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Risk Factors of Breast Cancer-Related Lymphedema

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Abstract

Introduction: Secondary lymphedema is one of the major important long-term complications of breast cancer treatment. The aim of this study is to determine patient- and treatment-related risk factors of lymphedema in breast cancer patients.

Patients and Methods: Patients, who had been operated on for primary breast cancer at Akdeniz University Hospital and followed regularly between August 1984 and December 2009 were included in the study. In order to evaluate the arm swelling objectively, measurements were performed with a flexible tape measure for both arms, and limb volume was calculated using a truncated cone volume formula. Participants, whose volume difference between the two arms was ≥5%, were considered as lymphedema-positive patients. The SPSS program (SPSS inc. Chicago, IL) was used for statistical analysis.

Results: The mean age of 455 patients was 50.6 years and the median follow-up time was 53 months. Lymphedema was found in 124 (27%) patients. Most of the patients with a history of postoperative wound infection (52%) and lymphangitis (57%) had lymphedema ($p=0.003$ and $p=0.002$, respectively). Addition of radiation therapy increased lymphedema risk 1.83 times ($p=0.007$). The mean duration of the axillary drainage and number of the removed lymph nodes were 7.8 days and 19, respectively. The rate of lymphedema in patients with early stage breast cancer was less than patients with advanced breast cancer (24% and 35.3%, respectively, $p=0.018$). Most of the patients (92%) with lymphedema had a high body mass index (BMI $\geq 25\,kg/m^2$), and obesity was another important factor for lymphedema ($p<0.001$).

Conclusions: The most important treatment and patient-related risk factors for breast cancer-related lymphedema were obesity ($\geq 25\,kg/m^2$), axillary lymph node dissection, postoperative radiotherapy, wound infection, history of lymphangitis, and duration of axillary drainage. Elimination or prevention of these risk factors may reduce the incidence of lymphedema.

Introduction

Breast cancer is the most common cancer and cancer related death among women in developed and developing countries including Turkey.[1] But, breast cancer mortality rate has been decreasing in developed countries due to mammographic screening and effective treatment.[2–4] As more women survive from breast cancer, the number of women affected by long-term side effects of its treatment is increasing. Secondary lymphedema is one of the major important long-term complications of breast cancer treatment and is also associated with adverse physical and psychosocial consequences.

Lymphedema in patients with breast cancer is caused by interruption of the axillary lymphatic channels by surgery and/or radiation therapy. Axillary dissection and radiation therapy has a synergistic effect on lymphedema risk which results in the accumulation of fluid in subcutaneous tissue in the arm, with decreased distensibility of tissue around the joints and increased weight of the extremity. Lymphedema may present immediately or years after axillary dissection. It has been reported as late as 30 years after treatment.[5] Although the incidence is generally accepted at approximately 20%, reported rates vary greatly, ranging between 6% and 30%.[6]

Lymphedema is regarded as a progressive, disfiguring, and disabling disorder that is difficult to treat; therefore it is

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essential to prevent or minimize this condition. The aim of this study is to determine patient- and treatment-related risk factors of lymphedema in breast cancer patients.

Patients and methods

After ethical approval, 455 patients, who had been operated for primary breast cancer at General Surgery Department of Akdeniz University Hospital (a tertiary care facility in Antalya, Turkey), between August 1984 and December 2009, and who had regular follow-up and accepted to come evaluation for lymphedema were included in the study. All of them gave written informed consent prior to participation.

Invited patients were examined and evaluated by the same physician. Age at operation, professions, body mass index [(BMI) = weight (kg)/height^2 (m^2)], early postoperative upper extremity physical activity, duration of the axillary drainage, history of cigarette smoking, diabetes mellitus, hypertension, arm injury, postoperative wound infection, history of lymphangitis, type of surgical procedure, axillary radiotherapy, stage of disease, number of the removed lymph nodes, and the metastatic lymph nodes were recorded.

In order to evaluate the arm swelling, four measurements with a flexible tape measure for each arm were performed. The first two measurements were at 4 cm proximal to the wrist and at 15 cm proximal to the first one. The third one was at 4 cm proximal to the olecranon, and the fourth one was 15 cm proximal to the third one. Limb volume (LV) was calculated using a truncated cone volume (V) formula, as follows: $V = \pi.h.(R^2 + r^2 + R.r)/3$ (R and r are radius of two consecutive circumference measurements, and h is height). This method demonstrated excellent inter- and intra-observer reproducibility in comparison to water displacement which is considered the gold standard.[7–9] Participants, whose volume difference between the two arms was ≥5%, were considered as lymphedema-positive patients. Patients who had 5%–10%, 10%—20%, and ≥20% volume differences between two arms were considered as mild, moderate, and severe lymphedema.

The SPSS (Statistical Package for Social Sciences) for Windows ver: 18.0 (SPSS inc. Chicago, IL) program was used for statistical analysis. The Mann-Whitney U test was used to analyze the difference between continuous variables of two groups. The Pearson Chi-square test was used to analyze the relationship between two categorical variables. For risk ratios of categorical variables, Odds ratio and 95% confidence intervals was calculated. A p level of less than 0.05 was considered statistically significant.

