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Frequency of Early-Stage Lymphedema and Risk Factors in Postoperative Patients with Breast Cancer

Meme Kanseri Hastalarda Cerrahi Sonrası Erken Dönem Lenfödem Görülme Sıklığı ve Risk Faktörleri

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ABSTRACT

Objective: Lymphedema is a chronic major complication that is seen frequently post-operatively and has negative effects on quality of life. In our study, determining the early-stage postoperative lymphedema frequency and specifying the risk factors in its development has been aimed.

Materials and Methods: One hundred one cases that were operated on for breast cancer were evaluated regarding the 12-month control of their clinical specifications, histopathological specifications, and specifications related with the surgical intervention retrospectively. The data related to the parameters envisioned as risk factors were evaluated.

Results: Lymphedema development was found in 7 (6.9%) out of 101 cases constituting the study group. No significant difference (p>0.05) in terms of lymphedema development was determined among age, body mass index (BMI), chemotherapy (CT), postoperative seroma or infection, mastectomy with the dominant arm, and breast-conserving surgery (BCS), which were evaluated as risk factors. There was a significance (p<0.05) between the other risk factors, which were axillary dissection (AD), number of positive lymph nodes (LN), radiotherapy (RT), the tumor size (T), and lymphedema existence. In every case in which lymphedema was determined, it was seen that there was axillary LN involvement and 15≤LN were ablated in the dissection (p<0.05).

Conclusion: It is seen that AD, RT applied to the breast cancer patients, and T are important risk factors in early-stage lymphedema development. No early-stage lymphedema development was determined in any of the patients to whom sentinel lymph node dissection (SLND) was applied.

Key words: Lymphedema, breast cancer, risk factors, incidence

ÖZET

Amaç: Lenfödem meme kanseri cerrahisi sonrası sık görülen ve hastanın yaşam kalitesini olumsuz yönde etkileyen kronik majör bir komplikasyondur. Çalışmamızda meme kanseri cerrahisi sonrası lenfödem görülme sıklığı ve gelişiminde etkili risk faktörlerinin belirlenmesi hedeflendi.

Yöntem ve Gereçler: Meme kanseri nedeniyle cerrahi tedavi uygulanan 101 olgunun cerrahi sonrası 12. ayda yapılan kontrollerinde değerlendirilen klinik, histopatolojik ve uygulanan cerrahi girişime ait özellikleri retrospektif olarak incelendi. Risk faktörü olarak öngörülen parametrelere ait veriler değerlendirildi.

Bulgular: Çalışma grubunu oluşturan 101 olgudan 7'sinde (%6,9) lenfödem gelişimi saptandı. Risk faktörü olarak değerlendirilen yaş, vücut kitle indeksi (BMİ), kemoterapi (KT), cerrahi tedavi sonrası seroma veya enfeksiyon gelişimi, dominant kol ile mastektomi ve meme koruyucu cerrahi (MKC) arasında lenfödem gelişimi açısından anlamlı fark saptanmadı (p>0,05). Diğer risk faktörleri olan aksiller diseksiyon (AD) uygulanması, pozitif lenf nodu (LN) sayısı, radyoterapi (RT) ve tümör boyutu (T) ile lenfödem varlığı arasında ise anlamlılık mevcuttu (p<0,05). Lenfödem saptanan tüm olgularda aksilla LN tutulumu olduğu ve yapılan diseksiyonda 15≤LN çıkarıldığı görüldü (p<0,05).

Sonuç: Meme kanseri hastalarda uygulanan AD, RT ve T'nin lenfödem gelişiminde önemli risk faktörleri olduğu görülmektedir. Dikkat çeken bulgu ise AD'nin genişliği ile artan lenfödem insidansıdır. Bunu önlemek amacıyla evreleme için yeterli olarak görülen 10 LN içerecek level I, II sınırlı AD'un tercih edilmesi ve klinik olarak aksilla negatif olgularda mutlaka sentinel lenf nodu biyopsinin (SLNB) rutin uygulanması gerektiği kanaatindeyiz.

