Implementation and evaluation of axillary reverse mapping technique in breast cancer patients using patent blue dye

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Introduction
Breast cancer is the most common malignancy among Egyptian women. Following axillary lymph node dissection, arm lymphedema can develop in 7–77% of cases. To detect and preserve upper-limb lymphatics and lymph nodes after axillary surgery, the axillary reverse mapping (ARM) technique was developed. This procedure may help avoid arm lymphedema.
Aim of work
To establish the ARM-node involvement of cancer cells and study their location to assess the effectiveness of ARM using patent blue dye.
Methodology
At Kasr Alainy University Hospital, this prospective randomized controlled study was carried out. There were 42 breast cancer patients in total, including 21 each in the study group and the control group. Following dye injection, stained ARM lymph nodes and lymphatics were preserved in the study group during axillary lymph node (ALN) dissection if grossly negative and removed if grossly positive, whereas individuals in the control group had the standard technique. After 1 month, all subjects underwent a second evaluation, during which the arm circumference was measured and recorded at a point 10 cm near the medial epicondyle.
Results
In the study group, in 18 patients (85.7%) their lymph nodes were stained. Six patients had suspiciously colored lymph nodes that were surgically removed, but no metastatic disease was apparent in the rest of the group. Early upper-limb lymphedema was not detected in the study group (0%), with 9.5% in the control group.
Conclusion
Arm lymphedema can be avoided by doing ARM while performing ALN dissection. Future research should be conducted on more patients and for a longer length of time, according to the findings of this study.

Keywords:
breast cancer, axillary reverse mapping, blue dye, lymphedema

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Introduction

Even if it is debatable in some circumstances, axillary lymph node dissection (ALND) is still a crucial component of surgical therapies for patients with invasive breast cancer and axillary lymph node metastases [1]. Due to its lower morbidity, sentinel lymph node biopsy (SLNB) has taken the role of ALND in clinical practice for N0 and select N1, who have completed neoadjuvant therapy [2].

According to Berg [3], typical ALND now entails removing lymph nodes at levels I and II. Such dissections facilitate disease stage and prognosis evaluations and provide therapeutic purposes [4]. Unfortunately, functional surgical treatment sequelae including lymphedema, paresthesia, range-of-motion limitations, and discomfort in the arm ipsilateral to the lymph node dissection are mostly caused by ALND.

According to reports, the risk of lymphoedema is still present with SLNB, even with removing a small number of axillary nodes. SLNB is linked to a 3–13% risk of lymphedema [5], while ALND is linked to a 7–77% risk of lymphedema [6].

It has been proposed that the obstruction of upper-limb lymphatic drainage is the primary cause of lymphedema following ALND or SLNB. By locating and maintaining upper-limb lymphatic drainage during ALND and SLNB [7], the axillary reverse mapping (ARM) approach may be able to reduce lymphedema.

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To locate and preserve lymphatic outflow from the arm during ALND or SLNB and reduce arm lymphedema, the axillary reverse mapping (ARM) technique was described [8].

According to the hypothesis behind ARM, the lymphatics arm drainage (LAD) and nodes that drain the arm are different from those that drain the breast. As a result, by protecting the axillary nodes that drain the arm, lymphedema may be avoided.

In 2007 [9], Thompson and associates used blue dye for the first time to locate ARM lymphatics and nodes. The upper inner arm was given a subcutaneous or dermal injection of 2.5 cc of blue dye. When blue lymphatics could be seen in the upper extremity, the injection site was massaged, and the arm was lifted for five minutes. In 18 (61%) patients, [10] ARM lymphatics were found. As a result, multiple researchers showed that blue dye may be used in ARM [10–12]. The identification rates of ARM nodes using blue dye alone, which ranged from 33.7 to 94.7% [13,14], were inadequate.

The goal of this study is to assess the axillary reverse mapping (ARM) technique as an effective tool for differentiating breast lymphatic and lymph nodes from those in the upper extremities.

Material and methods

Between November 2020 and May 2021, Kasr Alainy University Hospital hosted this prospective, randomized, controlled trial. The official research and ethics committee reviewed the study protocol and approved it. In all, 42 breast cancer patients were enrolled in this trial; 21 of them received ALND using the ARM method (Group 1) and 21 underwent ALND without the ARM technology (Group 2).

