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ORIGINAL ARTICLE

Factors influencing response to lymphedema treatment in patients with breast cancer-related lymphedema

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Abstract
Purpose In clinical practice, noticeable differences are seen in patient response to the treatment of breast cancer-related lymphedema. Although some factors influencing response to treatment are mentioned in the literature, there is no sufficient evidence and results are confusing. For this reason, our objective in this study is to identify predictive and response-related factors for response to treatment of breast cancer-related lymphedema.
Methods We analyzed data retrospectively from the files of patients with breast cancer-related lymphedema between 2006 and 2012. Patient demographics, clinical variables, and patient variables were recorded. Circumference measurements of lymphedema and healthy arms were recorded. We used a computer program (Limb Volumes Professional version 5.0) to transform these values to limb volumes in milliliters.
Results The average age of 331 patients was 54.4±10.9. The average length of lymphedema treatment was 2.92±1.3 weeks. A statistically significant positive correlation was found between postoperative weight gain and postoperative duration, number of chemotherapy (CT) cycles, duration of tamoxifen use, and duration of hormonal therapy ($p<0.05$). There was a statistically significant negative correlation between posttreatment arm volume and activity level, postoperative duration, and postoperative weight gain ($p<0.05$).
Conclusion The treatment methods used for treating breast cancer had no effect on the response to treatment of lymphedema. Weight gain during the treatment of breast cancer is important for both the development of lymphedema and the response to treatment. When treating breast cancer-related lymphedema, the relationship between activity level and postoperative weight gain may provide us guidance in clinical practice.

Keywords Breast cancer · Lymphedema · Treatment · Predictors

Abbreviations

CDT	Complete decongestive therapy
RT	Radiation therapy
CT	Chemotherapy
PEV	Percentage of excess volume
VL	Lymphedema arm
VH	Healthy arm
PREV	Percent reduction in excess volume
BMI	Body mass index

Introduction

Early diagnosis and effective treatment methods have significantly increased long-term survival in patients with breast cancer. Lymphedema is one of the most common complications of breast cancer and has a negative effect on the individual's quality of life [1]. Breast cancer-related lymphedema is caused by the accumulation of protein-rich lymphatic fluid as a result of decreased drainage due to surgery, radiation therapy, or lymphangitis [2]. Its incidence is estimated to range from 3 to 87 % in different studies [1, 3, 4]. This wide range has been speculated to be caused by different treatment regimens used, particularly the axillary dissection and radiation

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therapy (RT) [5]. Although some risk factors for lymphedema have been described, currently, there is no definite factor that may explain lymphedema's etiology. Lymphedema has negative effects on the patient's physical and psychological functioning. It also raises the risk for lymphangitis, cellulitis, and lymphangiosarcoma [6]. The most commonly used treatment method for lymphedema is the complete decongestive therapy (CDT) which includes manual lymphatic drainage (MLD), compression therapy, exercise, and skin care. In breast cancer-related lymphedema treatment, the CDT's success rate has been reported to be between 22 and 73 % [7]. This method is applied in two consecutive phases: intensive phase and maintenance phase. The intensive phase of treatment comprises a course of daily exercise and MLD to decongest the lymphedematous area of the body, followed by multiple-layer short-stretch bandaging to prevent the reaccumulation of fluid and create a counter force to muscle contraction in order to promote lymph flow and skin care. The compression garment replaces bandaging in the maintenance phase [2, 8]. CDT's effectiveness and safety has been backed up by the International Society of Lymphology [2]. Looking at the literature, we see that the focus is generally on the factors that affect/cause the development of lymphedema. Still, during our clinical practice and when we examine the literature, there is a wide range of patient response to treatment. We may have had the impression from the limited number of previous studies that the patient demographics and clinical variables could affect the patients' response to treatment. In fact, they have also suggested that patient characteristics such as advanced age, lymphedema duration, and body mass index can affect the response to treatment [4, 7, 8]. However, there have been some studies aiming at defining factors influencing treatment outcomes, but no consensus has been reached yet [4, 7, 8]. Therefore, in this study, we aimed at exploring primarily the relationship of complex decongestive therapy with the patient characteristics and clinical characteristics in breast cancer-related lymphedema and secondarily the factors that are predictive for the response to lymphedema treatment.

