Original Article

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Early Diagnosis of Lymphedema after Breast Cancer Treatment: Bio-Impedance Spectroscopy

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ABSTRACT

Objective: Breast cancer-related lymphedema is an important health problem. The aim of this study is to ensure early diagnosis of patients at risk of developing lymphedema and revealing the predisposing factors.

Materials and Methods: Measurements in the pre-operative period and in postoperative months 3, 6, 9 and 12 and years 2 and 3 were performed prospectively with bio-impedance spectroscopy for patients treated for breast cancer between November, 2013 and November, 2016. Demographic and clinical-pathological data of the patients were investigated to assess the factors that affect the development of lymphedema.

Results: 245 measurements were obtained from the 67 patients who participated in the study.

18 (26.8%) patients were diagnosed with lymphedema and 16 (89%) of these patients were clinically diagnosed with stage 0 and 2 (1%) patients with stage 1 lymphedema. The median age was 50.7

(32-77) years. Performing axillary dissection and positivity in more than 3 nodes were found to be statistically significant with a percentage of 63.3% (n=15) and 64.7% (n=11) p=0.049 and p<0.001, respectively.

Conclusion: Periodic measurements with bio impedance spectroscopy can be an effective method to diagnose early stage lymphedema after breast cancer, and enable selecting the group of patients who would benefit from early treatment.

Keywords: Lymphedema, early diagnosis, breast cancer, bio-impedance spectroscopy

Introduction

Lymphedema is a condition which is characterized by the generalized or regional accumulation of protein-rich interstitial fluid in the soft tissue as a result of the disturbance of lymphatic circulation due to certain congenital and acquired reasons. The most frequent reason for secondary lymphedema in the upper and lower extremities is cancer-related lymphedema (1).

Among patients receiving primary treatment for breast cancer, nearly one million patients globally fight the problem of lymphedema (2). The symptoms of breast cancer-related lymphedema (BCRL) may emerge at any time following surgery. BCRL generally starts in a stealthy way without any specific reasons. Patients may have symptoms such as swelling, painfulness, tightness of jewelry like rings and bracelets or garments, tingling and fatigue. Damage that occurs on the skin and lymphatic vessels caused by chronic inflammation, infection, minor traumas and fibrosis may cause lymphedema to progress. The initial changes in soft tissue are reversible; however, irreversible, permanent sequel and fibrosis may develop in advanced stages (3).

It is difficult to identify the actual incidence of BCRL due to differences in the diagnostic and measurement methods and follow-up periods (1, 2, 4). The lack of a standard in measurement standards and differences of approach among centers are some of the difficulties experienced in approaching lymphedema. Since there are no well-designed and sufficient randomized studies, there is no consensus on the appropriate treatment for lymphedema (5, 6).

When lymphedema becomes clinically significant, the difference between the two arms may be assessed using traditional methods such as measuring the arm diameter with a meter or volume measurement by water displacement test. However, the fact that these

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measurements are not standard (measurement points may change at every examination), interpersonal measurement differences and limited effectiveness at the early stage are the disadvantages for these methods (5). Early diagnosis before the development of clinical signs and early start of therapy for the patients may prevent lymphedema from progressing to further stages irrevocably. For that reason, it is of critical importance to recognize the group of patients that may develop lymphedema in advance. The method of bio-impedance spectroscopy (BIS) developed by Cornish et al. (7) in recent years enables precise measurement of any changes in the extracellular fluid and numerical assessment of the difference between the arms through a direct measurement of the electrical resistance of the extracellular fluid in the soft tissue of the arm, thereby making it possible to make a diagnosis of lymphedema before clinical signs occur, which are expressed as Stage 0. It has been reported that objective comparison can be made at follow-ups and the patients' clinical progress can be monitored by performing regular measurements and analyzing the numerical values obtained (7-11).

This study is aimed at assessing the effectiveness of prospectively applied BIS monitoring in identifying subclinical lymphedema, recognizing the patients that have a risk of developing lymphedema in advance and demonstrating the predisposing factors.