Anahtar sözcükler: Lenfödem, meme kanseri, risk faktörleri, insidans

Introduction

The increase in the survival time of breast cancer cases in the last 2 decades has brought health problems in the long term relating to treatment (1). Lymphedema development, which affects the quality of life negatively, is defined as interstitial tissue effusion rich in protein as a result of failure in the lymphatic system in patients who undergo surgical treatment and radiotherapy (RT) for breast cancer (2). Even though the lymphedema development rates are given as 30% in the literature, there are many studies which that it in a large range of 2%-83% (3-5). This large range difference is thought to depend on the technique of lymphedema measurement, differences in description, and the timing of the assessment. Lymphedema development is frequently seen during the first 18 months but sometimes weeks or years after the treatment (6, 7). As the presence of lymphedema prevents daily activities, it affects the patient psychologically, socially, and economically, as well (8). Lymphedema is considered to be an important complication of breast cancer surgery that comes

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into prominence, as information towards preventing its development is limited; its treatment is difficult, it is progressive, and it affects a patient's quality of life negatively. Many risk factors are mentioned in the development of lymphedema. Determining these parameters will help the determination of high-risk case groups, thus providing the preventive precautions to be applied. There are 3 basic subjects that are envisioned as risk factors in lymphedema development; these are the factors relating to the treatment, the disease, and the patient (9-11). The factors relating to the disease are the stage of the tumor (T), the number of lymph nodes (LN) dissected, and the localization of the T. The factors relating to the treatment include the type of the applied surgical treatment and other treatment combinations applied together with RT and chemotherapy (CT). The factors relating to the patient are age, body mass index (BMI), wound site infection, and excessive use of extremity. Even though the factors that might be related to arm lymphedema development in patients with breast cancer have been assessed in many studies, its etiology has not been fully understood yet.

In our study, we aimed to determine the rate of lymphedema development in cases to whom surgical intervention was applied in our clinic due to breast cancer to assess the risk factors and differentiate the case groups with high risk of lymphedema development.

Materials and Methods

One hundred one female patients diagnosed with one-sided breast cancer who had surgical intervention to the breast and axilla between January 2010-March 2011 were included in the study. In the routine follow-up of the cases, the clinical and histopathological data and the data relating to the surgical procedure assessed at the 12th month were examined retrospectively, and arm measurements were made for lymphedema evaluation. Among the factors relating to the patient envisioned as risk factors, age (<50 or ≥50), BMI (<25 kg/m2, ≥25 kg/m2), smoking status, arm dominance (present or not), the surgery of breast [mastectomy/breast-conserving surgery (BCS) and axilla (axillary dissection (AD)/sentinel lymph node dissection (SLND)] applied, dissected number of LN, LN positivity, postoperative seroma and infection development (present or not), CT or RT treatment, grade (1, 2, 3) relating to the T, size (T1, T2, T3), and parameters of histopathological type were evaluated (Table 1).

Arm Lymphedema Measurement Method

The circumferential measurement method was used. Circumferential measurements were made in four regions of both upper extremities: the metacarpophalangeal joint, wrist, and 10 cm distal and 15 cm proximal to the lateral epicondyle. A diameter difference of more than 2 cm in the measurements made at the four regions compared to the healthy side was evaluated as lymphedema presence (12).

All of the cases were informed of lymphedema and protective measures after the clinical evaluation. The cases in which lymphedema development was determined were taken into a treatment program by the Physical Treatment and Rehabilitation Clinic, and written informed consent was obtained from patients who participated in this study.

Statistical Analysis

The SPSS-17.0 statistical software package was used. Statistical evaluation of the data was performed using Pearson chi-square test and Mann-Whitney test. $p<0.05$ was considered statistically significant. Age and BMI values of the cases were shown as mean±SD (minimum-maximum).

