



## Original article

## Breast cancer related lymphedema in patients with different loco-regional treatments

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## ABSTRACT

**Introduction:** Lymphedema, a sequela of breast cancer and breast cancer therapy, changes functional abilities and may affect a patient's psychosocial adjustment and overall quality of life. Aim of this prospective observational study was to determine the rate of mid-term and late time period lymphedema in breast cancer patients with different loco-regional treatments, and factors associated with lymphedema.

**Materials and methods:** Patients surgically treated for early-stage breast cancer were prospectively enrolled in the study. Demographic, clinical, pathological, and loco-regional treatments data of patients and lymphedema rates were recorded. Patients were divided into six groups regarding different loco-regional treatments. Pre- and postoperative (12 months, and median 64 months after surgery) circumferences of arms were recorded.

**Results:** 218 patients, all female with a median age of 48 (19–82) years, were included in the study. The numbers of patients in breast conservation surgery group (BCS) ( $N = 104$ ), mastectomy group ( $N = 114$ ), sentinel lymph node biopsy group (SLNB) ( $N = 80$ ), axillary lymph node dissection group (ALND) ( $N = 138$ ), group with radiotherapy (RT) ( $N = 88$ ) and group without radiotherapy ( $N = 130$ ). Incidence of lymphedema after surgery in mid-term period was 24.8%. The rate of lymphedema at 64 months median follow-up time was 7.3%. (BCS: 11.1%, 4.2% and 0.5%; Mastectomy: 15.0%, 3.2% and 1.4%; SLNB: 8.0%, 1.9% and 0.5%; ALND: 18.0%, 5.3% and 1.4%; RT: 14.7%, 6.3% and 1.4%; without RT: 11.4%, 2.1% and 0.5%). When we excluded patients with both mid-term and late term lymphedema, only four patients developed lymphedema at late time, then re-calculated late term lymphedema rate was 1.8%. The factors affecting the lymphedema was ALND and radiotherapy (RT) and no lymphedema was detected in patients underwent breast conserving surgery and SLNB. Age and body mass index were not related to lymphedema at any time.

**Conclusion:** The incidence of lymphedema gradually increased in time and a quarter of patients experienced the complication at the end of year. The rate of lymphedema in patients with ALND was significantly higher than patients with SLNB alone. If RT added to SLNB the lymphedema rate was getting higher than SLNB alone. In all patients lymphedema rate was decreased one year after the surgery and further decreased at median 64 months follow-up time period.

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## Introduction

Breast cancer is the most common cancer in women worldwide. In developed countries, one of every eight women suffers from

breast cancer at some stage in life.<sup>1</sup> Surgery remains the mainstay of treatment for most patients with breast cancer and the surgical options will depend on the extent of the disease. Lymphedema is perhaps the most dreaded long term complication related to breast cancer surgery especially with axillary lymph node dissection (ALND). Once present it implies a lifelong problem. In addition to functional impairment, lymphedema may be a daily reminder of breast cancer and also has a psychological burden to the patient. The incidence of lymphedema is about 10–30% in women undergoing

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ALND<sup>2</sup> and it occurs from any time after operation up to 28 years later.<sup>3–8</sup> Upper extremity morbidity may cause difficulties in daily activities and corresponding stress and adaptation difficulties. Sentinel lymph node biopsy (SLNB) is considered as an alternative to ALND with less morbidity in patients with clinically negative axillary findings. Rate of arm swelling is lower in patients undergoing SLNB compared to those in patients undergoing ALND.<sup>8,9</sup>

Aim of this prospective observational study was to determine and compare the mid-term and late period rates of lymphedema in breast cancer patients with different loco-regional treatment modalities (surgery and RT).