Materials and Methods

Ondokuz Mayıs University Ethics Committee approval and patient consents were obtained. Patients were scheduled for follow-up via arm measurements following breast cancer treatment using the bio-impedance spectroscopy (L-Dex® U400 ImpediMed, Australia) device. Regarding the measurement protocol, measurements were scheduled to be made in the preoperative period and in postoperative months 3, 6, 9 and 12 followed by annual measurements. Those with a postoperative L-Dex score below 10 units and with more than 7 units of difference between the preoperative measurement and follow-up measurements despite the score being in normal limits were considered to have Stage 0 lymphatic edema and were planned to be included in the early treatment program. In order to assess the factors that influence lymphedema development, the demographic and clinical-pathological data of the patients; age, dominant arm, disease side, breast and axilla surgery, radiotherapy (RT) and the side receiving it, the total number of excised lymph nodes, additional diseases and association with the tumor stage were investigated.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS Inc.; Chicago, IL, USA) 18.0 program was used for statistical analyses. The data were demonstrated including the arithmetic average ± standard deviation (AO±SS), median (minimum-maximum) and frequency (%). The Shapiro-Wilk test was used in order to analyze the normal distribution of results pertaining to quantitative data. For comparing the two independent groups, the Student t-test was used for data with normal distribution and Mann-Whitney U test was used for data without a normal distribution. The frequencies were compared using the Continuous corrected chi-squared, Pearson chi-squared and Fisher Exact test. The statistical significance level was accepted as $p<0.05$.

Table 1. L-Dex scores obtained in patient follow-ups

			Lymphedema	
	Follow-up period	Number of patients (n%)	L-Dex score >10 (n%)	L-Dex score increase>7 (n%)
245 Follow-ups	Month 3	5 (7.4)	-	
	Month 6	9 (13.4)	4	
	Month 9	13 (19.4)	2	2
	Month 12	19 (28.3)	4	
	Year 2	9 (13.4)	2	
	Year 3	12 (17.9)	3	1
		Total: 67 (100%)	15 (22%)	3 (4.4%) 18 in total (26.8%)

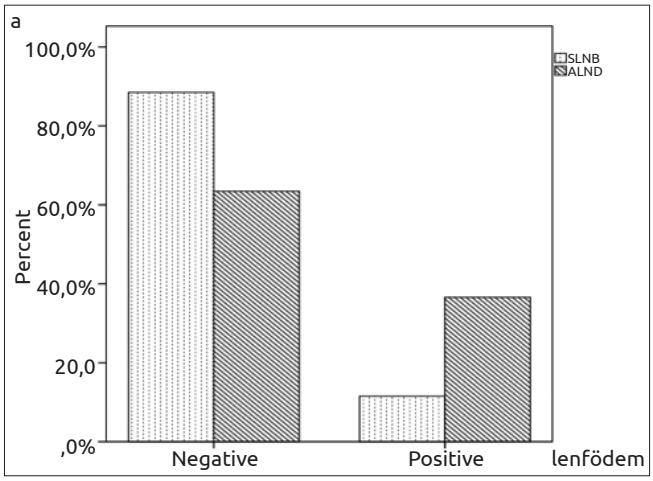
Table 2. Relationship between age, body mass index, history of hormone use, tumor size and lymphedema in patients

	Description	Average	SD	Median	min-max	p
Age	No lymphedema	50.9	10.3	53	32-77	0.717
	Lymphedema	49.9	11.5	46.5	32-76	
	In the entire group	50.6	10.6	51	32-77	
BMI	No lymphedema	28	4.9	28	19-42	0.837
	Lymphedema	28	5.1	26.5	20-42	
	In the entire group	28.2	4.9	28	19-42	
Hormone therapy	No lymphedema	2.43			0-60	0.546
	Lymphedema	5.67			0-72	
	In the entire group	3.3				
Tumor size	No lymphedema	13.86	9.7	13	1-35	0.547
	Lymphedema	12.1	7.4	13	1-28	
	In the entire group	13	91	13	1-35	

SD: standard deviation, BMI: body mass index; min: minimum; max: maximum

Results

In order to provide the preliminary results in the third year of the study, the assessment on follow-ups performed between November, 2013 and November, 2016 excluded 4 patients since they lacked follow-up and 1 patient due to exitus out of the 72 patients that were treated for breast cancer and took part in the study. In 245 measurements taken from 67 patients, the number of patients diagnosed with lymphedema was 18 (26.8%); in 15 (22%) patients, the L-Dex score was above 10 units and in 3 (4.4%) patients, the difference between follow-up measurements was more than 7 units (Table 1). Among these patients, 16 (89%) were diagnosed with Stage 0 lymphedema, 2 (1%) patients developed clinically significant Stage 1 lymphedema and the difference between the arms was 2 and 2.5 cm in arm circumference measurements. The patients' median age