Materials and methods

Subjects

We collected and analyzed data retrospectively from the files of patients with breast cancer-related lymphedema who presented to our rehabilitation clinic between 2006 and 2012. Many of the patients were referred to us from our university hospital's medical and radiation oncology clinics. Apart from this, the lymphedema patients who completed their primary cancer treatment (chemotherapy and/or radiotherapy) in other hospitals were being monitored in our unit. Differences had been found in the patients' arm circumference measurements during their routine examinations, and they were directed to us with a diagnosis of lymphedema. When further arm circumference measurements and volumetric assessments were performed in these patients in our lymphedema diagnosis and treatment unit, their diagnosis of lymphedema was ascertained. All patients had undergone either breast-conserving surgery or mastectomy. Patients with known arterial or venous disease, history of recurrent infections, active rheumatic disease such as systemic lupus erythematosus, history of organ transplantation, ulcers in the affected arm, or skin metastases and those with bilateral lymphedema were not included in the study. The files of 420 patients, who were included in the CDT program at the lymphedema unit due to breast cancer-related lymphedema, were reviewed. Nineteen patients were excluded from the study for having missing information in their files and 70 patients for meeting the exclusion criteria. Three hundred thirty-one patients were eligible for analysis.

Measurements

Patient demographics (age, weight, height, marital status, occupation, education, smoking history, age of menarche and menopause, other diseases, and level of activity) and clinical variables (diagnosis type, operation date and type, number of chemotherapy (CT) cycles, and RT sessions, whether they received tamoxifen, a hormonal therapy) as well as patient variables (weight gain after cancer treatment and time from surgery to lymphedema onset) were recorded.

The patients were monitored using the arm circumference measurement method during their treatment. Initially, right and left arm circumferences were measured at 5-cm intervals, starting from the carpometacarpal joint. We used a computer program (Limb Volumes Professional version 5.0) to convert these values into limb volumes in milliliters. After this, the percentage of excess volume (PEV) was calculated. This method minimizes the effects of body weight on the calculation of lymphedema severity [8].

The severity of lymphedema is defined as the PEV, the excess volume [the difference between lymphedema arm (VL) and healthy arm (VH)] relative to the healthy arm volume (VH), PEV = (baseline VL − VH) / VH×100 %. The PEV is better for defining the severity of lymphedema than the absolute difference volume [8]. The efficacy of CDT, which is the response to the therapeutic intervention, was quantified as the percent reduction in excess volume (PREV), PREV=100 %×(posttreatment VL − baseline VL) / excess volume. If PREV was −100 %, then the volume of the lymphedema arm was successfully reduced to the level of the healthy arm.

Treatment

All patients were treated with the CDT, which consisted of patient education, manual lymphatic drainage (self), compression therapy with a short-stretch bandage for 23 h per day, exercise, and skin care in the intensive phase. In the maintenance phase, compression bandages were replaced by low-stretch elastic garments. During the intensive phase, limb volumes were recorded in 1-week intervals. No drugs were used for lymphedema. Patients were advised to have plenty of liquid and follow a salt-free diet. They were also warned not to gain weight and follow an appropriate diet. All patients were given brochures covering the details of the treatment program, recommendations for protecting from lymphedema, illustrations of exercises, and frequently asked questions. These were reminded to patients during their weekly examinations. The treatment continued until the decrease in the limb volume has ceased [2]. The treatments and measurements were carried out by the same physiotherapist, and responses to treatment were assessed by the same physiotherapy specialist. In other words, the same physiotherapist and physiotherapy specialist worked in the lymphedema diagnosis and treatment unit in the course of performing the analyses.

Statistical analysis

The data were analyzed using the Statistical Package for the Social Sciences Program (SPSS Statistics Version 20.0 for Windows, Chicago, IL). Descriptive analyses were used for the demographic data, Spearman's rank correlation coefficient for finding the relationship between the variables, the Wilcoxon signed-rank test for comparing volume measurements of lymphedema and healthy arms, and the simple and multivariate linear regression analysis for determining the final predictive factors. The level of statistical significance was set at $p<0.05$.

Results

The data of 331 patients were analyzed. Their demographic characteristics are summarized in Table 1, clinical characteristics in Table 2, and lymphedema characteristics in Table 3.