All participants, who were randomly allocated (through a sequence developed in Microsoft Excel) in a 1:1 ratio to either the study or control groups, were advised to undergo Level I and II axillary lymph node dissection (ALND). When a patient gave their agreement to participate in the experiment and had the assigned operation, the method was carried out by surgeons with the same experience.

General anesthesia was used before a 2 ml intradermal injection of patent blue dye was administered into the medial aspect of the arm on the same side, just two fingers above the medial epicondyle (Fig. 1). To facilitate dye migration toward the axilla, massage the injection site, and elevate the arm for a short time. Axillary dissection was done following breast cancer surgery, either a modified radical mastectomy or breast conservative surgery (around 15 min after dye injection).

By observing stained lymphatics and stained lymph nodes draining the arm (inside the lateral compartment of the axilla), which were preserved in the ARM procedure during ALND, it was possible to identify lymphatic arm drainage (LAD) (Fig. 2). Lymphatics in the stained arm were examined for any differences in size and position.

Patients who have suspicious stained lymph nodes should have their stained lymph nodes removed. Amalgamated lymph nodes or LNs larger than 1 cm, hard or solid, are located anywhere other than lateral to or above the thoracodorsal pedicle.

The Histopathology Department received separately stained lymph nodes draining the arm for paraffin section examination separately from ALND specimens. However, stained LN had not been removed when it was not worrisome.

Group 2: Axillary lymph node dissection did not involve looking for lymph nodes or lymphatics in the upper limbs.

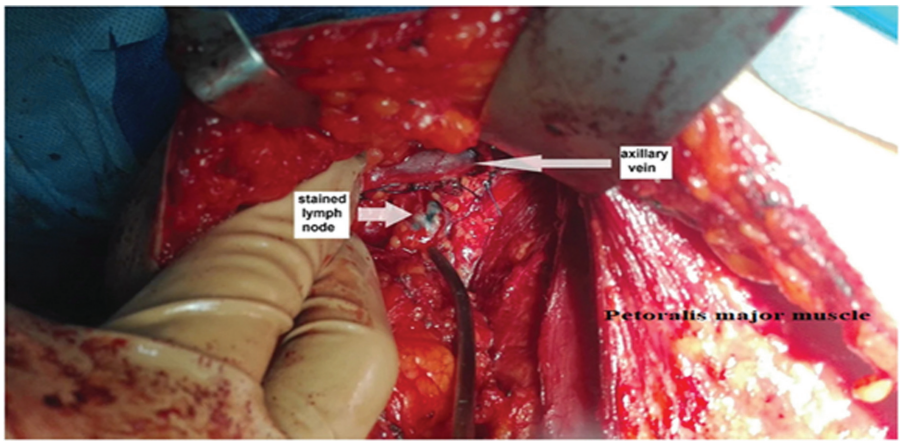
To prevent confusing early-onset postoperative swelling with lymphedema, all patients underwent a second evaluation after 3 months, and the incidence of lymphedema was noted.

The arm's circumference was measured 3 months before surgery at a point 10 cm in front of the medial epicondyle. Each group's variations in

Figure 1

Injection of blue dye.

Figure 2



Identification of a stained lymph node below the axillary vein.

ipsilateral and contralateral arm circumference were contrasted. Arm circumferences before surgery and 3 months after surgery were also compared on the ipsilateral side. A change of more than 2 cm in the circumference of the ipsilateral upper extremity throughout the follow-up period was considered arm lymphedema [15].

Results

The study designation recruited 42 female patients divided equally into two groups and yielded the following results:

Group 1: The patient underwent axillary lymph node dissection with the ARM technique with age ranging between 35 and 67 years with a mean age of 48.1±7.7 years. They were clinically node-positive (cN1) and confirmed to be pathological lymph nodes by axillary ultrasonography. Seven cases (33.3%) were cT2, six cases were cT3 (28.6%), 4 cases were cT4b (19%), and 4 cases were cT4d (19%). In terms of the kind of surgery, 61.9% received a modified radical mastectomy, compared with 38.1% of individuals who underwent conservative breast surgery and ALND.