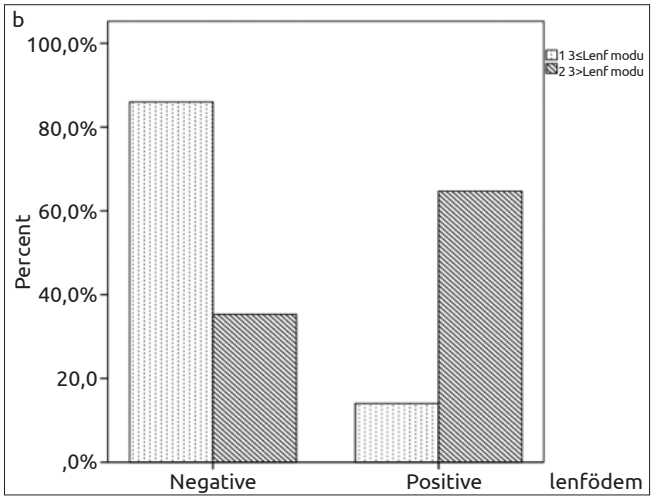


Figure 1. a, b. Relationship between axillary dissection and lymphedema;

Relationship between more than 3 positive lymph nodes in the axilla and lymphedema.

was 50.67 (32-77) (Table 2). In the patients, the dominant arm was the right one with 87% (n=58) and the diseases side was the left side with 79% (n=53) and no differences were identified in terms of lymphedema (p=1,0). Additional diseases [diabetes mellitus (5; 7.5%), hypertension (7, 10.4%), coronary artery disease (4, 6%), rheumatoid disease (4, 6%) and chronic obstructive pulmonary disease (4, 6%)] were present in 30% (n=20) of the patients. The ratio of patients receiving neo-adjuvant chemotherapy was 10.4% (n=7) and its effect on lymphedema was not identified (p=0.375). Among the patients that developed lymphedema, the effect of age, body mass index, tumor size, tumor type, stage, grade and hormone receptor status was not found to be significant (Tables 2 and 3). Among the surgeries performed on breast, the ratio of breast-conserving surgery was 66% (n=44) and mastectomy ± reconstruction rate 34% (n=23) and no significant differences were seen in terms of their effect on lymphedema (p=0.178). However, when comparison with sentinel lymph node biopsy (SLNB) was made with respect to surgery on the axillary side, lymphedema was 36.6% (n=15) in those that received axillary dissection (AD) while it was identified to be 11.5% (n=3) following SLNB and the difference was found statistically significant (p=0.049). Additionally, positivity of more than 3 lymph nodes (n=11, 64.7%) was another factor found to be associated with lymphedema (p<0.001) (Figure 1a, b) (Table 3). While the rate of treatment involving lymphatics in the radiotherapy field was 68% (n=46), its effect was not found to be statistically significant in terms of lymphedema (p=0.498).

Table 3. Effect of demographic, clinical and pathological characteristics of patients and treatment practices on lymphedema

	n	%	Lymphedema	%	p
Profession	9	13.4	3	16.7	0.693
Dominant arm, right	58	87	16	27.6	1
Diseased side, left	53	79	14	26.4	1
Additional disease: DM, HT, CAD, COPD, RD	20	30	2	11.2	0.276
NCT	7	10.4	1	5.6	0.665
Pathology IDC	58	86.6			0.684
ILC	4	6	15	83.3	
Mixed	4	6	2	11.1	
Medullary	1	1.5	1	5.6	
Grade 1	6	9			0.351
Grade 2	39	58.2	11	61.1	
Grade 3	22	32.8	7	38.9	
ER (+)	49	73	11	61.1	0.219
PR (+)	42	62.7	7	38.9	0.031
HER2 (+)	10	14.9	3	16.7	1
BCS	44	65.7	9	50	0.178
MRM	18	26.9	6	33.3	
MRM + Reconstruction	5	7.5	3	16.7	
ALND	41	61	15	36.6	0.049
SLNB	26	39	3	11.5	
More than 3 positive LNs	17	25	11	64.7	0.001
Stage 1a	12	17.9	2	11.1	0.459
1b	10	14.9	3	16.7	
2a	12	17.9	4	22.2	
2b	26	38.8	6	33.3	
3a	5	7.5	3	16.7	
3b	2	3			
RT lymphatic	46	68	14	30.4	0.498
10 or more LNs in total	45	67	15	33	0.157

DM: diabetes mellitus; HT: hypertension; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; RD: rheumatoid disease NCT: neo-adjuvant chemotherapy; IDC: invasive ductal carcinoma; ILC: invasive lobular carcinoma; ER: estrogen receptor; PR: progesterone receptor;

HER-2: human epidermal growth factor-2; BCS: breast-conserving surgery; MRM: modified radical mastectomy; ALND: axillary lymph node dissection; SLNB: sentinel lymph node biopsy; LN: lymph node

Discussion and Conclusion

On average, one fourth of patients receiving treatment for breast cancer develop lymphedema with the highest frequency being in the first 18 months following treatment (1-6). In addition to the burden caused by cancer diagnosis following breast cancer treatment, the physical limitation of the arm due to lymphedema and the resulting social limitation, labor loss of patients, body image-related worry, anxiety depression and adaptation problems, social and sexual problems put the patients in a difficult condition in their professional and private lives. Therefore, the problem of lymphedema should be importantly taken into consideration in the group of patients diagnosed with breast cancer as an important social problem (5, 6).