Of the patients, 54.7 % underwent a total mastectomy and an axillary dissection surgery and 36.8 % were receiving hormonal therapy with letrozole and 30.4 % with anastrozole and 29.2 % with exemestane.

The baseline PEV was 30.6±21.6 %, and it improved to 17.9±13.6 % with treatment (CDT). The percent reduction in excess volume was 41.6 %.

No statistically significant correlation was found between the response to treatment of related variables (arm volume, PEV, PREV) and the number of lymph nodes removed, operation type, CT, or RT ($p>0.05$). No statistically significant correlation was found between the duration of lymphedema treatment and any of the variables (patient demographics and clinical variables) assessed during the study ($p>0.05$).

Table 1 Demographic characteristics of patients

Characteristics	n=331
Age (mean± SD) (years)	54.44±10.9
Education level (n, %)	
Literate	27 (8.2)
Elementary school	134 (40.5)
Middle or high school	88 (26.6)
College	82 (24.8)
Marital status (n, %)	
Married	275 (83.1)
Single	14 (4.2)
Widowed	41 (12.4)
Occupation (n, %)	
Homemaker	210 (63.4)
Retired	79 (23.9)
Office worker	34 (10.3)
Other	8 (2.4)
Activity level (n, %)	
Sedentary	186 (56.2)
Walks for pleasure	91 (27.5)
Regular exercise (3/week)	44 (13.3)
Athletic (<4/week)	10 (3)
Dominant hand (right) (n, %)	254 (96.6)
Smoker (n, %)	68 (20.5)

Table 2 Clinic characteristics of patients

Ca type (n, %)	
Invasive ductal carcinoma	240 (72.5)
Invasive cribriform carcinoma	12 (3.6)
Invasive lobular carcinoma	29 (6)
Inflammatory carcinoma	8 (2.4)
Other	24 (7.2)
Unknown	27 (8.2)
Post-op duration (mean ± SD) (months)	36.7±38.1
Chemotherapy patients (n, %)	309 (93.4)
Number of chemotherapy cures (mean ± SD)	7.5±2.8
Radiotherapy patients (n, %)	279 (84.3)
Number of radiotherapy sessions (mean ± SD)	27.4±6.8
Other disease (n, %)	205 (61.9)
Tamoxifen users (n, %)	140 (42.3)
Duration of tamoxifen use (mean ± SD) (months)	31±20.2
Hormonotherapy patients (n, %)	171 (51.7)
Duration of hormonotherapy (mean ± SD) (months)	22.9±15.5
Post-op weight gain (mean ± SD) (kg)	10.8±13.5
Number of lymph nodes removed (mean ± SD)	19.1±8.3

Table 3 Lymphedema treatment data

Side of affected arm (*n*, %)	
Right	162 (48.9)
Left	169 (51.1)
Initial excess volume (ml)	674.8±473.4
Final excess volume (ml)	397.4±309.2
PEV before treatment (%)	30.7±21.6
PEV after treatment (%)	17.9±13.6
PREV (%)	12.7±16
Duration of treatment (mean± SD) (weeks)	2.92±1.3

PEV percentage of excess volume, *PREV* percent reduction in excess volume

A statistically significant positive correlation was found between the postoperative weight gain and the postoperative duration ($p<0.01$, $r=25$), the number of CT cycles ($p<0.05$, $r=0.11$), the duration of tamoxifen use ($p<0.01$, $r=0.34$), and the duration of hormonal therapy ($p<0.01$, $r=41$).

There was a statistically significant positive correlation between the pretreatment lymphedema arm volume and the age ($p<0.05$, $r=0.19$) and the duration of tamoxifen use ($p<0.05$, $r=0.21$). There was a statistically significant negative correlation between posttreatment lymphedema arm volume and activity level ($p<0.05$, $r=-0.13$), postoperative duration ($p<0.05$, $r=-0.29$), and postoperative weight gain ($p<0.05$, $r=-0.28$). No correlation was detected between the percent reduction in excess volume (PREV) and the weight gain, activity level, or postoperative duration ($p>0.05$) (Table 4). A statistically significant negative correlation was found between the posttreatment extra volume and the postoperative duration ($p<0.05$, $r=-0.21$) and the postoperative weight gain ($p<0.01$, $r=-0.32$). Simple linear and multiple linear regression analyses of related factors were performed.

