Original Article

Evaluation of Relative Abundance of Lymphedema after Reverse Axillary Mapping in Patients with Breast Cancer

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Abstract

Background: The axillary reverse mapping (ARM) technique identifies and preserves arm nodes during sentinel lymph node biopsy (SLNB) or axillary lymph node dissection (ALND). Here, we aimed to investigate the prevalence of lymphedema following ARM. **Materials and Methods:** This is a clinical trial that was performed in 2019-2020 in Isfahan on patients with breast cancer in the early stages. Demographic and initial information of all cases including age and body mass index (BMI) was collected. Patients were then underwent SLNB ± ALND associated with ARM and were followed up for lymphedema every 6 months to a year. The occurrence of lymphedema was assessed. **Results:** By evaluating data of 102 patients, we found that 10 patients (9.8%) had lymphedema and patients with lymphedema had significantly higher age (P = 0.004), higher BMI (P = 0.001), larger tumor size (P = 0.018), and longer surgery duration (P < 0.001). The frequency of menopausal women was higher in patients with lymphedema compared to other cases (P = 0.001). **Conclusion:** The prevalence of lymphedema was high among patients undergoing ARM that was associated with factors including higher age, higher BMI, prolonged surgery duration, larger tumor size, and menopause. We believe that further comparative studies should be conducted on this issue.

Keywords: *Breast neoplasms, lymphedema, sentinel lymph node biopsy*

Introduction

Breast cancer is the most common malignancy and the most common cancer leading to death in women. In the United States, 100,000 new cases of the disease are diagnosed each year, and about 30,000 patients die from this cancer.[1] The prevalence of breast cancer accounts for about one-third of all female cancers and is the second most common cancer after lung cancer and the most common cause of cancer death among women. In Iran, breast cancer accounts for 32% of all female cancers.[2,3]

Many factors such as geography, family history, menstrual status and pregnancy, proliferative breast lesions, and history of radiation have been considered as risk factors for breast cancer.[4,5] One of the common and effective treatment methods for breast cancer is a surgical operation. Lymph node dissection is also conducted based on the surgeon's decision, especially in cases of sentinel node involvements. Axillary reverse mapping (ARM) was first developed by Thompson and Noss in 2007 to identify lymph nodes and upper lymphatic pathways and to preserve these pathways during breast cancer surgery in patients.[6,7]

During ARM, the lymph nodes are mapped using methylene blue dye injection subcutaneously and gamma probe. It has been indicated that by using ARM, surgeons could dissect only the selected lymph nodes, and other nodes could be preserved that, in turn, lead to lower incidence of complications.[8]

One of the most important complications of breast cancer surgery and lymph node dissection is lymphedema. Lymphedema is a long-term complication in women who have undergone axillary surgery. The prevalence of this complication has been reported differently based on different classification criteria and measurements.[9] Its prevalence is reported to be 6% in patients undergoing sentinel lymph node biopsy (SLNB) and 20% in patients undergoing axillary lymph node dissection (ALND).[10,11]

During ARM, the target nodes are identified by injecting a tracer material into the upper

How to cite this article: Eshraghi Samani R, Ebrahimi H, Rafiee Zadeh A, Safaee M. Evaluation of relative abundance of lymphedema after reverse axillary mapping in patients with breast cancer. Adv Biomed Res 2022;11:36.

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Received: 06 September 2021
Revised: 01 November 2021
Accepted: 08 November 2021
Published: 29 April 2022

Access this article online

Website: www.advbiores.net
DOI: 10.4103/abr.abr_281_21
Quick Response Code:

limb before surgery, which is similar to the procedure performed in SLNB surgery, which usually uses blue dye, radioisotope, or fluorescence. Initially, it was hypothesized that the lymphatic pathways of the upper limb were separated from the breast and metastatic cells would not enter it, and that preserving this lymph node and lymphatic pathways would reduce lymphedema without increasing the risk of metastasis.[12,13]

However, some studies have shown that the prevalence of lymphedema in patients with ARM was 6%[14] and 13%,[15] respectively. The prevalence of lymphedema in case of SLNB with radiotherapy was 10%, ALND without radiotherapy was 19%, and in case of ANLD and simultaneous radiotherapy was 30%, which indicates the multifactorial nature of lymphedema in patients after breast surgery.[16]

These data suggest that using ARM could increase the chances of lymph node preservation and decrease the incidence of lymphedema, but further studies are also required in this field. In the present study, we aimed to investigate the prevalence of lymphedema in cases undergoing lymph node dissection using ARM.