Lymphedema was reported in the literature with difference rates of incidence such as 6-30% and 6-62.5% (4, 6, 12-15). Since the standards for evaluation are not consistent, there is no consensus on the actual incidence rate. However, it is most frequently reported as being 30% on average (1-4, 15). As a result of our study, the cumulative incidence was 26.8%, which was found to be consistent with the literature.

It has been demonstrated that the treatment methods applied for breast cancer are generally associated with lymphedema development; there is evidence in the literature that it generally occurs as a result of axillary lymph node dissection and/or axillary radiotherapy resulting in deterioration of the lymphatic in the upper extremity and it has been shown that preserving axillary surgeries such as sentinel SLNB reduce the risk (1, 2, 5, 9, 10, 16, 17). Among the factors influencing BCRL, performing dissection on the axilla was demonstrated as a reason contributing to the development of lymphedema in our study. Lymphatics were included in the radiotherapy treatment field at a high rate of 68% (n=46), however, no statistically significant result was obtained that it increased lymphedema (p=0.498). Coen et al. (16) identified in their series of 727 patients that BCRL incidence was 2% with tangential radiation and 9% with lymphatic radiation as a result of 10 years of radiotherapy in the entire breast. Jose' Luiz B. Bevilacqua et al. (15) and Bergmann et al. (17) reported in their studies that BMI, RT, post-operative seroma, age and chemotherapy on the same arm were independent factors associated with lymphedema. However, no relationship was identified in our study between age and BMI and lymphedema with p=0.717 and p=0.837, respectively.

Early diagnosis of lymphedema, i.e., its identification before it becomes clinically recognizable, enables the treatment to be started earlier and measures to be taken more effectively. Only this can make it possible to keep lymphedema under control before it results in sequelae, fibrosis and limitation (7, 10). From an economic point of view, the treatments and preventive services provided when lymphedema is at earlier stages (bandage, massage, exercise) are both more cost-efficient and promising in terms of treatment efficacy as compared to the treatment methods applied when advanced lymphedema develops (pumps applying pressurized massage, surgical procedures) (5, 9, 10). Lacomba et al. (18) reported in their study that early physiotherapy was effective in preventing lymphedema although it was not cost-efficient to include all the patients in the exercise program. For that reason, selection of patients with a high risk for developing lymphedema who would benefit from treatment becomes important (19).

BIS offers the advantage of identifying lymphedema as early as 4 months in advance as it provides more precise and standardized measurements as compared to conventional measurement methods (7, 10). This way, it may become possible to reduce long-term morbidity related to lymphedema. Soran et al. performed monitoring with BIS in their study where they were able to detect subclinical lymphedema with early diagnosis, made 28 (38.9%) subclinical lymphedema diagnoses in their series of 180 patients and managed to reduce clinical lymphedema incidence from 36.4% to 4.4% with early treatment (10).

Although the strength of our study is that it is a prospective and observational study, its limitations include the currently low number of patients and the lack of randomization possibility. The predisposing factors for lymphedema can be demonstrated more clearly in a larger patient group and with a longer follow-up period.

In conclusion, lack of standard diagnostic and treatment methods not only lead to difficulties in correctly identifying the incidence of lymphedema but also constitute an obstacle to creating a universal approach. However, the fact that awareness of lymphedema has been rising in recent years and early diagnosis may increase the success of preventive and treatment practices is promising. In the light of our knowledge, the first measures to be taken may include performing lymphatic-sparing surgeries in the axilla as part of breast cancer treatment based on the evidence that it increases the risk for lymphedema and avoiding wide dissections unless it is required for oncological reasons. The objective should be to evaluate lymphedema with an accurate and standard method in order to identify patients with high risk for lymphedema among those receiving treatment for breast cancer at an early stage, monitor them closely and to treat patients at an early stage before any clinical signs develop. BIS monitoring may provide the means to determine the group of patients that may benefit from treatment based on early diagnosis.

Ethics Committee Approval: Ethics committee approval was received for this study from Ondokuz Mayıs University.

Informed Consent: Informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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Conflict of Interest: No conflict of interest was declared by the authors.

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