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Factors affecting the formation of lymphedema due to breast cancer (Is primary systemic treatment an independent factor in the formation of breast cancer related lymphedema?)

Melek Kumcuoğlu[1], Semra Günay[2], Berk Gökçek[1]

[1]Department of General Surgery, University of Health Sciences Türkiye, Prof. Dr. Cemil Taşcıoğlu City Hospital, İstanbul, Türkiye
[2]Department of General Surgery, İstanbul Okan University Faculty of Medicine, İstanbul, Türkiye

ABSTRACT

Objective: This study aimed to evaluate the local and systemic risk factors associated with breast cancer-related lymphedema (BCRL), with a focus on whether primary systemic treatment (PST), particularly taxane-based chemotherapy, is an independent risk factor.

Material and Methods: A prospective clinical study was conducted on 80 breast cancer patients discussed at our institution's weekly breast cancer council. Patients were grouped based on PST status. Clinical examinations and measurements were performed preoperatively and postoperatively at 1, 6, 12, 18, and 24 months. Only the operated arm was assessed using tape measurements and the truncated cone formula. Arm volumes were calculated, and lymphedema (LE) was diagnosed based on a volume difference (≥200 mL or ≥2 cm circumference).

Results: No statistically significant differences were found between PST and non-PST groups regarding age, body mass index, menopausal status, smoking, or tumor characteristics. LE was detected in 7 (8.8%) patients, all Stage 1. PST and taxane-based chemotherapy were not significantly associated with LE development. However, seroma presence (p=0.038) and axillary radiotherapy (p=0.043) were significantly associated with LE. Arm volume increase was most significant at 1 and 18 months postoperatively (p=0.055 and p=0.044, respectively).

Conclusion: PST, including taxane-based chemotherapy, does not appear to be an independent risk factor for BCRL. In contrast, postoperative seroma and axillary radiotherapy are significantly associated with LE development. Early identification and management strategies should target these modifiable factors to reduce the risk of LE.

Keywords: Breast cancer, primary systemic treatment, lymphedema, radiotherapy, sentinel lymph node biopsy, risk factors

INTRODUCTION

Breast cancer is the most prevalent malignancy among women. Increased survival rates due to early detection and systemic treatment have led to a rise in treatment-related complications, particularly lymphedema (LE), which is influenced by multiple factors, including obesity, surgical intervention, radiotherapy (RT), and possibly primary systemic treatment (PST), and significantly impairs quality of life (1). The role of PST, especially taxane-based regimens, in LE development remains controversial (1-3).

This study investigates whether PST is an independent risk factor for LE, and identifies other potential predictors by comparing patients who did and did not receive PST.

MATERIAL and METHODS

Study Population and Design

Patients diagnosed with breast cancer are evaluated in the breast council and their treatments are planned. Among these patients, those who agreed to participate in the study, accepted the necessary follow-up and measurements to be made at the required time intervals and were included in the study. After Ethics Committee approval from the University of Health Sciences Türkiye, Prof. Dr. Cemil Taşcıoğlu City Hospital (decision no.: 69/21, date: 10 May 2022), 80 patients were prospectively enrolled. Participants were grouped based on PST status. According to the treatment plan, LE follow-up, examination, and measurements were recorded at 1, 6, 12, 18,

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Corresponding Author
Semra Günay
E-mail: gunaysemra@gmail.com
ORCID ID: orcid.org/0000-0001-6845-658X

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and 24 months before and after PST (n=40) and/or surgery (n=40) (Figure 1). All patients came for follow-up for at least 2 years.

Measurements

Arm volume of the operated side was calculated using circumferential tape measurements at 7 cm intervals and the truncated cone formula.

Circumferential measurements were initiated at the ulnar styloid process, with subsequent measurements taken at 7-cm intervals. The volume of each conical segment was calculated using the following formula, and the differences in volume between the arms were analyzed:

* $V: \sum \frac{h(C2 + Cc + c2)}{2\pi}$

• V: upper extremity volume

• C: circumference of the lower segment

• c: circumference of the upper segment

• π: 3.14

• h: distance between the measurements (set as 7 cm in this study).

