The Role of Axillary Reverse Mapping in Reducing Lymphedema in Patients with Early Breast Cancer: A Prospective Randomized Study

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Introduction: Breast cancer–related lymphedema (BCRL) is a frequent and debilitating complication of axillary lymph node dissection (ALND). Axillary reverse mapping (ARM) aims to identify and preserve lymphatic drainage pathways of the upper limb to reduce postoperative lymphedema risk.

Aim of work: To evaluate ARM feasibility, detection rate, and its efficacy in preventing lymphedema in early breast cancer.

Pathients and methods: In this prospective randomized study, 80 women with early-stage breast cancer (T1–T2, non-palpable axillary nodes) were randomized to ARM + ALND (n = 40) or standard ALND (n = 40). ARM involved subdermal injection of 3 mL methylene or patent blue into the upper arm, with preservation of blue-stained lymphatics unless oncologically suspicious. Arm circumference was measured preoperatively and at 6, 12, and 18 months post-operatively. Lymphedema was defined as ≥ 2 cm inter-arm difference at any anatomical site.

Results: ARM identified blue-stained lymph nodes in 100% of cases (1–3 nodes per patient). Lymphedema incidence was significantly lower in the ARM group at 6 months (0% vs. 15%, p = 0.042), 12 months (5% vs. 45%, p = 0.035), and 18 months (10% vs. 55%, p = 0.023). Mean arm circumference was significantly smaller in the ARM group at all postoperative time points (p < 0.05).

Conclusion: ARM is a feasible and effective technique for reducing postoperative lymphedema in early breast cancer patients undergoing ALND, without compromising oncological safety. Incorporating ARM into surgical practice may improve postoperative quality of life.

Key words: Axillary reverse mapping, lymphedema, early breast cancer.

Introduction

Breast cancer, with a predicted 1.69 million new cases each year, represents the most prevalent malignancy among women globally and ranks as the second leading cause of cancer-related death, after lung cancer.[1] Precise lymph node (LN) staging is critical for prognostication in early-stage disease and for guiding therapeutic strategies aimed at achieving regional disease control.[2]

Surgical resection remains the main approach for breast cancer management, with modified radical mastectomy (MRM) linked with axillary lymph node excision (ALND) being among the standard surgical approaches. ALND, however, is linked with a range of postoperative adverse events, including lymphedema, infections, seroma formation, as well as neurological and sensory deficits. Among these, upper-limb lymphedema represents the most common and extensively documented morbidity, with reported incidence rates ranging from 6% to 57%.[3-5]

Breast cancer–related lymphedema (BCRL) constitutes a frequent postoperative adverse events following operative treatment of breast cancer.[6] BCRL is known by a pathological buildup of protein-rich interstitial fluid, either generalized or localized, which leads to development of edema and persistent inflammation, potentially accompanied by fibrosis. This condition arises from impaired lymphatic drainage, resulting in a progressive elevation of intraluminal hydrostatic pressure, followed by lymphatic vessel congestion and dilation. BCRL represents a potentially serious postoperative complication that adversely impacts patients' functional capacity, aesthetic appearance, and psychological well-being, thereby significantly diminishing quality of life.[4] Therefore, the identification and preservation of these lymphatic vessels represents a compelling strategy to mitigate associated complications.[7]

Lymphedema symptoms in breast cancer patients may manifest up to 24 months following diagnosis and treatment. Consequently, vigilant monitoring for clinical signs such as swelling, pain, and tightness is imperative to facilitate timely diagnosis and intervention within this high-risk population.[8] The axillary reverse mapping (ARM) method enables the detection and maintenance of lymphatic pathways effluent the upper limb. By safeguarding these lymphatics during surgery, disruption of arm lymphatic drainage can be minimized, thus decreasing the incidince of lymphedema.This approach has the ability to decrease morbidity acompanied with ALND and enhance patients' postoperative well-being.[9]

Multiple studies have demonstrated that employing

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ARM in conjunction with selective axillary dissection markedly reduces the incidince of both lymphedema following breast surgery and patients' subjective experiences of this complication.[10-12]

Aim of work: The study sought to assess the suitability of the ARM technique, evaluate the detection rate and metastatic status of ARM nodes, and examine its effectiveness in reducing lymphedema among participants with early-stage breast cancer.