Group 2: The patient underwent standard axillary lymph node dissection with age ranging between 32 and 70 years with a mean age of 47.3±12 years. They were clinically node-positive (cN1) and confirmed to be pathological lymph nodes by axillary ultrasonography. Three cases were cT2 (14.3%), eight cases were cT3 (38.1%), five cases were cT4b (23.8%), and five cases were cT4d (23.8%). In terms of the kind of surgery, 61.9% got a modified radical mastectomy, compared with a conservative breast procedure and ALND for 38.1% of patients.

As mentioned in Table 1, 18 cases out of 21 cases in group 1 '85.7%,' the blue-stained lymph nodes could be identified intraoperatively. So, there were three cases in which we could not identify the arm-draining lymph nodes and accordingly, we removed them with the specimen according to the standard axillary dissection.

Table 1 Represents the descriptions of cases in groups 1 and 2

	Group 1 'ARM'		Group 2	
	Count	%	Count	%
CT stage				
T2	7	33.3%	3	14.3%
T3	6	28.6%	8	38.1%
T4b	4	19.0%	5	23.8%
T4d	4	19.0%	5	23.8%
CN stage				
N1	21	100.0%	21	100%
Neoadjuvant				
Yes	13	61.9%	18	85.7%
No	8	38.1%	3	14.3%
Intraoperative identification of blue-stained nodes				
Positive	18	85.7%		-
Negative	3	14.3%		-
Number of stained LNs				
0	3	14.3%		-
1	15	71.4%		-
2	3	14.3%		-
Grossly positive or negative				
Positive	6	33.3%		-
Negative	12	66.7%		-
Pathology of grossly positive (on paraffin basis)				
No malignancy	6	100.0%		-
Axillary surgery				
ALND	20	95.2%	21	100%
SLNB/ALND	1	4.8%	0	0%
Type of breast surgery				
BCS	8	38.1%	8	38.1%
MRM	13	61.9%	13	61.9%

Table 2 Represents comparisons between preoperative arm circumference in cm and postoperative arm circumference after 3 months in cm in both groups

	Group							
	Group 1 (ARM)				Group 2 (Standard)			
	Mean	SD	Minimum	Maximum	Mean	SD	Minimum	Maximum
Preoperative arm circumference in Cm	29.88	2.25	24.00	35.00	30.01	2.62	25.60	35.00
Postoperative arm circumference after 3 months in CM	30.47	2.35	24.30	35.30	31.05	2.90	26.00	37.00

The arm's circumference was measured 3 months before surgery at a point 10 cm in front of the medial epicondyle. Our study's findings revealed:

Group 1: The minimum increase in arm circumference was 0.2 cm (28.1>28.3 cm), while the maximum increase in arm circumference was 1.8 cm (30.2>32 cm), and no incidence of lymphedema was detected.

Group 2: Minimum increase in arm circumference was 0.3 cm (26>26.3 cm), while the maximum increase in arm circumference was 2.1 cm (35>37.1 cm). Lymphedema was detected in two cases out of 21 cases.

Comparisons between preoperative arm circumference in cm and postoperative arm circumference after 3 months in cm in two groups; the observations are shown in Table 2.

As shown in Table 3, a comparison between two groups as regards the incidence of lymphedema after 3 months of surgery was conducted, and there is no statistically significant difference (*P* value 0.488)

Getting into the core part of our study, the ARM technique was evaluated and the incidence of lymphedema was assessed after 3 months of operation. Taking into consideration that there were no cases of lymphedema detected in group 1 'ARM group,' the maximum increase in arm circumference in grossly positive cases was 1.8 cm (30.2>32 cm) and the minimum increase in arm circumference was 0.5 cm (29.5>30 cm). While in the grossly negative cases, the maximum increase in arm circumference was 0.7 cm (30.3>31 cm) and the minimum increase was 0.2 cm (29.1>29.3 cm). The mean increase of arm circumference in all grossly positive cases was 1.1 cm, while the mean increase in grossly negative cases was 0.3 cm.

Results of the correlation between an intraoperative gross picture of blue-stained lymph nodes, preoperative arm circumference, and postoperative arm circumference after 3 months in group 1 are shown in Table 4.