LE was defined by a volume difference of ≥200 mL or a circumference difference ≥2 cm. Arm volume differences over time were also analyzed.

Statistical Analysis

Data were analyzed using SPSS v25. Descriptive statistics, t-tests, Mann-Whitney U, chi-square, and repeated measures ANOVA were employed. P<0.05 was considered significant

All statistical analyses were performed using the Statistical Package for Social Sciences for Windows, version 25.0.

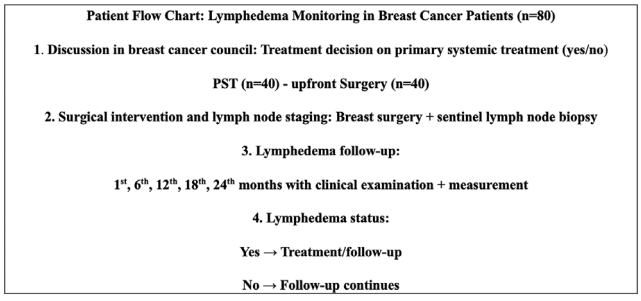

Figure 1. Patients diagnosed with breast cancer are evaluated in the breast council and their treatments are planned. Among these patients, those who agreed to participate in the study, accepted the necessary follow-up and measurements to be made at the required time intervals and were compliant were included in the study. According to the treatment plan, lymphedema follow-up, examination and measurements were recorded at the specified time intervals before and after PST and or surgery.

PST: Primary systemic therapy

RESULTS

Among 80 patients, LE was detected in 7 (8.8%), all of whom had Stage 1 LE (1,4). These patients were advised to elevate their limbs, to receive manual massage, and were followed up clinically, without any progression of their condition. The characteristics of the surgical techniques employed and the distribution of lymph nodes and tumor types are summarized in Table 1. When PST status, chemotherapy, and hormone therapy were evaluated separately, no statistically significant differences were observed between patients with and without LE. Likewise, the diagnostic and therapeutic approaches regarding LE did not differ significantly (Table 2).

Axillary RT (71.4% in LE group vs. 32.9% in non-LE group; p=0.043) and seroma (85.7% vs. 38.4%; p=0.038) were significantly associated with LE (Table 3).

When the measurements of both arms were considered during both the preoperative and postoperative periods, an increase in the left arm measurement was observed in patients with LE at 1 month postoperatively (Table 4). Moreover, when the relationship between inter-arm volume difference and LE was examined, the values at 1 and 18 months postoperatively were found to be significantly different (Table 5).

Volume differences in the operated arm were observed at 1 and 18 months in the LE group (p=0.055 and 0.044, respectively).

In all patients diagnosed with LE (whether right or left), the dominant side was the right. In the subgroup of patients with a right dominant arm, the measurements and their corresponding arm volumes for both right and left arms for patients with and without LE are illustrated in Figures 2 and 3. Although the median values did not reveal a significant difference overall, the 1- and 18-month time points were particularly notable.

At 1 month postoperatively, total arm volume was higher in patients with LE, reaching borderline statistical significance (p=0.055). At 18 months, the volume difference in patients with LE was significantly higher (p=0.044) (Figure 4).

DISCUSSION

The incidence of breast cancer is increasing, and advances in diagnosis and treatment are prolonging patient survival, while breast cancer treatment-related LE ranges from 8.4% to 21.4%, consistent with figures reported in the literature (4-6). Furthermore, its relationship with age has been examined, and age is not directly associated with the development of LE (7,8). A retrospective study by Donahue et al. (8) found that smoking did not affect the development of breast cancer-related LE over a 3-year follow-up period. These findings are consistent with our results.

