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The Effect of Breast Cancer Related Lymphedema on Health Related Quality of Life

Meme Kanserine Bağlı Lenfödemin Sağlıkla İlgili Yaşam Kalitesi Üzerine Etkisi

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ABSTRACT Objective: First, is there any difference in health related quality of life (HRQOL) scores between breast cancer-related lymphedema (BCRL) patients and healthy controls? Second, is there any difference in HRQOL scores of BCRL patients according to lymphedema severity? **Material and Methods:** The medical records of a total of 50 healthy volunteers and 78 unilateral BCRL patients were examined between 01 January 2012 and 31 December 2018 in the Physical Medicine and Rehabilitation Training and Research Hospital which is a tertiary center. Age, gender, BMI, surgical interventions (modified radical mastectomy (MRM) + axillary lymph node dissection (ALND) or lumpectomy), chemotherapy, radiotherapy, hormone therapy, pain, numbness, shoulder joint range of motion measurement, time after surgery, remove metastasis, metastatic lymph nodes, number of metastatic lymph nodes, number of resected lymph nodes, lymphedema status, and the SF-36 HRQOL scores of BCRL patients were noted from the files. **Results:** Seventy-eight women with BCRL and 50 healthy women were included in the study. When the parameters of the SF-36 HRQOL were compared between the BCRL group and the control group; physical functioning(42.57±8.3 vs. 46.84±7.4, p=0.004), physical role functioning (38.02±12.2 vs. 44.63±10.8, p=0.001), and physical component summary(40.47±8.4 vs. 45.30±9.7, p=0.005) scores were significantly lower in the BCRL group. Other SF-36 HRQOL parameters were similar between the groups (p>0.05). When the parameters of SF-36 HRQOL were compared between the lymphedema ≤ 3 cm and the lymphedema > 3 cm subgroups; all of the parameters were similar(p>0.05). **Conclusion:** In our study, compared to the lymphedema and control group SF-36, physical function, physical role function and physical component scores in lymphedema patients were lower and statistically significant. Interestingly, no statistically significant difference was found when SF-36 scores were compared between the lympedema ≤3 cm and >3 cm subgroups. These results show that the presence of lymphedema is much more important than the lymphedema severity in impairing quality of life.

Keywords: Breast cancer; lymphedema; quality of life

ÖZET Amaç: Meme kanseri ile ilişkili lenfödem (BCRL) hastaları ile sağlıklı kontroller arasında sağlıkla ilgili yaşam kalitesi (HRQOL) skorları açısından bir fark var mı? BCRL hastalarının HRQOL skorlarında lenfödem şiddetine göre bir fark var mı? **Gereç ve Yöntemler:** 1 Ocak 2012-31 Aralık 2018 tarihleri arasında üçüncü basamak merkez olan Fiziksel Tıp ve Rehabilitasyon Eğitim ve Araştırma Hastanesi'nde toplam 50 sağlıklı gönüllü ve 78 tek taraflı BCRL hastasının tıbbi kayıtları incelendi. Yaş, cinsiyet, vücut kitle indeksi (BMI), cerrahi müdahaleler (modifiye radikal mastektomi (MRM) + aksiler lenf nodu disseksiyonu (ALND) veya lumpektomi), kemoterapi, radyoterapi, hormon tedavisi, ağrı, uyuşma, omuz eklem hareket açıklığı aralığı, ameliyat sonrası geçen süre, metastaz varlığı, metastatik lenf nodu sayısı, rezeke edilen lenf nodu sayısı, lenfödem durumu ve BCRL hastalarının SF-36 HRQOL skorları kaydedildi. **Bulgular:** Çalışmaya BCRL'li yetmiş sekiz kadın ve 50 sağlıklı kadın dahil edildi. SF-36 HRQOL parametreleri BCRL grubu ile kontrol grubu arasında karşılaştırıldığında; fiziksel işlevsellik (42,57±8,3'e karşı 46,84±7,4, p=0,004), fiziksel rol işlevi (38,02±12,2 vs. 44,63±10,8, p=0,001) ve fiziksel bileşen özeti (40,47±8,4'e karşılık 45,30±9,7, p=0,005) skorları BCRL grubunda anlamlı olarak düşüktü. Diğer SF-36 HRQOL parametreleri gruplar arasında benzerdi (p>0,05). SF-36 HRQOL parametreleri lenfödem ≤3 cm ve lenfödem >3 cm olan alt gruplar arasında karşılaştırıldığında; tüm parametreler benzerdi (p>0,05). **Sonuç:** Çalışmamızda lenfödem ve kontrol grubu SF-36 ile karşılaştırıldığında lenfödem hastalarında fiziksel fonksiyon, fiziksel rol fonksiyon ve fiziksel bileşen skorları daha düşük olup istatistiksel olarak anlamlı idi. İlginç bir şekilde, lenfödemi ≤3 cm ve >3 cm olan alt gruplar arasında SF-36 skorları karşılaştırıldığında, istatistiksel olarak anlamlı bir fark bulunmadı. Bu sonuçlar, lenfödem varlığının, yaşam kalitesinde lenfödem şiddetinden çok daha önemli olduğunu göstermektedir.