Table 3 Represents comparisons between 2 groups in the incidence of lymphedema after 3 months of surgery; there is no statistically significant difference (*P* value 0.488)

	Group				
	Group 1 (ARM)		Group 2 (Standard)		
	Count	%	Count	%	*P* value
Incidence of lymphedema					
Yes	0	0.0%	2	9.5%	0.488
No	21	100.0%	19	90.5%	

Discussion

No incidence of lymphedema was found in the axillary reverse mapping (ARM) group in the current investigation, which was not statistically different from the incidence of 9.5% in the ALND group. The fact that our study only had a limited sample size of patients might be the cause of this lack of relevance; 52.7% of the 143 breast cancer patients evaluated by Tausch *et al.* in 2013 still had ARM. Although there was no preservation in that study's lymphedema incidence, which was 43% in the group without it, and only 23% in the ARM group, there was no discernible difference in incidence between the groups [16]. However, after enrolling 265 breast cancer patients, Yue and colleagues found a significant difference in lymphedema incidence

Table 4 Represents the correlation between intraoperative gross picture of blue-stained lymph nodes, preoperative arm circumference, and postoperative arm circumference after 3 months in group 1

	Grossly positive or negative								
	Positive				Negative				
	Mean	SD	Minimum	Maximum	Mean	SD	Minimum	Maximum	*P* value
Preoperative arm circumference in Cm	30.37	0.85	29.50	31.60	30.18	2.27	27.10	35.00	0.846
Postoperative arm circumference after 3 months in CM	31.50	0.89	30.00	32.50	30.53	2.27	27.40	35.30	0.336

(33.7% in the control group versus 5.93% in the ARM group, P 0.001) [17]. The incidence of lymphedema should be decreased theoretically by maintaining the arm lymphatics. The advantages of keeping ARM nodes have been mentioned by several publications. In the actual use of the ARM method, there are still a lot of issues that need to be fixed. The biggest worry is the possibility of losing positive nodes while keeping ARM nodes [18]. Although patients had multiple positive axillary lymph nodes in their early trials, Thompson *et al.* and Boneti *et al.* identified no cancer cells in the ARM nodes [11,19]. However, subsequent studies have shown ARM-node involvement by malignant cells [20–23].

In this study, we compared patients who received ALND after NA therapy witht those who underwent ALND without NA therapy to determine whether the group of patients had a higher rate of ARM lymph node metastatic involvement. There was no difference between the two groupings in the current investigation, and there was no metastatic involvement. The metastatic involvement of the ARM nodes was discovered in 13 of 79 patients (17%) in the NAC+ group as opposed to 7 of 19 patients (37%) in the NAC group (P=0.048), according to Beek and colleagues, who enrolled 112 female patients with breast cancer. It is challenging to infer a connection between neoadjuvant therapy and ARM involvement from our research as only 13 individuals who underwent neoadjuvant therapy were included in the study. Moreover, no associations between the prevalence of grossly positive ARM nodes and clinicopathological characteristics, such as age and clinical T and N staging, were discovered. By evaluating the percentage of residual ARM nodes, we might also use the ARM approach to identify which patients are predicted to have a high risk of lymphedema. Early therapies to avoid lymphedema should be given to patients with a low incidence of residual ARM nodes.

Patent blue dye, which is used to color lymph nodes, is safe for intradermal injection; allergic responses have only sometimes been reported. However, one disadvantage of using this color is skin tattooing, which may last anywhere between 1 week and 6 months. The inside surface of the upper arm may be selected as the injection location to assist in concealing the tattooed skin [24,25].

Conclusion

ARM is a minimally invasive procedure that is easily included in ALND and can aid in preventing arm lymphedema. In our research population, the use of ARM for mapping lymphatic arm drainage and avoiding the excision of arm lymphatics and nodes was associated with a reduced incidence of arm lymphedema than standard ALND surgery. To acquire statistically meaningful findings, we advise doing further research on the ARM technique in a bigger population of patients and for a longer length of time than 3 months. Despite its oncological safety, the ARM approach should be used with caution in clinical settings when trying to preserve lymph nodes and/or lymphatics. Furthermore, reduced metastatic involvement in the ARM lymph nodes is not associated with preoperative NAC.

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Conflicts of interest

There are no conflict of interest.

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