Regression model

The number of CT cycles received (2.9 %), the duration of hormonal therapy (27.3 %), and the duration of tamoxifen use (19.4 %) were found predictive for postoperative weight gain (in the quadratic model) ($p<0.05$).

Postoperative weight gain, $-0.666+2.332\times$number of CT cycles$-0.080\times$number of CT cycles^2, $R^2=2.9$ %.

Postoperative weight gain, $-1.172+0.906\times$duration of tamoxifen use$-0.010\times$duration of tamoxifen use^2, $R^2=19.4$ %.

Postoperative weight gain, $-4.659+1.397\times$duration of hormonal therapy$-0.020\times$duration of hormonal therapy^2, $R^2=27.3$ %.

No statistically significant predictive variable or significant regression model was found in terms of posttreatment arm volume-related factors ($p>0.05$).

Table 4 Correlation coefficients among variables

	Age	Post-op weight gain	Post-op duration	Activity level	Number of CT cycles	Duration of Tmx use	Duration of hormonotherapy	Pre-tx volume	Post-tx volume	Post-tx extra volume (PEV)
Age	1									
Post-op weight gain	0.39	1								
Post-op duration	0.17**	0.25**	1							
Activity level	−0.04	0.22**	0.9	1						
Number of CT cycles	−0.08	0.11*	0.21**	0.09	1					
Duration of Tmx use	0.28**	0.34**	0.60**	−0.10	0.16	1				
Duration of hormonotherapy	0.18**	0.41**	0.54**	−0.03	0.24**	0.15	1			
Pre-tx volume	0.19*	0.11	−0.8	0.09	0.05	0.21*	0.02	1		
Post-tx volume	0.08	−0.28*	−0.29*	−0.13*	0.01	0.08	0.03	0.90**	1	
Post-tx extra volume (PEV)	0.03	−0.32**	−0.21*	0.018	0.04	0.00	0.05	0.59**	0.61**	1

Tmx tamoxifen, *Tx* treatment

*$p<0.05$; **$p<0.01$

Discussion

Lymphedema incidence after breast cancer treatment has been reported to be between 3 and 87 % in different studies [1, 3, 4, 9]. Lymphedema causes physical and psychological morbidity in breast cancer survivors [10]. Reducing the excess volume is the main goal in treating lymphedema, and in order to improve the success rate, treatment outcome predictors are still being investigated [4]. Our study showed that there was no any significant correlation between breast cancer treatment methods and response to treatment of lymphedema-related variables. There was also no statistically significant correlation between the duration of lymphedema treatment and any of the variables. There was a statistically significant positive correlation between the pretreatment lymphedema arm volume and the age and duration of tamoxifen use. There was a statistically significant negative correlation between the posttreatment lymphedema arm volume and the activity level and postoperative weight gain. Since postoperative weight gain is associated with posttreatment lymphedema arm volume, we can think that the weight gain predictors can indirectly affect the treatment. Our study showed that the number of CT cycles (2.9 %), the duration of hormonal therapy (27.3 %), and the duration of tamoxifen use (19.4 %) were predictive for postoperative weight gain (in the quadratic model).

The average age of our patients was 54.4±10.9 years. Liao et al. reported a decreased response rate to CDT in older patients [8], and the mean age in their study was 52.8± 10.5 years. We found no significant correlation in our study between age and the duration of lymphedema treatment or volume change. However, we found a statistically significant positive correlation between age and pretreatment lymphedema arm volume. This result may suggest that the age is important in terms of lymphedema volume/severity.

In our study, the average onset of lymphedema after surgery was 36.7±38.1 months. This is very similar to the previously reported figures [8, 11]. Vignes et al. found in their study that the duration of lymphedema was predictive for the response to treatment [4]. We, on the other hand, considered the time passed from the surgery to the development of lymphedema, not the duration of lymphedema. Our literature survey did not yield any reference to the suggestion that the time from the surgery to the onset of lymphedema does not have any effect on the severity of lymphedema or response to treatment. We did not detect such an effect either. As we have not encountered any source or data on this in the literature, we can hardly make a comment on it. It seems that whether lymphedema develops in early or late period of cancer treatments does not affect the response to treatment of lymphedema.