Anahtar Kelimeler: Meme kanseri; lenfödem; yaşam kalitesi

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Breast cancer is the most frequently diagnosed cancer affecting women all over the world and its incidence has increased during the last decades.[1-4] Due to early detection and improved treatment facilities, there is an increased number of long-term breast cancer survivors.[1] Breast cancer 5-year survival rates range from 53 % in developing contries to 89% in developed countries worldwide.[5,6] Therefore, there is an increased focus on the health related quality of life (HRQOL).[7] As advances in the treatment of breast cancer continue to progress, health care providers and patients are increasingly focused on post-treatment quality of life.[8]

Breast cancer-related lymphedema (BCRL) is one of the most annoying complication of breast cancer treatment.[9,10] The main reason for lymphedema in the arm is the cessation of lymphatics coming from the arm as a result of axillary dissection and the drainage inadequate due to RT applied to the axillary region. As a result, the proteins in the interstitial fluid are not sufficiently cleaned and the protein concentration increases. As a result of increased colloid pressure, interstitial fluid escapes from the capillary area. A high protein lymphedema occurs. High levels of protein also stimulate inflammation and fibrosis. The arm becomes thick and stiff. As a result, upper limb functions are impaired. Lymphedema gives a feeling of heaviness in the limbs, prepares the ground for infection, negatively affects the patient's quality of life due to pain and reduced mobility.[11,12]

The aim of this study was as follows: First, is there any difference of HRQOL scores between BCRL patients and healthy controls? Second, is there any difference in HRQOL scores of BCRL patients according to lymphedema severity?

MATERIAL AND METHODS

In this study, the medical records of a total of 50 healthy volunteers and 78 unilateral BCRL patients were examined between 01 January 2012 and 31 December 2018 in the Physical Medicine and Rehabilitation Training and Research Hospital which is a tertiary center. BCRL patients had finished treatment including surgery, radiation, chemotherapy or hormone therapy at least 3 months before. Age, gender, BMI, surgical interventions [modified radical mastectomy (MRM)+axillary lymph node dissection (ALND) or lumpectomy], chemotherapy, radiotherapy, hormone therapy, pain, numbness, shoulder joint range of motion measurement, time after surgery, remove metastasis, metastatic lymph nodes, number of metastatic lymph nodes, number of resected lymph nodes, lymphedema status, and the SF-36 HRQOL scores of BCRL patients were noted from the files. The study protocol was approved by local institutional review board and performed according to the Declaration of Helsinki. The study was approved by Ethics Committee of Ankara Physical Medicine and Rehabilitation Hospital on 12 March 2013 with the number of 1651.