Results

The mean age of patients was 50.6 years (median 50, range 24–86) and the median follow-up time was 53 months. Lymphedema was found in 124 (27%) patients. Mild, moderate, and severe lymphedema rates were 37%, 29%, and 34%, respectively. Early lymphedema (0–6 months after surgery) was seen in 36% of patients, and only 9% of patients had late (2 years after surgery).

Surgical procedures were radical mastectomy (7.3%), modified radical mastectomy (71.6%), and breast-conserving surgery (lumpectomy and axillary dissection, 21%). Almost half of the patients with radical mastectomy had lymphedema. Lymphedema rates were 25.8% in patients with modified radical mastectomy, and 25.3% in patients with lumpectomy and axillary dissection. Lymphedema rate was significantly higher in patients with radical mastectomy than the patients with modified radical mastectomy and breast-conserving surgery [Odd's ratio: 2.71 (CI: 95% 1.31; 5.61), ($p = 0.006$), Odd's ratio: 2.78 (CI: 95% 1.21; 6.38), ($p = 0.014$), respectively]. There was no statistically significant difference between the patients who had modified radical mastectomy and breast-conserving surgery in the terms of lymphedema rate [Odd's ratio: 1.03 (CI: 95% 0.6; 1.75)] ($p = 0.924$).

Mean duration of the axillary drainages, and mean number of removed and metastatic lymph nodes were 7.8 days (range 0–80), 19 (range 3–50), and 3.46 (range 0–49), respectively.

More than half (52% and 57%) of the patients with wound infection and lymphangitis in the ipsilateral arm had lymphedema [Odd's ratio: 3.11 (CI: 95% 1.41; 6.82) ($p = 0.003$), Odd's ratio: 3.83 (CI: 95% 1.57; 9.34) ($p = 0.002$), respectively]. 83 (34%) of 246 patients treated with postoperative radiotherapy had lymphedema [Odd's ratio: 1.83 (CI: 95% 1.17; 2.84)] ($p = 0.007$).

Early breast cancer (Stage I, II) was found in 310 patients (68%), and 24% of them had lymphedema. Lymphedema rate was 35.3% (41/116) in patients with stage III breast cancer [Odd's ratio: 1.74 (CI: 95% 1.1; 2.76)] ($p = 0.018$). Obesity (BMI ≥25) was present in 79% of patients, and 32% of them had lymhedema [Odd's ratio: 3.94 (CI: 95% 1.97; 7.87)] ($p < 0.001$) (Table 1).

Conclusions

Lymphedema after breast cancer treatment is an important, long term and persistent complication which affects the patient's quality of life.[10,11] If it was not diagnosed and treated in early period, treatment may be difficult and becomes a chronic disease. Because of the increase in survival, and the younger and active women who were affected, the importance of lymphedema after breast cancer treatment has increased in recent years. Once developed, lymphedema cannot be cured; therefore it is important to avoid or minimize this condition.

Because of the majority of the arm lymphatics and sympathetic nerves are adjacent to the axillary vein, skeletonization of the axillary vein during axillary lymph node dissection is not recommended. Although risk factors for lymphedema after breast cancer treatment relate primarily to the axillary dissection or radiation therapy, other risk factors may play a role in lymphedema development, given that even sentinel node biopsy has been associated with a 0%–6% risk of lymphedema.[12] Boneti et al.[13] have stated that arm lymphatics are adjacent to the sentinel lymph node, likewise their relationship with axillary vein. Although it is rare, lymphedema after sentinel lymph node biopsy is seems to be associated with this anatomic variation. In our study, 16 patients with severe lymphedema had radical mastectomy and levels I, II, and III axillary dissection with skeletonization of axillary neurovascular elements. The lymphedema rate was higher in this group for this reason.

The incidence of lymphedema after breast cancer treatment has been reported in a wide range from 6% to 30%.[6] In our study, the lymphedema rate was high. This high rate may be related to the type of surgery (radical mastectomy, high axillary lymph node metastasis, high number of dissected lymph nodes) and number of patients received radiation

Table 1. Treatment and Patient Characteristics and Rate of Lymphedema According to Risk Factors

Risk factors	n *(%)*	*Number of patients with lymphedema (%)*	P *value*
Postoperative wound Infection			0.003
Yes	27 (6%)	14 (52%)	
No	428 (94%)	110 (25.7%)	
History of lymphangitis			0.002
Yes	21 (4.6%)	12 (57%)	
No	434 (95.4%)	112 (26%)	
Postoperative radiotherapy			.007
Yes	246 (54%)	83 (34%)	
No	209 (46%)	41 (20%)	
*Stage of breast cancer**			.0018
Stage I, II	310 (68%)	74 (24%)	
Stage III	116 (25.5%)	41 (35.3%)	
Body mass index			< .001
BMI ≥25	95 (21%)	10 (10.5%)	
BMI ≥25	360 (79%)	114 (32%)	
Type of operation			
RM	33 (7.3%)	16 (48.5%)	0.006
MRM	326 (71.6%)	84 (25.8%)	
RM	33 (7.3%)	16 (48.5%)	0.014
BCS	91 (20%)	23 (25.3%)	
MRM	326 (71.6%)	84 (25.8%)	0.924
BCS	91 (20%)	23 (25.3%)	