The percentages of response to treatment we found are similar to those in the literature [4, 12]. There was a statistically significant negative correlation between the posttreatment lymphedema arm volume and the activity level, postoperative duration, and postoperative weight gain. In our study, the average duration of intensive phase lymphedema treatment was 2.92±1.3 weeks. The duration of treatment was not found to be correlated with neither any of the patient demographics and patient variables (weight gain after cancer treatment, time from surgery to lymphedema onset) nor with clinical variables. Since weight and activity level are changeable risk factors, making appropriate arrangements in clinical practice seems will increase our success in treatment.

Most of the previous studies assessing the effect of a high body mass index (BMI) on the severity lymphedema utilized the weight at the start of treatment. We questioned patients' weight gains after the initiation of their cancer therapy. Various studies have reported a negative prognostic effect of a high BMI on the development and prognosis of lymphedema [7, 9]. Johansson et al. reported that a higher BMI at the time of surgery influenced the occurrence of lymphedema [13]. Weight gain after surgery was reported by Petrek et al. to be an independent risk factor for lymphedema [14]. Vignes et al. reported that a higher BMI was related to a larger absolute reduction of lymphedema volume [4]. They also reported that postoperative weight gain could be an independent risk factor for lymphedema [4]. In our study, the duration of hormonotherapy, postoperative duration, and number of CT cycles were found to correlate with the postoperative weight gain, but this correlation was not reflected on the PEV values. In our study, postoperative weight gain was found to be negatively correlated with arm volumes after CDT. Patients are weighed in our clinic at each weekly visit, and obese and overweight patients are strongly encouraged to lose weight. Lymphedema patients are also encouraged to limit their salt intake and increase their activity levels; walking, in particular, is recommended for all patients. This might be one of the reasons for the greater reduction in PEV in those patients who gained weight after their surgery.

Our study demonstrated that the duration of tamoxifen use was positively correlated with postoperative weight gain. This is consistent with the previously published data [15]. Interestingly, tamoxifen use was also found to correlate with PEV. Cutuli et al. reported that tamoxifen use caused an increase in the incidence of thromboembolic events and lower extremity lymphedema [16]. However, we have not come across any study reporting this correlation of tamoxifen with higher upper extremity PEV. This result may suggest that closer monitoring may be needed in patients using tamoxifen. Further studies examining this association would be helpful.

Our study's strong points are the inclusion of only those patients who developed lymphedema after breast cancer therapy, having been carried out in a single university hospital and having had a large sample size. Being a monocenter study

enabled us to use the same lymphedema treatment protocol on all patients. Most of the patients are still being routinely followed up at our clinic. Being retrospective and not considering BMI or the effect of climate on CDP outcomes in the statistical analysis are this study's limitations. In Izmir, where our hospital is situated, summer months tend to be quite hot and patients are not bandaged from July through September. The quality of life and the psychological effects of lymphedema could not be evaluated retrospectively. The patients who had lymphangitis or allergic reactions during their therapy were not included in this study. These factors may influence treatment outcomes. We did not categorize the patients into grades according to lymphedema severity. We instead assessed treatment response according to actual limb volumes. Fibrosis may be a predictive factor which was not evaluated in our study.

In conclusion, the response to the treatment of lymphedema varies among patients in clinical practice and the reasons for such differences are still not being fully understood. No significant correlation was found in our study between the duration of lymphedema treatment and the patient characteristics or clinical variables, nor between the lymphedema arm volume and the patient characteristics or clinical variables. However, considering the correlation we showed the post-treatment lymphedema arm volume to have with postoperative weight gain and activity level, these two variables deserve an in-depth consideration in clinical practice. With further studies that will exhibit the predictive factors of lymphedema treatment outcomes, it will be possible to improve our success rate in treatment and to make the treatment outcomes permanent in our clinical practice.

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Author's contributions S. Eyigor performed the conception and design, acquisition of data, analysis and interpretation of data, drafting the article and revising, and final approval of the version.

E. Cinar performed the acquisition of data, analysis and interpretation of data, drafting the article, and final approval of the version.

I. Caramat and B. Koc performed the acquisition of data, analysis and interpretation of data, final approval of the version.

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