In the evaluation of lymphedema, circumferential measurements from the affected metacarpophalangeal joint, wrist, 10 cm distal and 15 cm proximal of humeral lateral epicondyle were used. If the difference between the affected arm and the controlateral healthy arm at any of the measurement points was over 2 cm, it was considered as lymphedema.[11] According to these measurements, severity of lymphedema in the BCRL group was further subdivided into 2 degrees as ≤3 cm and >3 cm.

Shoulder joint restriction was measured with a goniometer. A difference of ≥20° between the non-operated side and the operated side in shoulder flexion, abduction, adduction or external rotation was considered as a limitation on the operated side.

Pain was assessed by visual analog scale (VAS). For this purpose, a line 10 cm long was drawn and it was numbered with 1 cm intervals. 0: painless and 10: the most severe pain was instructed to the patient and asked for the value mark corresponding to the pain. VAS ≥1 was defined as pain.

The feeling of numbness was evaluated according to a self-reported light touch examination focusing on normal dermatomal and peripheral nerve distribution.

The SF-36 HRQOLS was used to determine the quality of life. This scale was first designed to be used in the evaluation of health policies and general population studies in clinical practice and research by Ware.[12] The validity and reliability of the Turkish

version of the scale was proven by Koçyiğit et. al. previously.[13] This validated self-report questionnaire includes 36 questions that evaluate the following eight health concepts: 1. Physical functioning, 2. Physical role functioning, 3. Bodily pain,4. General health, 5. Emotional role functioning, 6. Social role functioning, 7. Vitality, and 8. Mental health. The first 4 items show physical component summary, and the second 4 items show mental component summary. Each subscale is standardized on a 0 to 100 scores; higher scores indicate better health status.

Analyses were conducted using the Statistical Package for the Social Sciences (SPSS) for Windows software (Version 16.0, SPSS, Inc., Chicago, IL). For descriptive statistics, discontinuous variables were shown as numbers and percentage (%); continuous variables were shown as mean ± standard deviation and median (minimum-maximum). For group comparisons, Chi-square test was used for categorical values, Student's t-test was used for continuous variables that distributed normally, and the Mann-Whitney U-test was used for continuous variables that did not distribute normally. P values less than 0.05 were considered to be statistically significant.

RESULTS

Seventy eight patients with a diagnosis of lymphedema developed after mastectomy due to breast cancer and 50 healthy women without breast cancer were included in the study. The mean age of the BCRL group was 52.7±10.2 years and the mean age of the control group was 50.7±13.4 years (p=0.46). A modified radical mastectomy was performed on 73 (93.6%) patients, simple lumpectomy was performed on 5 (6.4%) patients.

Comparison of the case and control group in terms of SF-36 subgroup scores is given in Table 1. When the physical function states, which are the sub-parameters of the SF-36 quality of life scale, are evaluated; the mean score in lymphedema was 42.57±8.32 and 46.84±7.43 in the control group, and there was a significant difference in the statistical evaluation between the groups (p=0.004). When looking at the physical role functions, the mean score in lymphedema cases was 38.02±12.26 and the control group mean score was 44.63±10.83 (p=0.001). When the mean scores between the physically combined groups of the quality of life scale were examined, the mean score in lymphedema was found to be 40.47±8.47 and 45.30±9.76 in the control group and there was a significant difference in the statistical evaluation (p=0.004).

Forty-four patients (56.4%) had lymphedema ≤3 cm and 34 patients (43.6%) had lymphedema >3 cm. The mean age, the accompanying diseases, the type of breast surgery, the time after surgery, metastatic lymph node status, chemotherapy, hormone therapy, distant metastasis, pain, numbness, and shoulder joint restriction were similar between the lymphedema subgroups (p>0.05). In the lympedema >3 cm subgroup, 88.2% of women had

TABLE 1: Comparison of the SF-36 parameters of the lymphedema group and the control group.

