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Lymphedema after treatment of breast cancer

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Abstract

Background: Lymphedema is one of the major long-term complications of axillary dissection. This study was designed to investigate the risk factors that are predicted to effect the development of lymphedema after complete axillary dissection.
Methods: Two hundred forty patients who had undergone modified radical mastectomy with complete axillary dissection were examined at least 18 months after the surgery. The effects of age, diabetes, smoking, hypertension, chemotherapy, radiotherapy, tamoxifen use, stage, body mass index, number of the removed and metastatic lymph nodes, and total volume of the wound drainage on the development of lymphedema were analyzed.
Results: Lymphedema developed in 68 (28%) of the 240 cases. Axillary radiotherapy and body mass index were found to increase the incidence of the lymphedema.
Conclusions: Women who had the combination of full axillary dissection and axillary radiotherapy carry a significant risk of lymphedema.

Keywords: Breast; Axillary dissection; Lymphedema

Although axillary dissection does not effect the survival of patients treated for breast cancer [1,2], it is performed because axillary lymph node status is the most valuable prognostic indicator [3,4], and is effective at controlling regional disease [5,6]. Pathological examination of the axillary lymph nodes is also required for planning of adjuvant chemotherapy and radiotherapy [7–9].

Lymphedema of the upper extremity is the most significant complication after axillary dissection [10–12] and could cause cosmetic disfigurement, physical discomfort, and loss of functional ability [13,14]. It may also lead to cellulitis, lymphangitis, and occasionally lymphangiosarcoma [15].

The aim of this study is to define the frequency of upper extremity lymphedema in patients who underwent modified radical mastectomy with full axillary dissection, and to clarify the demographic, oncologic and therapeutic factors that could possibly influence this morbidity.

Methods

Two hundred forty consecutive patients who had undergone modified radical mastectomy with complete axillary dissection between January 1998 and June 2000 in Ankara Oncology Hospital, and had surgery and adjuvant chemotherapy or radiotherapy, or both, at least 18 months earlier were eligible. The follow-up period ranged between 18 and 43 months with a median of 30 months. Patients who had systemic disease, locoregional recurrence, and bilateral breast cancer were excluded from the study. All patients had level I, II, and III axillary dissection. Pectoralis minor muscle was preserved, but its insertion was transected during operation. All the operations were performed by the same team, and the same procedure were typically performed in all patients. Closed suctions drains were placed under skin flaps and inside the axilla after mastectomy. Drains were removed when the drainage was less than 50 mL a day. Patients were given a booklet postoperatively and shoulder movements were started at fifth day. Adjuvant radiotherapy was applied to the axilla in the presence of four or more axillary lymph node metastases or extra capsular invasion of the nodal metastases. Chest wall, supraclavicular and internal mammary regions, and the apex of the axilla as well as central and lateral axillary regions were included in the

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radiotherapy field. Informed consent was obtained from the patients, and the research protocol was approved by the Ethics Committee of Ankara Oncology Hospital.

The following data about the probable risk factors for lymphedema were collected from the patients using a brief questionnaire and from the medical records of the patients: Age at operation, body mass index ([BMI]: weight [kg]/height^2 [m^2]), history of diabetes, hypertension, and cigarette smoking, axillary radiotherapy (yes/no), chemotherapy (yes/no), tamoxifen treatment (yes/no), number of the removed lymph nodes, metastatic lymph nodes (yes/no), total amount of the closed suction drainage, and stage of the disease.

Patients were assigned in three categories in respect to age (<40 years, 40 to 60, and >60 years), BMI (<20, 20 to 25, and >25), removed lymph nodes (<15, 15 to 25, and >25), and total amount of closed suction drain drainage (<500 mL, 500 to 1,000 mL, and >1,000 mL). Patients were also assigned in two categories (yes/no) in respect to history of diabetes, hypertension, and smoking, radiotherapy, chemotherapy, metastatic lymph nodes, and tamoxifen use.

When the patients referred for control, arm circumference at 5 and 10 cm proximal and at 5 cm distal to olecranon and at wrist level was measured, and the difference at any level compared with the opposite upper extremity was established. The difference of 2 cm or more was accepted lymphedema.

The categorized probable risk factors were entered into the logistic regression analysis as categorical covariates using a different reference category for each risk factor. The SPSS 10.05 for Windows (SPSS, Chicago, Illinois) computer program was used in data analysis. Univariate analyses were performed by the chi-square test, and the forward logistic regression model was used for the multivariate analysis. Relative risks were reported with a 95% confidence interval.

Results

The mean age of the patients was 51.3 years (median 50, range 28 to 80). The mean number of the removed lymph nodes was 18.9 (median 18, range 8 to 41). In all, 131 of the 240 patients had axillary metastases, 89 had adjuvant breast and axillary radiotherapy. The features of the patients are shown in Table 1.

Among the 240 cases of breast cancer 68 (28%) had developed arm swelling more than 2 cm, and 22 (9.2%) had more than 4 cm. When compared with the other arm, the incidence of lymphedema with respect to demographic features of the patients and type of treatment are also shown in Table 1. Univariate analyses showed that adjuvant radiotherapy and BMI greater than 25 were found to increase the incidence of lymphedema. Multivariate analysis also showed that BMI greater than 25 and adjuvant radiotherapy were the independent factors influencing lymphedema (Table 2).

