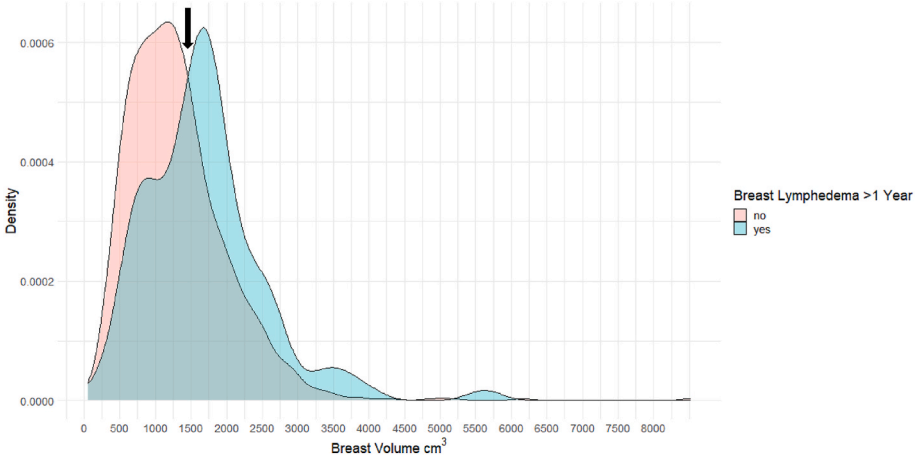

Fig. 1. Density curve of breast volumes for patients with and without breast lymphedema
*Arrow represents the 1500 cm^3 breast volume cutoff.

in the US alone [1,2]. But a true incidence of BL is difficult to determine since different studies have defined and evaluated it in numerous ways. For instance, one systematic review reported rates of breast lymphedema in patients undergoing BCT from 0% to 90.4 %; however, this wide range included both acute and chronic breast lymphedema [24]. Other potential reasons for this variability could include an overreliance on imaging to identify BL, a loss of patients to follow-up, inadequate post-surgical follow-up surveillance, inaccurate medical record documentation, and an overall lack of acknowledgement of BL as a true risk of breast cancer treatment.

We defined BL as persistent visible swelling for 1 year after RT because radiation-induced fibrosis typically emerges 4–12 months after the conclusion of RT, and it may even persist or advance over years [14]. Thus, the potential long-term nature of BL can have deleterious effects on quality of life and can hinder cosmetic outcomes. Following BCT, women may experience short-term and/or long-term physical impairment such as increased swelling, seroma, decreased range of motion, recurrent infection, pain, weakness, and paresthesia. Importantly, women with these complications may need to take time off work or may be unable to perform physical tasks, and women with BL could face up to 112 % higher out-of-pocket costs than women who do not develop this condition [26]. Therefore, efforts should be directed towards mitigating post-RT complications, and the utility of early surgical intervention for breast lymphedema requires more investigation.

Macromastia is an atypical enlargement of the breast tissue [27], and several studies have shown that women with macromastia undergoing BCT had higher rates of complications and poor cosmesis results secondary to radiation-induced fibrosis [28–30]. Also, women with macromastia may have a higher potential for significant breast disfigurement following BCT [18]. However, many studies have defined macromastia by bra cup size, which is an inexact and variable measure. In our study, we quantified breast size based on the density curve and determined 1500 cm^3 to be the cutoff between breast volumes associated with risk of BL, roughly comparable to an F cup size or larger, though bra size and brand inconsistencies make this estimation approximate. The potential mechanisms underlying the relationship between larger breast size and BL could be that excess adipose tissue absorbs more radiation or that excising larger tumor specimens may lead to more lymphatic tissue destruction. Because macromastia is a modifiable risk factor, clinicians might consider discussing with patients the possibility of oncoplastic reduction mammoplasty at the time of lumpectomy. This approach could help alleviate the weight of the edematous breasts, should breast lymphedema develop.

In our study, Black patients had nearly twice the odds of developing BL compared to White patients, though the link between race and BL remains unclear. One study of 276 patients who underwent lumpectomy with ALND and RT found that Black patients had the highest incidence of BCRaL at 37.2 %; however, the study did not specifically evaluate breast lymphedema [31]. Another study observed that Black women had a 2-fold increased risk of developing BCRaL relative to White patients [32]. And a large retrospective study showed that younger Black women with breast cancer had substantially higher 5-year risk of both arm and breast lymphedema [33]. This higher risk could be related to differences in skin characteristics and dermis, as African ancestry have been shown to have a higher prevalence of fibroproliferative diseases [34]. Changes in inflammatory pathways, such as heightened interleukin-4/interleukin-13 signaling observed in lymphedematous tissue, have also been suggested as a possible mechanism [35]. These findings underscore the need for clinicians to be more aware of racial disparities in breast cancer and suggest that further studies are essential.