	BCRL (n=78)	Control (n=50)	p value
Physical functioning	42.54±8.32	46.84±7.43	0.004*
Physical role functioning	38.02±12.26	44.63±10.83	0.001*
Bodily pain	45.47±9.39	46.94±11.39	0.431*
General health	44.24±8.93	46.19±10.07	0.269*
Emotional role functioning	41.26±14.56	41.43±9.37	0.664*
Social role functioning	44.53±10.97	47.47±7.91	0.221*
Vitality	49.35±9.64	49.67±9.19	0.665*
Mental health	44.00±10.29	46.05±9.95	0.235*
Physical component summary	40.47±8.47	45.30±9.76	0.004**
Mental component summary	46.27±11.56	46.01±7.73	0.387*

BCRL: Breast cancer related lymphedema; * Mann Whitney U test; **Independent Student T Test.

BMI >25, however, in the lymphedema ≤3 cm subgroup, 68.2% of women had BMI >25 (p=0.03). In the lymphedema >3 cm subgroup, 76.5% of women had undergone radiotherapy, however, 54.5% of women had undergone radiotherapy in the lymphedema ≤3 cm subgroup (p=0.04). The number of metastatic lymph nodes was higher in the lymphedema subgroup over 3 cm (6.53±5.85 vs. 3.98±3.40) but the difference was insignificant (p=0.06) (Table 2).

When the parameters of SF-36 were compared between the lymphedema ≤3 cm and the lymphedema >3 cm subgroups; all of the parameters were similar (p>0.05) (Table 3).

TABLE 2: Comparison of demographic and treatment characteristics of lymphedema subgroups.

	Lymphedema ≤ 3 cm (n=44)	Lymphedema > 3 cm (n=34)	p value
Age	53.49±9.24	51.62±11.46	0.29***
Accompanying diseases (n, %)	17 (38.6%)	10 (29.4%)	0.27*
Body Mass Index			
>25	30 (68.2%)	30 (88.2%)	0.03*
25	14 (31.8 %)	4 (11.8%)	
Surgery (n, %)			
Mrm+Axillary Dissection	41 (93.2%)	32 (94.1%)	0.62*
Lumpectomi	3 (6.8%)	2 (5.9%)	
Time after surgery (months)	7.93±3.72	8.59±2.98	0.15**
Number of resected lymph node	1.07±0.59	1.06±0.65	0.96**
Remove metastasis (n, %)	2 (4.6%)	3 (8.8%)	0.38*
Metastatic lymph node (n, %)	33 (75%)	26 (76.5%)	0.55*
Number of metastatic lymph node	3.98±3.40	6.53±5.85	0.06**
Chemotherapy (n, %)	39 (88.6%)	30 (88.2%)	0.61*
Radiotherapy (n, %)	24 (54.5%)	26 (76.5%)	0.04*
Hormonotherapy (n, %)	28 (63.6%)	23 (67.6%)	0.45*
Pain (n, %)	20 (45.5%)	19 (55.9%)	0.25*
Numbness (n, %)	19 (43.2%)	13 (38.2%)	0.42*
Shoulder joint restriction (n, %)	15 (34.1%)	10 (29.4%)	0.43*

*Chi-square test , **Mann Whitney U test, ***Independent Student T Test.

TABLE 3: Comparison of the SF-36 parameters of the lymphedema subgroups.

	Lymphedema ≤ 3 cm (n=44)	Lymphedema >3 cm (n=34)	p value
Physical functioning	42.35 ± 9.03	42.80 ± 7.44	0.97*
Physical role functioning	38.25 ± 12.20	37.74 ± 12.51	0.84*
Bodily pain	44.37 ± 9.12	46.90 ± 9.67	0.27*
General health	43.50 ± 10.15	45.20 ± 7.08	0.53*
Emotional role functioning	40.94 ± 14.91	41.68 ± 14.33	0.97*
Social role functioning	44.54 ± 11.80	44.52 ± 9.97	0.81*
Vitality	47.96 ± 9.37	51.16 ± 9.84	0.15**
Mental health	43.98 ± 9.96	44.04 ± 10.87	0.86*
Physical component summary	39.96 ± 8.35	41.15 ± 8.72	0.54**
Mental component summary	45.95 ± 11.08	46.70 ± 12.32	0.74*

DISCUSSION

The most common cancer in women worldwide is breast cancer.[14,15] In terms of our country, breast cancer ranks first among the ten most common cancer types among women.[16] It is observed that the frequency observed in breast cancer does not reflect the same rates of mortality. In parallel with the developments in breast cancer treatment, the positive impact of incidence and survival, the comprehensive learning of the problems experienced by patients regarding the treatment, disease and recovery process becomes more important.