Patients and methods

This prospective, double-blind study was executed on 80 female participants diagnosed with early-stage breast cancer, who had treatment at the Surgical Oncology Unit, General Surgery Department, Tanta University Hospital, between March 2023 and August 2024.

Inclusion criteria

The study encompass participants > 18 years who were identified with early breast cancer, defined as carcinoma in situ (Tis), T1, or T2 tumors with non-palpable axillary LNs, according to the American Joint Committee on Cancer (AJCC) staging criteria.[13]

Exclusion criteria

It comprised pregnant or lactating women, patients with synchronous or metachronous malignancies, individuals with relapsing breast carcinoma, and those with prior surgical interventions involving the upper limb, axilla, supraclavicular, or cervical regions.

Randomization

Participants were randomly divided into two equal groups (GPs): GP (A) (n=40): ARM GP and GP (B) (n=40): Control GP, by choosing a closed envelope for either GP (A) or GP (B).

All participants underwent complete history taking, clinical examination that include local and systemic examination and investigations that included bilateral ultrasonography for patients aged < 35 years and mammography with complementary ultrasound for patients aged ≥ 35 years, the identification of breast cancer was histologically confirmed by fine-needle aspiration cytology and/or Tru-cut biopsy and metastatic Work-Up that included chest X-ray, pelvi-abdominal ultrasound, chest computed tomography, and Bone Scan.

ARM technique

Under strict aseptic conditions, 3 mL of methylene or patent blue dye was applied in four to six aliquots in a linear band pattern into the subdermal layer of the ulnar volar region of the upper arm, approximately 6 cm distal to the axilla. The site of adminstration was subsequently massaged while the arm was raised to facilitate dye passage through the axillary region **(Fig. 1).** Surgical exposure was achieved either by extending the mastectomy incision in a superolateral oblique direction or via a superiorly placed axillary counter incision. Twenty minutes following dye administration, level I and II ALND was performed with preservation of blue-stained LNs and lymphatic vessels **(Fig. 2).** Blue-stained LNs exhibiting suspicious features—such as a size exceeding 1 cm, firmness, fixation, multiplicity with amalgamation, or location outside the thoracodorsal bundle—were excised. The wound was closed in layers after placing two drains: one in the axilla and one in the breast bed. This technique was applied to GP (A), while the ordinary technique without ARM was performed in GP (B).

Fig 1: The blue dye injection and arm massage.