Table 1. Distribution of patients according to applied surgical technique, lymph node and tumor type, PST status, presence of lymphedema, and treatment approach

Variable	n (%)
Surgical	
Mastectomy + SLNB	27 (33.7)
MKC + SLNB	53 (66.3)
Axilla	
SLNB	80 (100.0)
SLNB + AD	20 (25.0)
SLNB method	
Isosulfan blue (IB)	73 (91.3)
Radiocolloid	6 (7.4)
IB + radiocolloid	1 (1.3)
Lymph node count	
1/2/3/4/5/6/7	6/13/23/24/7/3/4
Number of positive lymph nodes	
01/2/3/4/5/6	54 (67.5)/5/10/8/1/1/1
Tumor type: DCIS/invasive	2 (2.4)/78 (97.6)
ER status	
Negative/positive	15 (18.8)/65 (81.2)
PR status	
Negative/positive	32 (40.0)/48 (60.0)
CERB2	
Negative/positive	71 (88.8)/9 (112)
Neoadjuvant endocrine therapy	
Did not received/received	71 (87.5)/8 (12.5)
Neoadjuvant chemotherapy-taxane based	
Did not receive/recived	9 (22.5)/31 (77.5)
Lymphedema no/yes	73 (91.3)/7 (8.7)
Detected lymphedema side (surgical side)	
Right/left	2 (71.4)/5 (28.6)
Axillary RT no/yes	51 (61.7)/29 (36.3)
Aspiration/seroma	
No/yes	46 (57.5)/34 (42.5)
Preop FNAB axilla	
Not done/done	46 (57.5)/34 (42.5)
Preop IIAB axilla result	
Benign/malignant	62 (65.0)/38 (35.0)

PST: Primary systemic treatment, SLNB: Sentinel lymph node biopsy, ER: Estrogen receptor, PR: Progesterone receptor, FNAB: Fine needle aspiration biopsy, DCIS: Ductal carcinoma *in situ*.

Although direct comparisons of LE rates have not been made in studies that have focused predominantly on non-invasive methods for axillary staging, there is strong evidence to support the idea that even minimal surgical interventions in the axilla may affect the planning of diagnostic and treatment strategies. However, no significant differences were detected (9,10). A study by Nakagawa et al. (11) suggested that Chemotherapy may be a causal factor for LE. Their aimed was to determine whether chemotherapy affects the lymphatic vessels and blood vessels in the skin and subcutaneous fat and to investigate how these Changes relate to the degree of edema after Chemotherapy. In contrast, several studies have shown that neoadjuvant chemotherapy, especially taxane-based agents, plays a role in

Table 2. Relationship between neoadjuvant treatment status and lymphedema

Variable	No lymphedema [n=34-(%)]	Lymphedema present [n=6-(%)]	p
NET			
Tamoxifen			
Did not receive treatment	29 (85.2)	6 (100)	0.977
Received treatment	5 (14.8)	0 (0)	
Filgrastin			
Did not receive treatment	30 (88.2)	6 (100)	0.852
Received treatment	4 (11.8)	0 (0)	
NACT			
Paclitaxel			
Did not receive treatment	7 (20.6)	2 (33.3)	0.490
Received treatment	27 (79.4)	4 (66.7)	
Cyclophosphamide			
Did not receive treatment	7 (20.6)	3 (50)	0.125
Received treatment	27 (79.4)	3 (50)	
Transtuzumab			
Did not receive treatment	28 (82.4)	5 (83.3)	0.953
Received treatment	6 (17.6)	1 (16.7)	
Doxorubicin			
Did not receive treatment	8 (23.5)	3 (50)	0.152
Received treatment	26 (76.5)	3 (50)	
Carboplatin			
Did not receive treatment	31 (91.2)	6 (100)	0.657
Received treatment	3 (8.8)	0 (0)	

NET: Neoadjuvant hormone therapy, NACT: Neoadjuvant chemotherapy.