Materials and Methods

This is a clinical trial that was performed in 2019-2020 in Omid Hospital affiliated to Isfahan University of Medical Sciences. The current study was conducted on patients with breast cancer in the early stages. The study protocol was approved by the Research Committee of Isfahan University of Medical Sciences, and the Ethics committee has confirmed it (Ethics code: IR.MUI.MED.REC.1399.148, Iranian Registry of Clinical Trials (IRCT) code: IRCT20200909048672N1).

The inclusion criteria were female gender, diagnosis of breast cancer by expert oncologists, being a candidate for SLNB ± ALND, patients candidates of total or partial mastectomy + ALND, patients with operable tumors, and signing the written informed consent to participate in this study. The exclusion criteria were previous chemotherapy or radiotherapy, previous axillary surgery, and patient's will to exit this study.

The sampling method of the present study was accessible and easy so that until the completion of the required sample volume ceiling, the sampling study was performed among eligible patients. We assessed 120 eligible patients for this study. Demographic and initial information of all cases including age, body mass index (BMI), and patient arm volume before surgery was collected. Patients were then underwent SLNB ± ALND associated with ARM.

The ARM was conducted by the following method:

After surgical site prep and draping, 1.0 mCi unfiltered technetium sulfur colloid that was diluted to 4 cc was injected under an areola in the involved site. Then, using a gamma detector hand probe, the exact location of the hot lymph nodes was determined, and then a skin incision was made and the affected lymph nodes were identified and removed. ARM technique was performed by injecting 2–5 mL of methylene blue into the subcutaneous tissue of the upper inner ipsilateral arm before surgery. After the injection, the upper hand was held, and the injection site was massaged for 3 min. After injection, the SLNB technique was continued through mastectomy incision or intra-axillary incision.

Dual mapping (via the upper limb and breast network) identifies possible lymph nodes that overlap between the two networks, in which case the overlapping lymph nodes were also removed. After identifying the overlapping lymph nodes and removing them, the number and anatomical location of these glands during surgery were examined and recorded. Finally, the patient, s skin was suppurated.

It should be noted that in patients in whom ARM lymph nodes were not detectable in this way, the ALND + SLND technique was performed. When the SLN was positive and a complete mastectomy was performed, complete ALND was performed through a previous axillary incision. Zones I and II lymph nodes were completely removed, and the blue glands and lymph nodes that represent the ARM lymphatic system were preserved. At this stage, the lymph nodes, which were both blue and radioactive, were also removed.

After primary surgery, patients were followed up for lymphedema every 6 months to a year. To measure the patient's arm circumference, it was measured from the highest point of the patient's shoulder joint to the lowest point of the patient's elbow joint, and between these two points, the patient's arm was marked and measured using a meter.

The obtained data were entered into the Statistical Package for Social Sciences (SPSS) (version 24, SPSS Inc., Chicago, IL, USA). Quantitative data were reported as mean ± standard deviation and qualitative data as frequency distribution (percentage). Independent *t*-test and Chi-square test were used to analyze the data. $P < 0.05$ was considered as a significance threshold.

Results

In this study, 122 patients with breast cancer entered the study. During the study, 20 patients were excluded due to lack of proper cooperation ($n = 13$), patient's will ($n = 5$), and previous radiotherapy ($n = 2$). Data of 102 patients were analyzed.

Based on initial analysis, the mean age of patients was 38.78 ± 9.0 years and the most common type of cancer was invasive ductal carcinoma (78.4%). Sixty-two patients (60.7%) had right breast involvements and the most common involvement location was upper outer quadrant (60.8%). Only 17 patients (16.8%) were in

menopausal status and 48 patients (47.1%) had previous oral contraceptive pills (OCPs) usage. The duration of OCP use was over 1 year in all cases. The most common cancer stage was IIA (42.1%). These data are indicated in Table 1.