BCS, breast-conserving surgery (lumpectomy and axillary dissection); BMI, body mass index;
MRM, modified radical mastectomy; RM, radical mastectomy.
*TNM pathological classification.

therapy. It has been reported that there is an increase in the incidence of lymphedema by the lengthening of the surgical follow-up.[14] In our study, 64% of patients were diagnosed with lymphedema 6 months after surgery. But most of the studies showed that lymphedema was diagnosed in 6 months after surgery in most of the patients.[15,16]

Ozcinar et al. have reported that axillary dissection and radiotherapy to regional lymphatics were related to lymphedema, but chemotherapy was not.[17] Radiation therapy leads to secondary lymphedema by causing occlusion of lymph vessels due to the scatrization and fibrosis of lymph vessel walls. In our study, the risk of lymphedema in patients receiving postoperative radiotherapy was 1.83 times higher compared to those who did not. This rate was statistically significant ($p = 0.007$). There was no statistically significant association between chemotherapy and the risk of lymphedema ($p = 0.36$).

Mak et al. found that an arm or chest infection is a major risk factor for development or aggravation of lymphedema.[18] In our study, we demonstrated that the risk of developing lymphedema in patients with a history of wound infection was 3.11 times more than those without wound infection ($p = 0.003$), and in patients who had a history of lymphangitis, the risk was 3.83 times higher than those who had not ($p = 0.002$). Both of these findings were statistically significant. The majority of the studies report that moderate lymphedema is more frequent than mild or severe lymphedema, whereas there is a balanced distribution in our study (mild, moderate, and severe lymphedema rates were 37%, 29%, and 34%, respectively). However, it is remarkable that the majority of severe lymphedema patients in our study are the patients with a history of lymphangitis. Interestingly, two patients had permanent and severe lymphedema as a result of lymphangitis, which was developed after bee stings. We suggest that the development of severe lymphedema can be prevented or reduced by paying attention to hand and arm hygiene and by protecting them from injuries and bites to reduce the risk of lymphangitis.

We found that the long duration of the axillary drain was another risk factor for secondary lymphedema, which statistically significantly increases the risk of lymphedema ($p = 0.045$). This result supports that the injury of the arm lymphatics during axillary dissection increases the rate of lymphedema. Tsai et al. have stated that radical mastectomy and extended axillary dissection are risk factors for lymphedema.[19] Radical mastectomy was abandoned in the 1980s, but thirty-three patients had radical mastectomy as a surgical procedure in our study. We demonstrated that the risk of developing lymphedema in patients undergoing radical mastectomy was statistically significantly higher than the risk of lymphedema in patients undergoing modified radical mastectomy or breast-conserving surgery ($p = 0.006$, and $p = 0.014$, respectively). There was no statistically significant difference between patients who underwent modified radical mastectomy and breast-conserving surgery (lumpectomy and axillary dissection, $p = 0.924$).

Most studies examining the relationship between the stage of breast cancer and the risk of lymphedema argue that there is no statistically significant relationship between these two entities. In our study, however, the risk of lymphedema was statistically significantly higher in patients with advanced breast cancer (Stage III) than patients with early-stage breast cancer (Stage I, II) ($p = 0.018$). In the present study, 92% of the patients with lymphedema were obese (BMI $\geq 25\,kg/m^2$). Mahamaneerat et al.[20] found that the risk of lymphedema is increased in patients with BMI greater than 30 and who had cancer at dominant arm side. We did not evaluate the dominant arm; however, the increase in BMI was correlated with the increased rates of lymphedema and found statistically significant in our study ($p < 0.001$).

Gurdal et al.[21] pointed out that the combination treatment modalities including intermittent pneumatic compression with self-lymphatic drainage, and manual lymphatic drainage with compression bandage, are both effective and tolerable modalities in the treatment of arm lymphedema. In our study, decongestive therapy was given to 22 (18%) of 124 patients whodeveloped lymphedema; and 16 (73%) of the patients treated benefited from the treatments. Ratio of therapy given lymphedema patients was low, while the ratio of success of treatment in patients who were treated was high. This seems to be connected to the physicians who do not consider the importance of the treatment of lymphedema. Only one patient in our study had a lympho-venous anastomosis operation for severe lymphedema. The patient was treated partly in terms of lymphedema by this microsurgical procedure, whereas the operation was extremely helpful in

terms of palliation of pain. We could not find any statistically significant relationship between cigarette smoking, diabetes mellitus, hypertension, occupation, age, number of the removed lymph nodes, early postoperative upper extremity physical activity, and the risk of development lymphedema.

As a conclusion, our results suggest that the most important treatment and patient-related risk factors for breast cancer-related lymphedema were obesity ($\geq 25\,kg/m^2$), axillary lymph node dissection, postoperative radiotherapy, wound infection, history of lymphangitis, and duration of axillary drainage. Elimination or prevention of these risk factors may reduce the incidence of lymphedema.

Author Disclosure Statement

No competing financial interests exist.

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