Table 1
Patient characteristics and frequencies of lymphedema in each category of risk factors

Factors	n (%)	Number of patients with arm circumference >2 cm (%)	*P* value
Age			
<40‡	41 (17.0)	10 (24.3)	NS
40–60	136 (56.6)	36 (26.4)	
>60	63 (26.2)	22 (34.9)	
BMI			
<20‡	56 (23.3)	8 (14.3)	0.001*
20–25	107 (44.6)	22 (20.5)	NS†
>25	77 (32.0)	38 (49.3)	
Smoking			
Yes	26 (10.8)	7 (26.9)	NS
No‡	214 (89.2)	61 (28.5)	
Diabetes mellitus			
Yes	22 (9.2)	9 (40.9)	NS
No‡	218 (90.8)	59 (27.0)	
Hypertension			
Yes	56 (23.3)	19 (33.9)	NS
No‡	184 (76.6)	49 (26.6)	
Number of removed lymph nodes			
<15‡	77 (32.0)	23 (29.8)	NS
16–25	131 (54.6)	36 (27.4)	NS
>25	32 (13.3)	9 (28.0)	
Metastatic lymph nodes			
Yes	131 (54.6)	42 (32.0)	NS
No‡	109 (45.4)	26 (23.8)	
Chemotherapy			
Yes	163 (67.9)	50 (30.6)	NS
No‡	77 (32.1)	18 (23.3)	
Radiotherapy			
Yes	89 (37.1)	37 (41.6)	0.001
No‡	151 (62.9)	31 (20.5)	
Tamoxifen use			
Yes	76 (31.6)	16 (21.0)	NS
No‡	164 (68.4)	52 (31.7)	
Closed suction drainage			
<500 cc‡	54 (22.5)	18 (34.6)	
500–1000 cc	134 (55.8)	30 (22.4)	NS
>1000 cc	52 (21.7)	20 (37.0)	
Stage			
I‡	28 (11.6)	6 (21.4)	NS
II	176 (73.4)	49 (27.8)	NS
III	36 (15.0)	13 (36.1)	

* BMI <20 versus BMI >25.
† BMI 20–25 versus BMI >25.
‡ Reference category used in logistic regression analyses.
BMI = body mass index; NS = not significant.

Comments

The incidence of lymphedema after axillary dissection has been reported in a wide range from 10% to 37%. This

Table 2
Factors predictive of arm edema on multivariate analysis

	P value	Relative risk*	95 % CI*
BMI >25	0.001	5.55	2.28–13.51
Axillary radiotherapy	0.001	2.75	1.48–5.08

* Adjusted for all the probable risk factors mentioned in Table 1
CI = confidence interval; BMI = body mass index.

wide range is mainly related to different definitions of lymphedema and different patient groups in the studies [16,17]. Axillary radiotherapy had a greater proportion in older series [18–21], whereas in recent series radiotherapy had a lesser proportion or was not included in the studies [11,22]. Although simple circumferential comparison between the normal and potentially abnormal arm was used as in our study, volumetric comparisons such as water displacement technique or calculation of the arm volume were also used in different studies [16,18,20,22–24].

Lymphatic obstruction is not the only responsible mechanism in the pathophysiology of lymphedema. Total arm blood flow and vascular bed size also appear to be increased in lymphedema [25]. It has been reported that body weight or BMI are the important factors that increase lymphedema [10,11,21]. However, body weight was not found to influence the lymphedema in the series reported by Larson et al [17]. In our series BMI greater than 25 also was found to be an independent prognostic factor for lymphedema.

Pezner et al [26] have reported that the incidence of lymphedema was 25% at age greater than 60 years and 7% at age under 60, whereas Kiel and Rademacker [27] reported an incidence of 56% for age over 55 years and 23% for age under 55. In other studies, age was not found to influence the development of lymphedema [10,11,16,20,22].

Edwards [10] found that the number of the removed lymph nodes was not correlated with lymphedema. Roses et al [11] stated that the number of the removed lymph nodes was not a risk factor in multivariate analysis, but in univariate analyses it increased the risk. On the other hand, other authors demonstrated that as the number of the removed lymph nodes increased lymphedema increased as well [17,27,28]. In our series, there was no correlation between lymphedema and the number of the removed lymph nodes.

Suneson [28] and Kiel and Rademacker [27] reported that the presence of axillary metastases increased the development of lymphedema. In addition, Senofsky et al [29] pointed out that gross axillary metastases correlated with lymphedema. In other series axillary metastases was not found to be a risk factor in the development of lymphedema as in our series [10,11,17,24].

In the present study radiotherapy was found to be the most significant factor in development of lymphedema. Many studies support our study [12,18,19,27,29,30]. However, it has also been reported that adjuvant radiotherapy to axilla did not correlate with the development of lymphedema [10,11,26]. Hypertension, diabetes, cigarette smoking, adjuvant chemotherapy and tamoxifen use did not influence the lymphedema [10,11,17,20,26,27]. In our series these factors were also found not to have an effect.

Tadych and Donegan [31] suggested that total amount of closed suction drainage after the operation correlated with lymphedema. However, the present study did not support this finding. On the other hand, oblique skin incision and division of pectoralis minor muscle during operation have been shown to increase lymphedema [21,26].

Adjuvant radiotherapy to axilla and high BMI were found the independent detrimental factors in our study. Radiotherapy is applied in the presence of four or more metastatic lymph nodes or extra capsular invasion of the nodal metastases in our hospital, and is indispensable as a therapeutic modality. Because axillary radiotherapy after axillary clearance increased the risk of lymphedema 2.75-fold, and lymphedema is also high in patients who had not radiotherapy, we think that the selection of the patients with negative axillary metastatic lymph nodes by sentinel lymph node biopsy is of paramount importance to avoid unnecessary axillary dissection.

The patients who had axillary radiotherapy or who had BMI greater than 25 must be considered as potential candidates to have lymphedema after complete axillary dissection. Therefore, these patients must be informed during the follow-up period about this morbidity, the preventive measures, and the treatment.

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