Receiving neoadjuvant and adjuvant chemotherapy, particularity taxane-based agents, were significantly associated with a higher risk of developing BL in our study. All 52 patients who had chemotherapy and developed BL, had received taxane-based agents, known for their role in breast cancer treatment. These drugs, which can cause neuropathy, lymphedema, and compromised lymphatic function, may promote BL by inducing fluid retention due to increased capillary permeability, leading to transient interstitial edema and systemic lymphatic dysfunction [22, 36–38]. Other studies have shown significant increases in breast cancer-related lymphedema with docetaxel and paclitaxel [22,36, 39–42], although, these studies did not distinguish BCRaL and BL. Therefore, until less toxic alternative chemotherapies become available, careful monitoring for lymphedema is crucial when using taxane-based agents.

Generally, the most common early sequelae after breast cancer surgeries are cellulitis, hematoma, seroma, and abscess [17,43–46]. A large retrospective study of over 100,000 breast surgery patients found that 5.4 % developed lymphedema, with these patients having a significantly higher incidence of cellulitis, underscoring a close relationship between the two conditions [47]. In our study, women with postoperative cellulitis who required antibiotics had an almost 4-fold increased risk of developing BL. Factors contributing to cellulitis included re-excision lumpectomy, ALND or sentinel lymph node biopsy, seroma aspiration, RT, and neoadjuvant and adjuvant chemotherapy [46,48–51]. Post-RT cellulitis may result from lymphangiectasis secondary to lymph stasis following BCT, alteration to the biocomposition of the breast, reduced tissue perfusion due to radiation-induced fibrosis disrupting lymphatics and vascular drainage [13,52,53]. Collectively, these factors predispose patients to soft tissue infection, increasing the risk of lymphedema. Preexisting patient attributes and comorbidities also heighten

Table 3
Demographic and clinical characteristics of patients with (n = 99) and without (n = 953) breast lymphedema.

Characteristic	(no BL) n = 953	(BL) n = 99	*P* value
Age, years	63.1 ± 11.1	61.4 ± 10.6	0.147
Race/Ethnicity			0.002
Black	358 (37.6)	55 (55.6)	
White	564 (59.2)	42 (42.4)	
Other	31 (3.3)	2 (2.0)	
BMI, kg/m^2	30.9 ± 6.9	33.8 ± 7.6	<0.001
Smoking status			0.902
Current	88 (9.2)	9 (9.1)	
Former	309 (32.4)	30 (30.3)	
Never	556 (58.3)	60 (60.6)	
Comorbidities			
Type 2 diabetes	281 (29.4)	31 (31.3)	0.792
Hypertension	633 (66.4)	73 (73.7)	0.173
Congestive heart failure	56 (5.9)	11 (11.1)	0.070
End-stage renal disease	8 (0.8)	2 (2.0)	0.543
ALND at time of surgery	93 (9.8)	25 (25.3)	<0.001
Oncoplastic reduction mammoplasty	39 (4.1)	5 (5.1)	0.850
Chemotherapy			
Neoadjuvant	65 (6.8)	16 (16.2)	0.002
Adjuvant	214 (22.4)	36 (36.4)	0.003
Lumpectomy specimen volume, cm3	142.2 ± 275.8	175.2 ± 265.7	0.256
Follow-up time after RT, months	51.2 ± 20.4	48.5 ± 18.5	0.197
Preoperative breast volume, cm^3	1317.4 ± 726.4	1684.8 ± 837.9	<0.001
Preoperative breast volume category			<0.001
≥1500 cm^3	305 (32.0)	58 (58.6)	
<1500 cm^3	648 (68.0)	41 (41.4)	
Total radiation dose, Gy	58.5 ± 15.3	62.8 ± 20.7	0.010
Radiation category			0.107
Whole breast	928 (97.4)	93 (93.9)	
Whole breast and axillary	25 (2.6)	6 (6.1)	
Outcomes	81 (8.6)	8 (8.2)	0.268
Radiation Dermatitis	777 (82.4)	81 (82.7)	
Grade 1	84 (8.9)	8 (8.2)	
Grade 2	1 (0.1)	1 (1.0)	
Grade 3	10 (1.0)	1 (1.0)	
Grade 4			
Unknown			
Cellulitis	68 (7.1)	24 (24.2)	<0.001
Hematoma	51 (5.4)	11 (11.1)	0.036
Seroma	341 (35.8)	48 (48.5)	0.017
Surgical wound dehiscence	16 (1.7)	5 (5.1)	0.057
Reoperation	4 (0.4)	2 (2.0)	0.190
Chronic arm lymphedema	45 (4.7)	20 (20.2)	<0.001

Data are presented as number (%) and mean ± standard deviation.
ALND, axillary lymph node dissection; BMI, body mass index; BL, breast lymphedema; Gy, grey; ORM, oncoplastic reduction mammoplasty; RT, radiation therapy; SLNB, sentinel lymph node biopsy.

postoperative cellulitis, including age, breast size, upper outer quadrant tumor location, diabetes, and many others [46,51,54]. Therefore, when applicable, preventive measures such as thorough patient histories, preoperative physical examinations, comorbidity management, and the adoption of minimal-access breast surgery strategies can help lower the likelihood of cellulitis and BL in BCT patients [55].