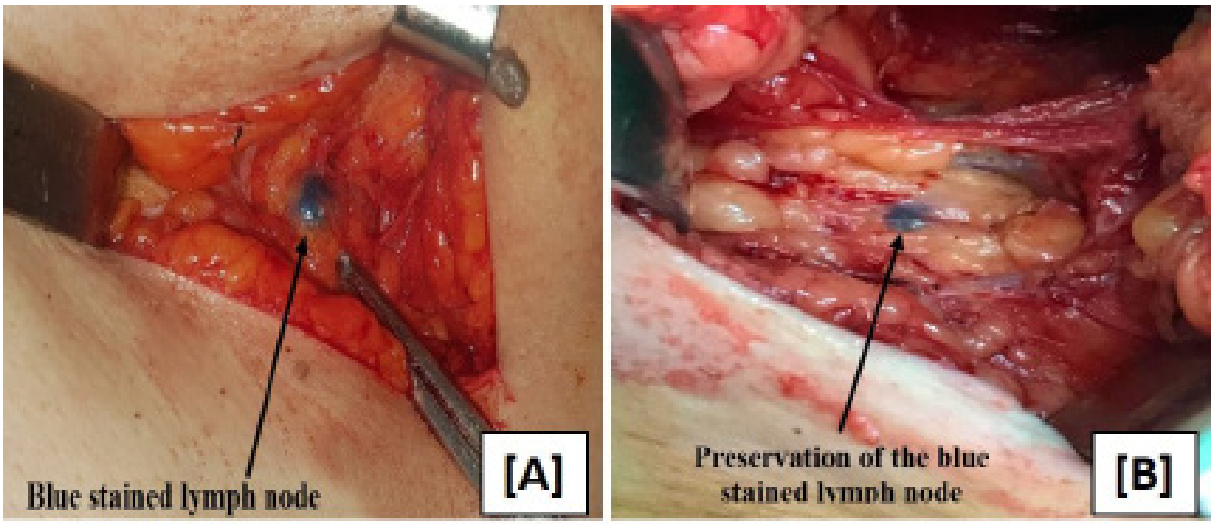

Fig 2: (A,B) Identefication of the blue stained LN (Arrows).

Postoperative follow up

The drain was removed when the volume collected per 24 h was 30 cc or less. At the first visit, a few days after surgery, patients were examined for the presence of lymphedema clinically (Mild type and usually lasts a short time). Patients were followed up at an initial visit between 4 and 6 weeks postoperatively, and subsequently every 6 months until study completion. Upper extremity lymphedema was assessed through circumferential measurements via a standardized measuring tape at specified anatomical landmarks. Measurements were obtained sequentially on both the affected and contralateral arms at four anatomical landmarks: the metacarpophalangeal joints, the wrist, 10 cm distal to the lateral epicondyle, and 15 cm proximal to the lateral epicondyle. A measurement difference of ≥2 cm at any site spanning the affected and unaffected arms was deemed indicative of clinically significant lymphedema.[14]

Patients were followed up every 6, 12, and 18 months for lymphedema, and the three stages were recorded: stage 1 was known as mild (Circumference difference ≤ 2 cm), stage 2 was moderate (Circumference difference 2.1–3 cm), and stage 3 was severe (Circumference difference > 3 cm).

The clinical variables were analyzed that included age, weight, body mass index, tumor location and size, histopathological features, postoperative complications, especially lymphedema (Time of onset, severity, and linkage with the number and positivity of dissected LNs and their management), and operative and anesthesia timing.

Statistical analysis

It were executed via SPSS v26 (IBM Inc., Armonk, NY, USA). The Shapiro-Wilk test and histograms were applied to determine the normality of the data distribution. Quantitative parametric data are shown as mean and standard deviation (SD) and were analyzed via an unpaired Student's t-test. Qualitative data were shown as frequency and percentage (%) and were analyzed via the chi-square test or Fisher's exact test when appropriate. A two tailed P value ≤ 0.05 was statistically significant.

Results

Most participants within the ARM GP were ≤ 55 years old, with a non-marked P-value of 0.174. The size of the primary tumor ranged from T1 to T2 in both study GPs, with the highest incidence being T2 (55% and 60%) in the ARM and control GPs, respectively, with a non- marked P-value of 0.675.

Blue-stained LNs were detected intraoperatively in 40 (100%) participants, 26 (65%) patients had one LN stained, 6 (15%) patients had two LNs stained, and 8 (20%) patients had 3 stained LNs. **(Table 1)**

There were non-marked difference among the two GPs regarding axillary surgery, type of breast surgery and preoperative arm circumference. Six months post-operatively, the mean of arm circumference in the ARM was 29.57 ±3.56 cm), while the average of arm circumference in control GP was 31.47± 3.74 cm, with significant P-value (p value= 0.042). Twelve months post-operatively, the mean of arm circumference in the ARM GP was 30.07± 4.06 cm. while arm circumference in control GP with mean circumference of 33.47± 5.74 cm, with significant P-value (p value= 0.035). Eighteen months post-operatively, the mean of arm circumference in the ARM GP was 30.87± 4.86 cm. while arm circumference in control GP with mean circumference of 37.57 ± 9.75 cm, with significant P-value (p value= 0.023). The occurrence of lymphedema 6-month post-operative was significantly variant among the GPs (P-value=0.042). The occurrence of lymphedema