## Materials and methods

### Patients

This study was designed as a prospective observational cohort study targeting patients undergoing surgical treatment for early-stage breast cancer (Stage I, II, cT1,2 N0). Study population was selected from patients treated in the Breast Units, Department of General Surgery, Istanbul University Istanbul Medical Faculty and Marmara University School of Medicine, Istanbul. All patients were clinically N0 and all underwent SLNB (blue dye +/- radioisotope), if SLNB was positive, ALND was performed. All patients were enrolled into six groups according to loco-regional treatment modality (BCS, mastectomy, SLNB, ALND, RT and without RT).

### Study inclusion criteria

1. Early-stage (I and II) unilateral breast cancer,
2. Surgical treatment as primary therapy,
3. Patient's informed consent.

### Study exclusion criteria

1. Advanced-stage breast cancer,
2. Patients who had previously received loco-regional or systemic neoadjuvant therapy,
3. Bilateral breast cancer,
4. Recurrence of breast cancer,
5. Death from breast cancer or other causes during the follow-up,
6. Previously diagnosed lymphedema, locomotor or neurological diseases at ipsilateral arm, shoulder or axilla.

### Study design

After patients with a histological diagnosis of breast cancer were informed of the study and their informed consent were received preoperatively, arm circumferences were measured, and demographic data (age, gender, body mass index [BMI], smoking and alcohol consumption, education, marital status) were recorded.

The most common method of lymphedema measurement is the circumference 10 cm above and below the olecranon process, and previously described by Golshan et al.<sup>8</sup> For this reason, arm circumference was measured 10 cm proximal and distal to the olecranon at operated arm. Pre- and postoperative (12 months, and median 64 months after surgery) circumferences of arms were recorded. Arm circumference measurements greater than 2 cm compared to measurements obtained before surgery were considered as lymphedema.

The type of surgery (BCS, mastectomy, SLNB and ALND), drainage methods and retention time, total number of lymph

nodes extracted from axilla, pathology report details (histology and stage of the cancer), radiation therapy (to the breast + boost in patients with BCS and to the chest wall in patients with mastectomy and tumor size >4 cm, and to the regional lymphatics in patients with  $\geq 4$  lymph nodes) and systemic adjuvant therapy (type and time), and treatment-related complications were recorded.

All patients were invited for clinical follow-up in early (1 week), mid-term (9–12 months) and late periods (once in a year after the first year) after surgery. In each follow-up, arm circumference was measured.

### Ethics

Study was approved by the Ethics Committee for Clinical Research of Marmara University School of Medicine. Enrolled patients were informed about the study and their informed consents were received after they had been hospitalized.

### Statistics

All information was collected in a data base created using the SPSS 16.0 program. Unpaired *t*-test, chi-square test and logistic regression analysis were performed for statistical analysis, where appropriate. All values were expressed as mean  $\pm$  SD. Value of  $p < 0.05$  was considered significant.

## Results

A total of 221 patients were enrolled in this prospective study between January 2004 and June 2008, of which 177 were treated in the Breast Unit, Department of General Surgery, Istanbul University, Istanbul Medical Faculty and 44 were treated at the Department of General Surgery in Marmara University School of Medicine. Three patients were died during the study period therefore they were excluded from the study. Data of remaining 218 patients were assessed in early, mid-term and late periods. Median follow-up time of this group was 64 (24–82) months. We discussed here only the results of mid-term and late period.

### Patient characteristics

Median age and mean BMI of 218 patients were 48 (19–82) years and 27.2 (17.7–41.7), respectively. Age ( $\leq 45$  vs  $> 45$  years old) and BMI ( $\geq 30$  kg/m<sup>2</sup>) were not found to be statistically related with lymphedema at any time period. Seventy-six percent of patients were cigarette smoker and alcohol consumption rate was less than 5%. Both cigarette smoking and alcohol consumption, also marital status and education of patients were not related with lymphedema.