Upper extremity lymphedema following breast cancer surgery can lead to physical disability and requires long-term management. In our study, women who developed BCRaL were at 3-fold higher risk of also developing BL, underscoring the importance of treatment strategies to avoid this complication. The LyMPHA technique, which is a surgical technique that can restore lymphatic drainage, may be a reasonable option during BCT to reduce BCRaL and, consequently, BL risk in those who undergo ALND. Further investigation into new techniques to prevent all forms of lymphedema following breast cancer therapy is crucially needed.

Table 4
Multivariate regression analysis of risk factors associated with breast lymphedema after radiation therapy.

Variable	OR (95 % CI)	*P* value
Preoperative breast volume ≥1500 cm^3 (referent <1500 cm^3)	2.34 (1.40–3.91)	0.001
Race (referent White)		
Black	1.78 (1.12–2.82)	0.015
Other	1.34 (0.28–6.33)	0.713
BMI	1.02 (0.98–1.06)	0.294
ALND at time of surgery	1.76 (0.94–3.30)	0.079
Neoadjuvant chemotherapy	3.05 (1.28–7.30)	0.012
Adjuvant chemotherapy	2.14 (1.29–3.55)	0.003
Radiation total dose	0.99 (0.98–1.01)	0.253
Cellulitis	3.94 (2.20–7.06)	<0.001
Hematoma	1.54 (0.70–3.38)	0.281
Seroma	1.35 (0.85–2.14)	0.206
Chronic arm lymphedema	2.94 (1.50–5.77)	0.002

ALND, axillary lymph node dissection; BMI, body mass index; CI, confidence interval; OR, odds ratio.

Future rigorous prospective studies with standardized methods and definitions might best be done by recruiting patients through survivorship clinics. A robust body of standardized data will be needed to refine standards and guidelines around breast cancer surgical decision making, allowing surgeons to offer procedures and optimize treatments to mitigate the risk of BL and other related complications.

4.1. Limitations

While this study was limited by its retrospective nature, it did include a large population of diverse women who had long-term follow-up and included a large group of women with macromastia. Another constraint was the insufficient statistical power, precluding analysis of patients undergoing oncoplastic reduction mammoplasty. This was a single-center study, which may limit generalizability. Lastly, the absence of a standardized grading system for breast lymphedema severity restricted our ability to assess its impact on patients' quality of life.

5. Conclusions

In our study, the incidence of breast lymphedema lasting 1 year or longer after RT in women undergoing BCT for early-stage breast cancer was 9.4 %. Importantly, women who had larger breast volumes ≥1500 cm^3 were at higher risk of BL, suggesting that this group may need more vigilant monitoring after completion of RT, and more in-depth discussions about treatment strategies may be warranted for this group. Additionally, chemotherapy was associated with higher risk of BL, indicating that women undergoing BCT alongside chemotherapy may need heightened monitoring for lymphedema complications. Lastly, Black patients were disproportionately represented in the BL case group, and this health disparity requires urgent investigation. Overall, our study provides a comprehensive clinical snapshot of the features promoting the risk of developing BL in patients receiving BCT.

CRediT authorship contribution statement

Summer Sami Yono: Writing – review & editing, Writing – original draft, Project administration, Data curation. **Cara Cannella:** Writing – review & editing, Writing – original draft, Validation, Software, Resources, Formal analysis, Data curation. **Madeleine Gonte:** Writing – review & editing, Methodology, Data curation. **Sanjay Rama:** Writing – review & editing, Writing – original draft, Methodology, Data curation. **Simeng Zhu:** Writing – review & editing, Writing – original draft, Methodology, Data curation. **Jenna Luker:** Supervision, Project administration. **Maristella S. Evangelista:** Writing – review & editing, Supervision, Project administration, Investigation. **Jessica**

Bensenhaver: Writing – review & editing, Supervision, Project administration. **Eleanor M. Walker:** Writing – review & editing, Supervision, Project administration, Investigation, Conceptualization. **Dunya Atisha:** Writing – review & editing, Supervision, Investigation, Funding acquisition.

Data availability

Available upon request from the corresponding author.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used chatbolt/Chat GPT-3 in order to improve English grammar and punctuation. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

Funding

This research project was supported by a private donation made to Henry Ford Hospital specifically designated to create a comprehensive lymphedema program. Lymphedema grant number [F60581].

Declaration of competing interest

Dr. Dunya Atisha is a senior medical consultant for MTF Biologics. The rest of authors declare that there is no conflict of interest regarding the publication of this article.

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