the development of breast cancer-associated LE by increasing capillary permeability and promoting protein accumulation in the interstitial space. In a prospective study conducted by Nguyen Stringer et al. (12), only 74 out of 273 patients who underwent an axillary lymph node dissection (ALND) developed breast cancer-associated LE. Notably, all of these patients received taxane-based chemotherapy. The risk of developing LE was found to be three times higher in patients who received taxane-based chemotherapy than in those who did not (12-14). In contrast, in a prospective cohort study conducted by Montagna et al. (15), when the risk and findings were analyzed, no statistically significant difference was observed in the rates of LE according to the chemotherapy regimen. When taxane-based regimens were evaluated as a separate group (n=31), statistical analysis yielded a p-value of 0.490. In our series, no significant difference was found between the groups receiving and not receiving Taxane-based chemotherapy.

Table 3. Relationship between patients' treatment/procedural status and lymphedema

Variable	No lymphedema [n=73-(%)]	Lymphedema present [n=7-(%)]	p
Surgical			
Mastectomi + SLNB	24 (32.9)	3 (42.9)	
MKC + SLNB	49 (67.1)	4 (57.1)	0.594
Axilla			
SLNB	73 (100.0)	7 (57.1)	
SLNB + AD	17 (23.3)	3 (42.9)	0.253
SLNB technique			
Isosulfan blue (IB)	67 (91.8)	6 (85.7)	
Radiocolloid	5 (6.8)	1 (14.3)	
IB+ radiocollaoid	1 (1.4)	0 (0.0)	0.744
Axillary RT			
No	49 (67.1)	2 (28.6)	
Yes	24 (32.9)	5 (71.4)	**0.043**
RT			
Thoracic RT	23 (31.5)	2 (28.6)	
Whole-breast RT	50 (68.5)	5 (71.4)	1.000
Aspiration/seroma			
No	45 (61.6)	1 (14.3)	
Yes	28 (38.4)	6 (85.7)	**0.038**
Preop FNAB axilla			
Not done	44 (60.3)	2 (28.6)	
Done	29 (39.7)	5 (71.4)	0.129
Preop FNAB axilla result			
Bening	49 (67.1)	3 (42.9)	
Malignant	24 (32.9)	4 (57.1)	0.232

SLNB: Sentinel lymph node biopsy, RT: Radiotherapy, FNAB: Fine needle aspiration biopsy.

The risk of breast cancer-associated LE was strongly associated with ALND. There are different results in studies on this subject, and it is known that routine ALND increases the rate of LE when it is performed for curettage rather than for staging purposes. No relationship was observed between axillary surgery for diagnosis or staging purposes and LE in our series. A large prospective study by Warren et al. (16) showed that axillary RT significantly increased the risk of LE compared with whole breast/chest wall irradiation. Similarly, a 15-year follow-up study by Poortmans et al. (17).

Breast cancer LE as a risk factor for RT. Axillary RT was a risk factor for LE (p=0.043), while RT to the whole breast and chest wall was not associated with a risk of LE (p=1.00). Axillary management and its universal approaches have become a focus in recent years. Numerous studies, along with relevant reviews and meta-analyses, emphasize minimizing the extent of axillary surgery (18). The risk of breast cancer-associated LE was most strongly associated with ALND. There are different results in studies on this subject, it is known that routine ALND increases the rate of LE when performed for curettage rather than staging purposes (18). It is widely accepted that the origin of breast cancer LE is multifactorial (19,20) and can be modified by the city, surgical techniques, and extent of lymph node dissection after surgery.

A study published in 2019 showed that lymph node metastasis is a significant risk factor for the development of LE in breast cancer patients. In addition, the risk of LE was associated with the number and characteristics of metastatic lymph nodes. In independent lymphadenectomy (LE) with 10 or more metastatic

Table 4. Relationship between follow-up measurements of the right and left arms and lymphedema