Results

Age, BMI, smoking status, and arm dominance, which were considered as the risk factors of the cases, were examined: the mean age of 101 cases was 52±10 (32-76), whereas it was 51±12.9 (38-68) in 7 cases (6.9%) where lymphedema was found. Lymphedema was found in 4 out of 50 cases aged under 50 and 3 out of 51 cases aged over 50 (p:0.706). BMI evaluation of all cases showed a mean value of 28.9±4 (20.9-42.5); 17 cases had a BMI value under 25, and 84 cases had a value of 25 and over. Lymphedema was found in 1 case whose BMI value was under 25 and in 6 cases whose BMI values were over 25 (p:1.000). In the whole study group, 5 cases (4.9%) were smokers, but none of the 7 cases in which lymphedema development was found was a smoker. Arm dominance was present in 3 out of 7 cases (42.9%) (p:0.699).

When the factors relating to the applied treatment, such as the surgery of the breast (mastectomy/BCS) and axilla (AD/SLND), dissected number of LN, number of positive LN, postoperative seroma or infection development, and RT and CT treatments, were examined, lymphedema development was found in 4 (57.1%) cases to which mastectomy was applied and in 3 cases (42.9%) to which BCS was applied (p:0.102). It was seen that AD was performed in every case in which lymphedema development was found (p:0.040) and that there was no lymphedema development in patients to whom SLND was applied (p:0.014). In every case to which AD was applied and lymphedema development was found, it was seen that the number of LN excited was ≥15 (p:0.013). The number of LN dissected in every case to which AD was applied was 15 (9-24) and 28 (22-34) in the cases in which lymphedema was found (p:0.069). When the positivity of the dissected LN was evaluated, the positive LN number in the whole case group was 1 (0-5) but 8 (7-26) in the lymphedema group (p: 0.019). Lymphedema development was found in 3 (9%) out of 33 (32.7%) cases in which postoperative seroma developed (p:0.680) and 1 (16.6%) out of 6 (5.9%) cases in which infection developed (p:1.000). It was seen that every case in which lymphedema was seen had RT (p:0.041) and CT (p:1.000) treatment.

When the factors relating to the disease, such as the T grade, T value, and parameters of T histopathology, were assessed as the risk factors relating to the disease, it was seen that the T grade was 2 in all cases in the lymphedema group. T1 was determined in 2 (28.6%), T2 was determined in 3 (42.9%), and T3 was determined in 2 (28.6%) of the cases in which lymphedema was found (p:0.025). As for T histopathology, invasive ductal carcinoma was seen in 6 (85.7%) and inflammatory carcinoma was seen in 1 (14.3%) case in the group with lymphedema.

Discussion and Conclusions

Breast cancer is among the most frequent cancer types seen in women, and its frequency has shown an upward inclination in recent years (13, 14). When cancer data of the Ministry of Health in Turkey were examined, it was seen that the frequency of breast cancer in 2006 was 37.6 per 100,000, while it became 38.5 in 2007 and 41.6 in 2008 (15). Besides the increasing frequency of breast cancer, the survival time has lengthened significantly through the current early diagnosis methods for breast cancer and multidisciplinary treatment approaches, while the problems affecting the quality of life negatively have been encountered more frequently. Of these problems, lymphedema differs from others, as it is seen frequently in the long term during the postopera-

tive period.

The most important reason of such a large range of lymphedema incidence is the timing differences in detection and evaluation (16). In the evaluation of lymphedema, volumetric measurement, circumferential measurement, tissue tonometer, or imaging techniques are used. While it is known that volumetric measurement techniques give more accurate results, the circumferential measurement technique is used more frequently because of its higher practicability (17). For this reason, we used the circumferential measurement technique in our study. The 6th postoperative month is envisioned as the best time for the evaluation, when the adjuvant CT and RT are usually completed and the lymphedema