12-month post-operative was markedly variant among the GPs (P-value= 0.035). The occurrence of lymphedema 18-month post-operative was markedly variant among the GPs (P-value= 0.023). **(Table 2, Fig. 3).**

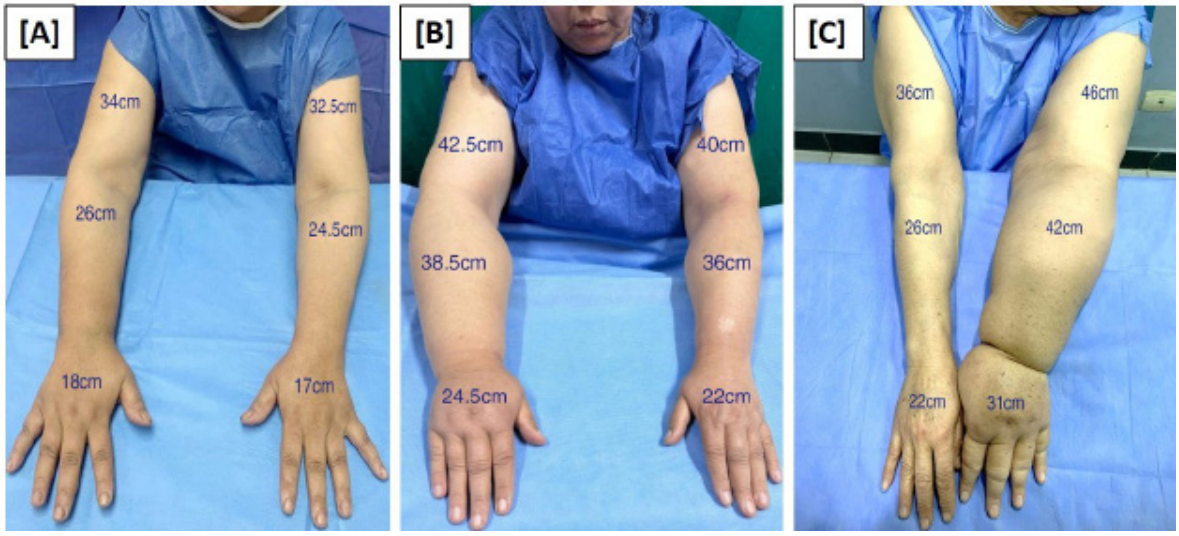

Fig 3: (A) Female patient aged 42 years in GP (A) 6 months post-operative with mild type lymphedema, (B) Female patient aged 51 years in GP (B) 12 months post-operative with moderate type lymphedema, (C) Female patient aged 59 years in GP (B) 18 months post-operative with Severe type lymphedema.

Table 1: Intraoperative detection of blue-stained nodes of the studied GPs

Intraoperative detection of blue-stained nodes	Positive	40 (100%)
	Negative	0 (0%)
Number of stained LNs	3	8 (20%)
	2	6 (15%)
	1	26 (65%)

Data are presented as frequency (%). LNs.

Table 2: Axillary surgery, type of breast surgery, pre-operative arm circumference (cm), 6, 12 and 18 months post-operative arm circumference (cm) of the studied GPs

		GP (A) (n=40)	GP (B) (n=40)	P value
Axillary surgery	ALND	40 (100%)	30 (75%)	1.000
	SLNB/ALND	0 (0%)	10 (25%)	
Type of breast surgery	MRM	24 (60%)	28 (70%)	0.507
	BCS	16 (40%)	12 (30%)	
Arm circumference	Preoperative	28.85 ± 3.45	29.8 ± 2.98	0.358
	6 months post-operative	29.57 ± 3.56	31.47 ± 3.74	0.042*
	12 months post-operative	30.07 ± 4.06	33.47 ± 5.74	0.035*
	18 months post-operative	30.87 ± 4.86	37.57 ± 9.75	0.023*
Incidence of lymphedema	6 months	0 (0%)	6 (15%)	0.042*
	12 months	2 (5%)	18 (45%)	0.035*
	18 months	4 (10%)	22 (55%)	0.023*

Data are shown as mean ± SD or frequency (%). ALND: axillary lymph node excision, SLNB: sentinel LN biopsy, MRM, BCS: breast-conserving surgery, *: statistically significant as p <0.05.