Further evaluations showed that 10 patients (9.8%) had lymphedema, 76 patients (74.6%) underwent SLNB, and 46 patients (45.1%) had sentinel lymph node involvements. The mean tumor size among patients was 25.5 ± 10.3 mm, the mean number of involved lymph nodes was 3 ± 3, and the arm circumstance before and after surgeries was 32.6 ± 5.1 and 33.1 ± 7.3 cm, respectively. These data are indicated in Table 2.

We compared different variables between patients with or without lymphedema. These data showed that patients with lymphedema had significantly higher age (P = 0.004), higher BMI (P = 0.001), larger tumor size (P = 0.018), and longer surgery duration (P < 0.001). The frequency of menopausal women was higher in patients with lymphedema compared to other cases (P = 0.001). No other differences were observed between two groups regarding the following variables: number of involved lymph nodes, SLNB or ALND administration, and side of involvement, tumor location and OCP usage (P > 0.05 for all). These data are indicated in Table 3.

Discussion

In the present study, we evaluated the occurrence of lymphedema in patients with breast cancer undergoing SLNB ± ALND associated with ARM. Based on our data, lymphedema occurred in 10% of cases. Furthermore, by assessing different characteristics, we observed that lymphedema was more frequent in patients with higher age, higher BMI, larger tumor size, and longer surgery duration. Based on the results of our study, conduction of ARM had no significant effects in lymphedema.

These data show that ARM could be used as an effective method in mapping the involved lymph nodes, but the frequency of lymphedema was almost high among patients. Previously, studies have evaluated the occurrence of lymphedema in similar cases and various results have been reported. Most of these studies have reported significantly decreased lymphedema among patients undergoing ARM, and in this study, we showed a similar incidence of lymphedema compared to other studies. We should also note that the ARM procedure was conducted successfully in all patients and no complications were reported.

In 2017, Tummel *et al.* evaluated the effects of ARM on the prevention of lymphedema. By evaluating 654 patients, they reported that lymphedema rates for SLNB and ALND were 0.8% and 6.5%, respectively, and also demonstrated that by ARM, identification of arm lymphatics in the axilla could be conducted successfully that could, in turn, have significant clinical usage.[17] In another study by Yue *et al.* in 2015, they assessed data of 265 patients with breast

Table 1: Evaluation of basic data of patients

Variable	Mean±SD or *n* (%)
Age (year)	38.78±9.0
BMI (kg/m^2)	25.9±3.6
Type	
IDC	80 (78.4)
ILC	17 (16.7)
Medullary carcinoma	5 (4.9)
Side of involvement	
Right	62 (60.7)
Left	40 (39.3)
Location	
Central	16 (15.6)
LIQ	1 (0.9)
UIQ	12 (11.8)
UOQ	62 (60.8)
LOQ	11 (10.9)
Menopausal status	
Yes	17 (16.6)
No	85 (83.4)
OCP use	
No	54 (52.9)
Yes	48 (47.1)
Stage	
IB	31 (30.3)
IIA	43 (42.1)
IIB	28 (27.6)

SD: Standard deviation, BMI: Body mass index, IDC: Invasive ductal carcinoma, UOQ: Upper outer quadrant, OCP: Oral contraceptive pill, ILC: Invasive lobular carcinoma, LIQ: Lower inner quadrant, UIQ: Upper inner quadrant, LOQ: Lower outer quadrant

Table 2: Evaluation of patient's information

Variable	Mean±SD or *n* (%)
Lymphedema	
No	92 (90.2)
Yes	10 (9.8)
SLNB administration	
No	26 (25.4)
Yes	76 (74.6)
SLNB frozen section lymph node	
Not involved	30 (29.4)
Involved	72 (70.6)
ALND administration	
No	30 (29.5)
Yes	72 (70.5)
Adjuvant chemotherapy	
No	19 (18.7)
Yes	83 (81.3)
Tumor size (mm)	25.5±10.3
Time of surgery (min)	61±18
Number of involved lymph nodes	3±3
Arm circumstance before surgery (cm)	32.6±5.1
Arm circumstance after surgery (cm)	33.1±7.3

SD: Standard deviation, SLNB: Sentinel lymph node biopsy, ALND: Axillary lymph node dissection