These patients were divided into six groups regarding loco-regional treatment; these were breast conservation surgery group (BCS) ( $N = 104$ ), mastectomy group ( $N = 114$ ), sentinel lymph node biopsy group (SLNB) ( $N = 80$ ), axillary lymph node dissection group (ALND) ( $N = 138$ ), group with radiotherapy (RT) ( $N = 88$ ) and group without radiotherapy ( $N = 130$ ). Closed drainage system was applied to 160 patients (73.0%) and their average retention time was 11.8 (1–60) days (Table 1). The usage of drainage system and drainage time was not statistically related with lymphedema.

Invasive ductal cancer was most frequently encountered malignant tumor ( $n = 175$ , 80.3%). Half of patients were in stage II. Median number of lymph nodes removed from patients who underwent ALND was 15 (7–42). A total of 88 patients (40.4%) received adjuvant RT. In addition, 38 patients (17.4%) received adjuvant CT (Table 1). The histological types of tumor, tumor stage,

**Table 1**

Demographic and general characteristics of patients, tumoral and adjuvant treatment characteristics of patients enrolled in the study.

Age; median (range)	48 (19–82)
Body Mass Index; median (SD)	27.2 (4.99)
Smoking history; n (%)	
Non-smoker	52 (23.9)
Smoker	166 (76.1)
Surgery type; n (%)	
Mastectomy	114 (52.3)
Breast conserving surgery	104 (47.1)
Type of axillary intervention; n (%)	
Only SLNB <sup>a</sup>	80 (36.7)
SLNB + ALND <sup>b</sup>	138 (63.3)
Drainage; n (%)	
Yes	160 (73.0)
No	58 (27.0)
Drainage retention time; mean day (SD)	11.75 (9.38)
Tumor histology; n (%)	
Ductal carcinoma in situ	9 (4.2)
Invasive ductal cancer	175 (80.3)
Invasive lobular cancer	15 (6.9)
Other	19 (8.6)
Pathologic stage; n (%)	
0	9 (4.2)
1	68 (31.1)
2	109 (50.0)
3	32 (14.7)
Number of removed lymph nodes <sup>c</sup> ; median (range)	15 (7–42)
Radiotherapy; n (%)	
No	130 (59.6)
Yes	88 (40.4)
Chemotherapy; n (%)	
No	180 (82.6)
Yes	38 (17.4)

<sup>a</sup> SLNB: Sentinel lymph node biopsy.<sup>b</sup> ALND: Axillary lymph node dissection.<sup>c</sup> Only in patients undergoing ALND.

number of excised lymph nodes at axillary dissection and adjuvant CT were not related to lymphedema.

In patients who had one SLN excised had no lymphedema at long term and patients with 2 and more excised SLNs had 8.3% lymphedema rate.

### Lymphedema

#### Mid-term period

In mid-term postoperative period, 54 patients (24.8%) developed lymphedema. ALND ( $p = 0.002$ ), drainage ( $p = 0.005$ ) and RT to axilla (level III; supraclavicular and internal mammarian area) were found to be statistically significant factors ( $p < 0.001$ ) for lymphedema development. In multivariate analysis, only ALND ( $p = 0.02$ ) and RT to axilla ( $p = 0.04$ ) were identified as independent factors affecting lymphedema. Lymphedema rates were shown at Table 2. Lymphedema rate of SLNB + RT patients was 11.1% and 77.1% of patients with lymphedema had RT. When we divided patients into two groups as loco-regional RT (breast + boost) and regional lymphatics (axillary, supraclavicular and internal mammarian area) vs local RT (breast and boost), there was no statistically significant difference detected.

**Table 2**

Lymphedema rate of different therapeutic modalities.