Discussion

Breast cancer represents the most commonly identifed malignancy across numerous countries globally and persists a primary cause of cancer-accompanied mortality among women. BCRL is a prevalent complication arising from surgical and/or radiation treatment, adversely impacting the comfort, functionality, and overall well-being of a substantial proportion of breast cancer survivors. The development of BCRL is primarily attributed to inadvertent disruption or removal of the lymphatic pathways draining the upper limb.[15]

In the current study, the age of patients in the ARM GP varied from 35 to 60 years, with an average age of 48.55 ± 7.1 years. In the control GP, patient ages varied from 36 to 58 years, with an average of 45.65 ± 6.11 years. The majority of patients in the ARM GP were aged 55 years or younger; however, this variation was not statistically marked (P = 0.174). These results align with those of Faisal et al. 16 who documented an average age of 52 ± 11 years in their study population. In the present study, primary tumor sizes ranged from T1 to T2 across both GPs, with T2 tumors being the most prevalent, accounting for 55% and 60% of cases in the ARM and control GPs, respectively; this variation was not statistically notable (p = 0.675). Similarly, Tummel et al.,[17] reported that from 619 participants with invasive breast cancer, 64.1% (397/619) had T1 tumors, 27% (167/619) had T2 tumors, and 8.9% (55/619) had T3 tumors.

In this study, within GP A (ARM GP), 24 patients (60%) underwent MRM, while 16 patients (40%) received BCS. In GP B (Control GP), 28 patients (70%) underwent MRM, and 12 patients (30%) underwent BCS; this difference was not statistically notable (P = 0.507). These results align with those of Faisal et al., 16 who reported that 27.1% of their cohort had a conservative breast surgery (Wide local excision), whereas 72.9% had MRM, with a non-marked p-value(0.330).

In our work, it was found that in GP (A) (ARM GP), the blue-stained LNs could be identified intraoperatively in 40 (100%) patients, 26 (65%) patients had one LN stained, 6 (15%) patients had two LNs stained, and 8 (20%) patients had three stained LNs.

These results are in line with those documented by Beek et al.,[18] who identified ARM lymphatics and corresponding nodes in 35 paticipants (76.1%) within the standard-ALND GP and in 38 paticipants (79.2%) in the ARM-ALND GP. Retention of ARM lymphatics and respective LNs was achieved in 36 of 38 paticipants (94.7%) in the ARM-ALND cohort. Notably, in deviation from the methodology, one paticipants in the standard-ALND GP did not have the ARM lymphatics and LNs resected. There was no significant difference in axillary LN metastasis between the GPs, with 23 of 46 paticipants (50%) affected in the standard-ALND GP versus 23 of 48 paticipants (47.9%) in the ARM-ALND GP. Kumar et al.,[19] reported no evidence of metastatic involvement in stained arm nodes situated lateral to the thoracodorsal nerve and vessels. Similarly,Padma and Shanmuga Sundaram,[20] demonstrated successful identification of ARM nodes and sentinel lymph nodes (SLNs) in all 45 patients during surgery (100%). Of 99 SLNs harvested, only 2% harbored metastatic cells among patients undergoing ALND.

In the current study, circumferential bilateral arm measurements were obtained sequentially at four anatomical landmarks the metacarpophalangeal joints, wrist, 10 cm distal to the lateral epicondyle, and 15 cm proximal to the lateral epicondyle at 6, 12, and 18 months following surgery.