Table 1. The distribution of parameters in the case groups

Risk Factors	All case groups (n:101) %	Lymphedema (+) group (n:7) %	p value
Age	52±10 (32-76)	51±12.9 (38-68)	
• 50>	50 (49.5%)	4 (57.1%)	0.756
• 50≤	51 (505%)	3 (42.9%)	
BMI	28.9±4 (20.9-42.5)	30.4±5 (24.21-35.98)	
• 25>	17 (16.8%)	1 (14.3%)	1.000
• 25≤	84 (83.2%)	6 (85.7%)	
Smoking status	5 (4.9%)	0	
Arm dominance	55 (54.5%)	3 (42.9%)	0.699
Mastectomy/BCS			
• Mastectomy	29 (28.7%)	4 (57.1%)	
• BCS	72 (71.3%)	3 (42.9%)	0.102
AD/SLND			
• AD	54 (53.5%)	7 (100%)	**0.040**
• SLND	47 (46.5%)	0	**0.014**
The number of LN dissected in cases to whom AD has been applied	15 (9-24)	28 (22-34)	0.069
LN positivity	1(0-5)	8 (7-26)	**0.019**
Cases with 15≤LN dissection	51 (50.5%)	7 (100%)	**0.013**
Seroma development	33 (32.7%)	3(42.9%)	0.680
Infection development	6 (5.9%)	1 (14.3%)	1.000
RT treatment (+)	62 (61.4%)	7 (100%)	**0.041**
CT treatment (+)	92 (91.1%)	7 (100%)	1.000
Tumor			
• Grade			
1	5 (4.9%)		
2	89 (88.1%)	7 (100%)	
3	7 (6.9%)		
• Size (T)			
T1	25 (24.8%)	2 (28.6%)	
T2	71 (70.3%)	3 (42.9%)	**0.025**
T3	5 (4.9%)	2 (28.6%)	
• Histopathological type			
• Invasive ductal carcinoma	85 (84.1%)	6 (85.7%)	
Tubular carcinoma	3 (2.9%)	0	
Papillary carcinoma	3 (2.9%)	0	
Medullary carcinoma	2 (1.9%)	0	
İnvasive lobular carcinoma	2 (1.9%)	0	
Apocrine carcinoma	3 (2.9%)	0	
Inflammatory carcinoma	2 (1.9%)	1 (14.3%)	

BMI: Body mass index; BCS: breast-conserving surgery; AD: axillary dissection; SLND: sentinel lymph node dissection; LN: lymph node; RT: radiotherapy; CT: chemotherapy

Table 2. Studies reporting the prevalence of lymphedema following different surgical interventions in the literature

Study	Applied Surgical Procedure	Lymphedema Definition	Follow-up Period (month)	Number of cases	Incidence of lymphedema (%)
Kissin et al. (30)	Unidentified	≥2 cm	9	200	25.5
Werner et al. (20)	AD, RT	≥2.5 cm	37	282	19.5
Lin et al. (31)	RM, MRM, SM + AD, and RT	≥2 cm	24	283	16
Keramopoulos et al. (32)	SM/MRM + AD	≥2 cm	6	104	17
Deutsch et al. (33)	RM/Mastectomy+ RT Only Mastectomy	≥2 cm	36	1665	46.3
Clark et al. (5)	Mastectomy/SM	PVD ≥20% $aPVD_{change}$ ≥5%	36	188	20.7
Wilke (29)	SLND	>2 cm	6	2904	7
Lucci (35)	SLND	≥2 cm	12	411	6
Langer (34)	SLND	>2 cm	31 (average)	431	3,5
McLaughlin et al. (36)	SLND	>2 cm	60 (average)	600	5

MRM: Modified radical mastectomy; PVD: volume difference ratio; RM: radical mastectomy; RT: radiotherapy; SM: segmental mastectomy; AD: axillary dissection; SLND: sentinel lymph node dissection

symptoms became measurable (18). In our study, lymphedema development was found in 7 (6.9%) cases at the assessment at the 12th month.

When the risk factors were assessed in patients with lymphedema development, no statistically significant difference was found between the cases aged over 50 and under 50 in terms of lymphedema development (p: 0.706). Geller et al. (9) reported a significant increase in lymphedema development risk in women aged under 50. In many studies where age is assessed in the literature, similar to the results we obtained, this factor did not show a significant effect on lymphedema development (5, 7, 9, 11, 19).