Variables	No lymphedema (n=73)	Lymphedema present (n=7)	p
Pre-op right	1598.0±330.5	1660.7±240.1	0.627
Pre-op left	1587.8±317.3	1680.4±206.3	0.453
Post-op right	1578.2±320.2	1722.7±196.0	0.246
Post-op left	1570.4±306.0	1674.3±198.6	0.383
1. month right	1607.0±339.6	1740.5±219.1	0.313
1. month left	1588.9±335.5	1765.7±137.3	**0.016**
6. month right	1594.5±349.9	1686.1±160.7	0.497
6. month left	1574.2±335.8	1732.2±255.1	0.230
12. month right	1590.9±331.0	1724.2±154.5	0.297
12. month left	1570.7±325.3	1747.6±270.8	0.168
18. month right	1600.3±349.6	1740.7±200.1	0.301
18. month left	1577.9±326.9	1745.0±273.4	0.195
24. month right	1593.9±335.0	1695.5±175.7	0.433
24. month left	1569.8±321.5	1742.9±273.0	0.173

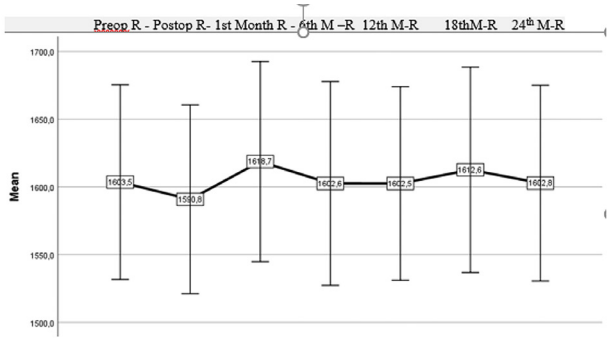

Figure 2. Changes in the mean right arm volume measurements over the follow-up period.

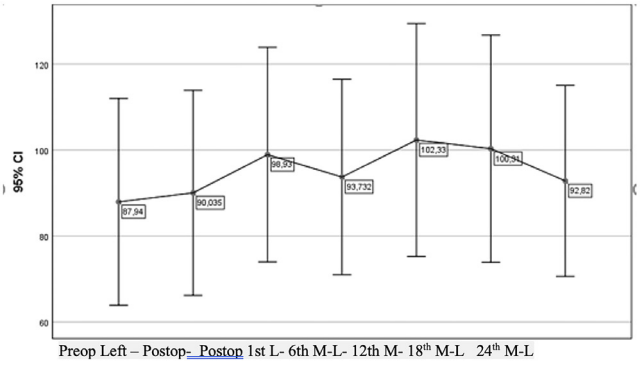

Figure 3. Changes in the mean left arm volume measurements over the follow-up.

CI: Confidence interval

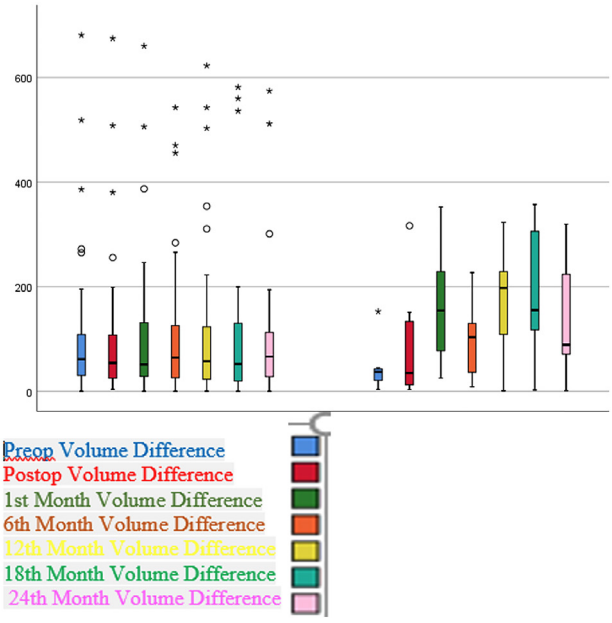

Figure 4. Relationship between the median difference in arm volume and lymphedema status.

At 1 month po. with LE, reaching borderline statistical significance (p=0.055).