Patients who are cured after breast cancer treatment face many difficulties throughout their lives due to complications. The most common and life-limiting problems in patients following treatment are those related to upper extremity functions. Upper limb lymphedema is one of the most severe complications in the treatment of breast cancer. Lymphedema can affect health-related quality of life in a variety of ways, causing a wide range of discomfort and disability. In cases where lymphedema treatment is not effective or lymphedema treatment is not considered; lymphedemic women experience problems such as physiological, social, psychological problems related to changing body structure and decreased quality of life due to inability to perform daily life activities.[17,18] In the modern treatment of breast cancer, the quality of life of survivors is as important as survival.

The most important factor affecting the functional life and daily life activities of the patients is the musculoskeletal problems of the affected upper limb. Sensory disorders, tension-related pain, loss of strength, limited movement, susceptibility to infection and skin sensitivity develop in the arm developing lymphedema.[19] The discomfort in lymphedema during arm movements results in decreased joint movements or loss. Lack of range of motion also affects one's daily life activities and self-care *(İmamoğlu N. Meme kanseri tedavisi sonrası lenfödem gelişen olgularda eğitimin üst ekstremite fonksiyonlarına etkisi. DEÜ Sağlık Bilimleri Enstitüsü; 2011)*. As a result of physiological problems experienced due to lymphedema, women's quality of life is negatively affected.[20]

In our study, BCRL patients and healthy controls were compared with SF-36; physical function, physical role function and physical component scores were lower in lymphedema patients. The negative effect of upper extremity morbidity on quality of life has been shown in many studies. In our study, when lymphedema and control groups were compared with regard to SF-36; In lymphedema patients, physical function, physical role function and physical component scores are lower and statistically significant in lymphedema patients. As mentioned earlier, a decrease in physical function score limited performing all physical activities including washing and dressing. The decrease in physical role function score was defined as having problems at work or other daily activities as a result of deterioration of physical health. Due to lymphedema, physical complications such as pain, tenderness, numbness, weight gain in the arm cause difficulties. Women may be unable to perform everyday activities such as wearing tight-fitting clothes, putting on tight jewellry, difficulty in writing, difficulties in career work, housework, or shopping.[21] As a result of these complications, women may be prevented from returning to the level of activity they experienced prior to breast cancer diagnosis.[21] In the study of Voogd et al., the most common physical problems of women are deterioration in arm and hand movements, loss of sensation, loss of power, sleep disturbance and difficulty in their work.[22] In other studies, it has been reported that women are unable to fulfill many responsibilities such as looking after children, eating, shopping and maintaining order in the home, and this affects the family life of individuals.[9,23,24]

In general, this study showed the physical component was more affected than the mental component. Similarly to our study, Lee et al. compared HRQOL in breast cancer patients with lymphedema who survived more than one year after surgery with the general population and there were statistically significant differences on all scales of SF-36 except for the mental components.[25] This result is thought to be closely related to the survival time. Within 1 year after breast cancer surgery, patients can adapt to the disease and treatment, and become mentally stable.[25] In our study, BCRL patients had finished treatment

at least 3 months before and in BCRL group, approximately 8 months had passed after surgery. It is possible that women with known lymphedema had developed adaptation mechanisms to cope with lymphedema and these mechanisms affected mental health differently from physical health. Another reason for not affecting the mental component is the physical examination, counseling and, if necessary, appropriate medical intervention in the rehabilitation clinic after discharge from the patients. These series of actions may have had a significant impact on stabilizing patients' mental health. The reason why women experience the most physiological difficulties can be explained by the fact that lymphedema causes difficulties such as pain, tenderness, drowsiness, increased weight in the arm, disruption in sleep patterns, not being able to do household chores, not going to shopping or carrying goods.