	BCS (%)	Mastectomy (%)	SLNB (%)	ALND (%)	RT (%)	w/o RT (%)
Mid-term period	11.1	15.0	8.0	18.0	14.7	11.4
Late period	4.2	3.2	1.9	5.3	6.3	2.1
Late period without mid-term lymphedema patients	0.5	1.4	0.5	1.4	1.4	0.5

**Table 3**Factors effecting the lymphedema at late period ( $X^2$  test,  $p < 0.05$ ).

Factors	Lymphedema ( $p$ )
ALND + RT vs ALND	<b>0.030</b>
ALND vs SLNB	<b>0.005</b>
RT to axilla vs no RT	<b>&lt;0.001</b>
SLNB vs ALND + RT	0.083

#### Late period

Most of the mid-term lymphedema patients (42/54, 78%) got benefit from lymphedema treatment and lymphedema did not appear in these patients at late time period, but 12 patients still had lymphedema at late term. In addition to these patients, four patients developed lymphedema in late postoperative period. And lymphedema rate was 7.3% (16/218). Eleven of them received RT to regional lymphatics, two patients had RT to the breast and/or chest wall and three patients had no RT, respectively.

ALND ( $p = 0.005$ ) and RT to regional lymphatics ( $p < 0.001$ ) were identified as statistically significant factors for lymphedema development in late period. There was no statistically significant relation detected between lymphedema and SLNB + RT and ALND + RT. Patients with ALND + RT had statistically increased rate of lymphedema than patients with ALND and without RT ( $p = 0.030$ ) (Table 3). There was no patients developed lymphedema underwent BCS and SLNB. Lymphedema rates were shown at Table 2. Lymphedema rate of SLNB + RT patients was 3.3% and 81.3% of patients with lymphedema had RT. When we divided patients into two groups as loco-regional RT (breast + boost and axilla, supraclavicular and internal mammarian area) vs local RT (breast + boost), there was no statistically significant difference detected.

There were no relationship detected between lymphedema rates of patients with BCS + SLNB vs BCS + ALND, BCS + SLNB vs Mastectomy + SLNB, BCS + ALND vs Mastectomy + SLNB in mid-term and late periods. Only significance detected in mastectomy + ALND group vs BCS + SLNB, BCS + ALND, mastectomy + SLNB,  $p = 0.028$  (Table 4).

When we excluded patients with LE diagnosis in mid-term, only four patients had LE diagnosis in late term, and lymphedema rate was 1.8%. Three of them had loco-regional RT and one patient had no RT, respectively. Due to small sample size, there was no statistically significant relation detected between lymphedema and ALND, RT, SLNB + RT vs ALND + RT. Also, there was no relation between patients with ALND + RT and patients with ALND and without RT.

### Discussion

In this prospective observational study, overall incidence of postoperative lymphedema in the mid-term and late periods were 24.8% and 7.3%, respectively. Factors affecting development of lymphedema were ALND and RT administration to regional lymphatics. Patients with BCS and SLNB had no lymphedema in this study population.

**Table 4**  
Lymphedema rates of different surgical procedures.

Factors	Lymphedema present		Lymphedema absent		Total		P
	n	%	n	%	n	%	
BCS + SLNB	0	0.0	58	28.7	58	26.6	
BCS + ALND	5	31.3	29	14.4	34	15.6	
Mastectomy + SLNB	1	6.3	28	13.4	28	12.8	
Mastectomy + ALND	10	62.5	87	43.6	98	45.0	0.028*
Total	16	100.0	202	100.0	218	100.0	

$\chi^2$  test, \* $P < 0.05$ .

There are several strengths of the present study. It is designed as a prospective observational study and most patients were followed more than 24 months. All patients were monitored on a regular basis and assessed by constant physician. All lymphedema measurements were done objectively.<sup>8</sup>

SLNB has replaced axillary lymph node dissection as the standard method of axillary staging for women with early-stage breast cancer. When it was introduced, it was assumed that there would be minimal morbidity associated with SLNB.<sup>4–10</sup> In this study, there was 1.9% lymphedema rate at long term follow-up period with SLNB patients and it was 5.3% in patients with ALND.