At 18 months, with LE was significantly higher (p=0.044).

LE: Lymphedema.

lymph nodes, the risk was 1.78 times higher than in those with three or fewer metastatic lymph nodes and 2.17 times higher than in those without lymph node metastasis (21). Similar studies with a 5 year follow-up have shown that both axillary lymph node metastases and advanced cancer stage are associated with LE (22,23). In our series, the detection of LE was more frequent in patients who received PST, which is consistent with information about the relationship between cancer stage and LE. However, an analysis was not performed on this relationship. No relationship was observed between axillary surgery for diagnosis or staging purposes and LE. Additionally, when considered in terms of the number of LE nodes, no association with LE was detected in our patients who underwent axillary surgery for staging purposes, and the number of lymph nodes was limited.

In a retrospective cohort study conducted by Toyserkani et al. (24), involving all unilateral breast cancer patients treated between 2008 and 2014, LE was developed in 291 out of 1,822 patients, with seroma being identified as an independent risk factor. In contrast, a prospective study by Koelmeyer et al. (25) found no significant association between seroma and breast cancer-related LE. The surgeon's patient volume and experience may be effective in this regard (26). Our patients were operated on by physicians experienced in breast surgery; however, only two of the patients diagnosed with LE (25%) were operated on specifically by a breast surgeon.

To summarize, the LE incidence rate of 8.8% aligns with prior

Table 5. Relationship between the median difference in arm volume and lymphedema status

Variable	No lymphedema (n=73)	Lymphedema present (n=7)	p-value
Pre-op volume difference	61.3 (30,1108,5)	37.2 (20,842,6)	0.125
Post-op volume difference	54.4 (24,9107,6)	35.0 (12,4133,6)	0.621
1. month volume difference	51.2 (28,3131,1)	154.2 (77,4228,9)	**0.055**
6. month volume difference	64.4 (25,8125,7)	103.3 (36,4129,6)	0.714
12. month volume difference	57.3 (22,7123,2)	197.6 (108,6228,9)	0.104
18. month volume difference	52.1 (19,4130,0)	155.1 (117,3305,9)	**0.044**
24. month volume difference	66.3 (27,8112,4)	89.0 (71,1223,7)	0.217

literature. Although some studies implicate PST and taxanes in LE development, our findings do not support this association. Axillary RT and postoperative seroma were the only modifiable risk factors significantly linked to LE. Dominant arm status and surgeon experience were also explored, though conclusions were limited by sample size. With close and regular follow-up, early diagnosis and a conservative approach, LE can be kept under control. In our very limited series of patients, the stage in terms of LE remained the same during follow-up.

Study Limitations

The study's prospective design and consistent measurement protocol strengthens its findings, though the small number of LE cases and limited statistical power remain limitations.

CONCLUSION

This study aimed to determine to determine whether PST (especially taxane-based neoadjuvant chemotherapy) is an independent risk factor for breast cancer-associated LE and to evaluate the impact of early diagnosis and prevention on quality of life.

Our results did not reveal a statistically significant association between PST or taxane-based chemotherapy and LE. However, postoperative seroma and axillary RT were significantly associated with the development of LE.

We conclude that early LE may be related to surgical factors and seroma, while later LE is likely related to RT. Emphasis should be placed on longer follow-up of patients and on early diagnosis and preventive strategies.

Ethics

Ethics Committee Approval: After Ethics Committee approval from the University of Health Sciences Türkiye, Prof. Dr. Cemil Taşcıoğlu City Hospital (decision no.: 69/21, date: 10 May 2022), 80 patients were prospectively enrolled.

Informed Consent: Informed consent documents, obtained before treatment from each patient are available in patient files.

Acknowledgments

The Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013).

Footnotes

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Author Contributions

Concept - M.K., S.G.; Design - M.K., S.G.; Data Collection or Processing - S.G.; Analysis or Interpretation - S.G., B.G.; Literature Search - M.K., S.G., B.G.; Writing - M.K., S.G.

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