When BMI was assessed as a risk factor, it was seen that there was no statistically significant difference between the BMI values of >25 or ≤25 on lymphedema development (p:1.000). In the studies, lymphedema development risk shows a 2-fold increase in cases where BMI is over 30. Even though its etiology is unclear, it is thought to occur because of increased fat and the subcutaneous tissue's role as a lymphatic fluid resource or the increase in lymphatic damage as a result of the need for more ecartation in axillary intervention (20).

In many studies present in the literature where smoking status and arm dominance are assessed, they are not found to be potent risk factors in lymphedema development, similar to our findings (7, 21, 22).

It is reported that the range of surgery of the breast and axilla and adjuvant treatments, such as RT, may increase the risk of lymphedema (23). Schunemann and Willich et al. (24) reported lymphedema development rates after radical mastectomy without postoperative RT, modified radical mastectomy (MRM), and BCS of 22.3%, 19.1%, and 6.7%, respectively. In most of the studies in the literature, it is reported that there is a relation between AD range and lymphedema incidence. Siegel et al. (25) reported that the lymphedema incidence of 37% with level I, II, and III dissection reduces to 8% when only level I and II dissection is applied. Moreover, in a study where BCS was applied, the lymphedema rate of 15% in the cases in which lumpectomy and AD were performed reduced to 3% in cases with only lumpectomy (26). In many studies, the LN number dissected was found to increase the lymphedema risk (18, 27, 28). It is reported that the lymphedema frequency is 5-7 times less in SLND, which is recommended to be performed in axilla-negative cases today compared to AD (29-36).

When different procedures for breast cancer, such as mastectomy, RT, and axillary procedures (AD/SLND), were assessed in terms of lymphedema development, it was seen that lymphedema rates varied between 16% and 46.3% during a follow-up period of 6 to 37 months, but in the last few years, it has also been seen in studies examining the cases to which SLND is applied that the lymphedema incidence is far lower, such as 3.5%-7% (Table 2). In our study, even though no statistically significant difference was seen between the cases to which mastectomy and BCS were applied (p:0.102), it was found that AD was applied to every case where lymphedema had developed, and no lymphedema development was found in any case in the early-stage cases (p:0.014). When the dissected LN number in the cases to which AD was applied was assessed, it was seen that the lymphedema incidence increased with increasing LN number dissected (p:0.069) and LN positivity (p:0.019).

In our study, RT treatment seemed to be one of the major factors that increased the lymphedema incidence (p:0.041). In the literature, even cases without surgical intervention with RT to the axilla showed increased lymphedema incidence; moreover, with the combination of AD, it is reported to increase the lymphedema risk even more by showing a synergistic effect (37). In similar studies, the lymphedema incidence in patients to whom RT was applied in addition to surgery was 41%, while this ratio was 17% in patients in whom surgery was performed alone (38, 39).

It is reported in the literature that infection and seroma development with adjuvant CT treatment do not increase the lymphedema incidence. No significant difference in these parameters in terms of lymphedema development was found in our study (p>0.05).

In all 7 (6.9%) cases in which lymphedema development was found, the T grade was 2. T histopathology revealed invasive ductal carcinoma in 6 (85.7%) cases and inflammatory carcinoma in 1 (14.3%) case.

When the relationship between the T value and lymphedema incidence was assessed, T1 was seen in 2 (28.6%), T2 was determined in 3

(42.9%), and T3 was determined in 2 (28.6%) cases. When compared to the whole case group, a significant difference was determined between T size and lymphedema incidence (p: 0.025). In many studies, T diameter was found to be a potent factor in lymphedema development (7, 40, 41).

As a result, a statistically significant relationship has been determined with the range of the AD (15≤ LN), dissected positive LN number, RT, and T and early-stage lymphedema incidence (p<0.05). The widespread prevalence of cases with early-stage breast cancer diagnosis, small T sizes, and absence of application of RT to the axilla (as the axillary involvement is lower), as well as the routine preference of SLND in cases where the axilla is clinically negative, are the basic reasons of the low lymphedema rates in our study group.

We do not have enough of a sample size to compare the groups based on the variables and no preoperative baseline measurements.

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