Traditionally, finding 2 or more cm difference in arm between the affected side and the normal side, or 200 ml volume difference and 10% increased in arm volume is described as lymphedema.<sup>8,11–14</sup> Specifically, the surgical treatment for breast cancer ALND and mastectomy is considered as major risk factor for lymphedema.<sup>15,16</sup> The extent of lymph node dissection has also increased the risk of lymphedema.<sup>16</sup> Over the past decade, BCS and SLNB have reduced the overall incidence of lymphedema.<sup>17,18</sup> Despite of all women having BCS also received RT. BCS with RT is generally considered as a more conservative treatment than mastectomy. In this study, patients undergoing mastectomy had a rate of 3.2% lymphedema and, conversely there was no lymphedema detected in patients undergoing BCS.

McLaughlin et al., have published a comparison of the prevalence of objectively measured lymphedema at a median follow-up of 5 years, in 936 women having SLNB alone or SLNB + ALND. In the population of SLNB alone, lymphedema rate was 5%.<sup>5</sup> Goldberg et al., revealed that, patients with no axillary surgery has also lymphedema with a rate of 6% and patients with SLNB had 7% lymphedema.<sup>19</sup> Helyer et al., reported the incidence of objectively measured lymphedema in a series of 137 women undergoing SLNB alone or with completion ALND. They found no association between number of lymph nodes removed and lymphedema.<sup>20</sup> Therefore, in patients undergoing ALND, there is no relationship between number of lymph nodes removed and the risk of lymphedema has been reported.<sup>19</sup> However, the findings of multiple other series that report no association between lymphedema and number of excised lymph nodes.<sup>21–23</sup> In a multicentric prospective study in Sweden, a statistically significant difference was observed in ALND group regarding arm pain, limitation of shoulder movements and lymphedema compared to those in SLNB group.<sup>10</sup> In ASOCOG 2001 study, number of excised lymph nodes is considered the most important factor in development of paresthesia in arm within the first postoperative 30 days.<sup>17</sup> ALMANAC (Axillary Lymphatic Mapping Against Nodal Axillary Clearance) working group examined effects of standard level I–II AD and four-lymph-node sampling on arm edema and patients' QoL in early-stage breast cancer treatment in their multicentric, randomized trial. They concluded that at the end of 18 months, arm edema was two-fold higher in ALND group (14% vs 7%).<sup>9</sup> In randomized study of Veronesi et al., arm morbidity and patients' QoL were shown to be better in SLNB group.<sup>24</sup> In present study, rates of upper extremity

lymphedema on the operated side were 24.8% in mid-term period, and 7.3% in long-term period. In this study, patients with SLNB has 1.9% lymphedema rate and there is no correlation between number of excised lymph nodes and lymphedema in patients undergoing SLNB.

A broad spectrum of risk factors resulting in arm morbidity has been suggested, mastectomy, ALND, RT, chemotherapy (CT), age, body mass index (BMI).<sup>25–28</sup> In previous studies incidence of lymphedema was found to be between 6% and 43%<sup>29–32</sup>, and lymphedema may occur even months or years after treatment.<sup>33,34</sup> Secondary factors affecting lymphedema include ALND,<sup>35</sup> RT administration to axilla,<sup>36</sup> operation on dominant side,<sup>37</sup> BMI of 26 and above<sup>23</sup> and previous administration of RT.<sup>38</sup> In one study, RT administration to breast and axilla was shown to cause more significant lymphedema when compared to administering RT only to breast.<sup>9</sup> Liljegren et al.,<sup>39</sup> showed that RT administration to breast has no effect on lymphedema. For high risk patients treated with adjuvant RT to a dissected axilla, the risk of subsequent lymphedema is greatly increased, with reported rates of 45%.<sup>38</sup> In this study RT to regional lymphatics had statistically significant effect on lymphedema. There was no statistically significant relation detected between lymphedema and CT, BMI and age of the patients.

Among independent factors affecting lymphedema, ALND and RT administration to axilla were found to be significant.

As conclusion, cancer related lymphedema is a common post treatment condition, incidence of lymphedema gradually increased in time and a quarter of patients experienced the complication at the end of year. But, it decreased at the late follow-up period (64 months).

### Conflict of interest

There are no conflicts of interests by any of the authors with regard to that paper.

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