Schou et al. reported that at the diagnosis of breast cancer and three months after, patients reported significantly more insomnia, appetite loss and diarrhoea than the general population, however, the symptoms declined between 3 to 12 months, to such a degree that patients reported similar or fewer symptoms than the general population at 12-months.[26] However. Velanovich and Szymanski et al. showed that patients with lymphedema had significantly lower scores in the domains of role-emotional and bodily pain.[27] Ahmed et al. showed that HRQOL was significantly lower in breast cancer survivors with diagnosed lymphedema or with arm symptoms without diagnosed lymphedema compared with survivors without lymphedema or arm symptoms.[9] Differences in participant age, follow-up time, type of quality of life scales, or other aspects of study design may contribute to differences among studies.

Results from the study of Wilson et al. suggest that the SF-36 possesses relatively weak discriminative power with regard to emotional well-being, failing to demonstrate mental health differences between women with lymphedema secondary to breast cancer and women with breast cancer without lymphedema which were detected using the Functional Living Index-Cancer (FLIC) survey. Wilson et al. reported large differences in physical functioning, but no group differences were found when SF-36 mental components were compared. The authors noted that the SF-36 contains only 2 items addressing anxiety and 3 items assessing depression and suggested that this instrument's coverage of mental health symptoms may be too limited to be able to detect the types of emotional problems experienced by patients with breast cancer.[28] These findings imply that disease specific surveys such as FLIC may be more sensitive to measure emotional status for breast cancer and lymphedema than generic HRQOL surveys.[28] However, the SF-36 may be a suitable generic alternative to all cancer types, particularly to make comparisons of the health status of cancer survivors to population norms, the general population or other disease groups.

In our study, interestingly, no statistically significant difference was found when SF-36 scores were compared between the lympedema ≤3 cm and >3 cm subgroups. Likewise, in the study of Lee et al., lymphedema patients underwent bioimpedance measurements and completed the disabilities of the arm, shoulder, and hand questionnaire, it was reported that the severity of lymphedema did not appear to have a significant relationship with HRQOL.[29] These results show that the presence of lymphedema is much more important than the lymphedema severity in disturbing quality of life.

In our study, body mass ındex and radiotherapy was found to be associated with lymphedema severity. Excess body weight is a significant risk factor for many cancers, especially breast cancer and the development of lymphedema.[30,31] Patients with breast cancer or those with a history of the disease who are overweight have an increased risk of therapy-related morbidity, recurrence, and breast cancer-related mortality.[30] Obesity may also independently affect quality-of-life factors, including sexual dysfunction, neuropathy, cardiotoxicity, and chronic fatigue.[30] A meta-analysis reported the incidence of BCRL increases after modified radical mastectomy and regional nodal radiation when compared to lumpectomy alone without adjuvant radiation.[32]

There are some limitations in this work such as the relatively low number of patients and the fact that

our patients had not been evaluated before the operation. Because we recruited patients after mean time of 8 months, we cannot compare the HRQOL at diagnosis or early treatment period. Thus, in the future, prospective studies from the time of diagnosis of breast cancer including breast cancer treatment and complications will be needed.

Informing women about lymphedema during breast cancer treatment may lead to more awareness of the women, which makes early diagnosis of lymphoedema, facilitation of lymphedema treatment, reduction of difficulties, and increasing HRQOL. The initiation of treatment early may result better results due to the softness of the tissues, the absence of excess skin and fibrotic tissue. We recommend screening programmes for early detection of lymphedema. In addition, early education about lymphedema for women diagnosed with breast cancer is important, such that women are aware of the risk factors, symptoms, and HRQOL implications associated with the lymphedema.

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