Table 3: Comparison of variables between patients with or without lymphedema

Characteristic	Lymphedema		*P*
	Yes (*n*=10), *n* (%)	No (*n*=92), *n* (%)	
Age (year)	43±9*	37±8	0.004
BMI (kg/m^2)	27.8±3.1	25.1±3.5	0.001
Tumor size (mm)	30.6±12.5	23.4±8.4	0.018
Time of surgery (min)	75±15	54±15	<0.001
Number of involved lymph nodes	4±3	3±3	0.135
SLNB administration			
No	3 (30)	23 (25)	0.330
Yes	7 (70)	69 (75)	
ALND administration			
No	3 (30)	27 (29.3)	0.374
Yes	7 (70)	65 (70.7)	
Menopausal status			
Yes	1 (10)	16 (17.3)	0.001
No	9 (90)	76 (82.7)	
Side of involvement			
Right	6 (60)	56 (60.8)	0.525
Left	4 (40)	36 (39.2)	
Location			
Central	1 (10)	15 (16.3)	0.609
LIQ	0 (0.0)	1 (1.1)	
UIQ	2 (20)	10 (11.1)	
UOQ	6 (60)	56 (60.8)	
LOQ	1 (10)	10 (10.7)	
OCP use			
No	4 (40)	50 (54.3)	0.769
Yes	6 (60)	42 (45.7)	

BMI: Body mass index, SLNB: Sentinel lymph node biopsy, ALND: Axillary lymph node dissection, LIQ: Lower inner quadrant, UIQ: Upper inner quadrant, LOQ: Lower outer quadrant, UOQ: Upper outer quadrant, OCP: Oral contraceptive pill

cancer. They showed that patients that received ARM before lymph node biopsy and dissection had significant effects in lymph node preservation and contributed to decreasing the frequency of lymphedema. Based on their study, 30.07% of control group and 5.93% of ARM group experienced lymphedema.[18] Boneti *et al*. also reported that among 114 patients who underwent ARM, lymphedema was diagnosed in 3.5% of the SLNB cases and 7% of the combined SLNB + ALND cases.[19] The results of our study were somehow in line with these reports. As mentioned above, we found that 10% of our cases developed lymphedema after the procedures that are relatively higher than previous reports.

The differences between our results and previous studies could be due to various factors, including the BMI and obesity of patients, radiotherapy of the affected area, and poor postprocedure care strategies such as physical activities or hand elevation. However, these data could not cast doubt on the effectiveness and complication rates of ARM.

Other findings of our study were that lymphedema was more frequent in patients with higher age, higher BMI, larger tumor size, longer surgery duration, and among women with menopause. In a study by Ochoa *et al.* in 2014, they investigated 360 patients undergoing SLNB and/or ALND. It was mentioned that the incidence of lymphedema was higher among older and obese patients and menopause women.[20] It has also been discussed in previous studies that lymphedema could occur more often in patients with higher BMI and larger tumor size.[21,22] In another study by Faisal *et al.*, it was mentioned that postprocedure care should be precisely conducted and observed, especially in patients with higher age to prevent lymphedema.[23] Based on a recent systematic review and meta-analysis in 2020, ARM could significantly reduce the occurrence of lymphedema; however, this issue is more probable among patients with previous medical condition, older patients, and those with prolonged surgery duration.[24] These results are consistent with our findings.

We demonstrated that the prevalence of lymphedema was almost higher in our study compared to others, but the important point is that we found the possible correlating factors such as higher age, larger tumor size, higher BMI and prolonged surgery duration. These data were in line with previous studies. The limitations of our study were restricted study population, not comparing the patients

with control group and lack of postintervention follow-up evaluation. However, the results of our study could indicate that conducting ARM might not reduce the possibility of lymphedema in patients. We believe that further studies are required in this regard. We recommend that further clinical trials should be conducted to establish the effect of ARM in our regional health-care system.

Conclusion

Taken together, we showed that the prevalence of lymphedema was high among patients undergoing ARM that was associated with factors including higher age, higher BMI, prolonged surgery duration, larger tumor size, and menopause. We believe that further comparative studies should be conducted on this issue.

Financial support and sponsorship

This study was granted by Isfahan University of Medical Sciences.

Conflicts of interest

There are no conflicts of interest.

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