In the ARM GP, it was found that the Pre and 6 months post-operative arm circumference was insignificantly different, while in the control GP, 6 patients developed mild lymphedema with a circumference difference ≤ 2 cm between the arms in the studied GPs. Also, it was found that in the ARM GP Pre and 12 months post-operative 2 patient developed mild type of lymphedema with circumference difference ≤ 2 cm between arms while in the control GP 10 patients developed mild type of lymphedema with circumference difference ≤ 2 cm between arms and 8 patients developed moderate type of lymphedema with circumference difference 2.1–3 cm between arms. In the ARM GP pre-and 18 months post-operative, 4 patients developed mild lymphedema with a circumference difference ≤ 2 cm between the arms, while in the control GP, 6 patients developed mild lymphedema with a circumference difference ≤ 2 cm between the arms, 12 patients developed moderate lymphedema with a circumference difference of 2.1–3 cm between the arms, and 4 patients developed severe lymphedema with a circumference difference of > 3 cm.

These results align with those documented by Yue et al.,[10] who demonstrated the efficacy and oncological safety of the ARM technique. With a median follow-up duration of 20 months, their study observed arm lymphedema—assessed via circumferential measurements—in 42 participants (33.07%) within the control GP compared to 7 patients (5.93%) in the studed GP, representing a statistically marked variation (p < 0.001).

While, Padma and Shanmuga Sundaram,[20] revealed that there was no marked variation in arm circumference in 89% of participants–24-30 months post-treatment.

In the current study, the incidence of lymphedema at 6 months postoperatively differed significantly

between the study GPs. There was no lymphedema 6 months post-operative in all patients in the ARM GP, while 6 patients with mild lymphedema were recorded in the control GP, with a marked P-value of 0.042. The incidence of lymphedema 12-month post-operative was also markedly different among the GPs.

In ARM GP there are 2 patients with mild type lymphedema, while 10 patients with mild type lymphedema and 8 patients with moderate type lymphedema were recorded in the control GP, with significant P-value= 0.035. The incidence of lymphedema 18-month post-operative was also significantly different between the GPs. In ARM GP there are 4 patients with mild type lymphedema, while 6 patients with mild type lymphedema, 12 patients with moderate type lymphedema and 4 patients with severe type lymphedema were recorded in the control GP, with significant P-value= 0.023. Variations of 2 cm or more at any point relative to the oppisite arm were considered clinically marked.

These data are in line with Yuan et al.,[21] who documented that among patients undergoing ALND, objective lymphedema measured volumetrically occurred in 3.3% (18/543) of those receiving ALND combined with delayed arm preservation and resection technique (DEPART), compared to 15.3% (99/648) in the ALND-only GP. Subjective reports of arm lymphedema were noted in 6.1% (33/543) of participants in the ALND plus DEPART GP versus 16.0% (104/648) in the ALND GP. Conversely,Padma and Shanmuga Sundaram, 20 demonstrated that at 24 to 30 months post-treatment, only 4% (2 participants) developed lymphedema, defined as a circumference difference exceeding 2 cm from the contralateral arm. Furthermore, the incidence of lymphedema did not significantly differ between patients undergoing mastectomy with ALND and those undergoing mastectomy alone (P = 0.003). Additionally, Tausch et al.,[22] reported a lymphedema incidence of 43% in patients without lymphatic preservation compared to 23% in those who underwent ARM.

Limitations

The limitations of the present study include a dimesioned sample size, its single-center design, and a fairly short duration of follow-up.

Conclusion

ARM reliably facilitates the intraoperative identification of blue-stained LNs in a substantial proportion of participants with early-stage breast cancer. This technique ought to be regarded as a valuable adjunct for preserving lymphatic drainage pathways and mitigating the probability of lymphedema in patients with clinically nonpalpable axillary LNs undergoing axillary surgery.

List of abbreviations

ARM: Axillary Reverse Mapping.
BCRL: Breast Cancer–Related Lymphedema.
ALND: Axillary Lymph Node Dissection.
LN: Lymph Node.
MRM: Modified Radical Mastectomy.
BCS: Breast-Conserving Surgery.
SLNB: Sentinel Lymph Node Biopsy.
AJCC: American Joint Committee on Cancer.
SD: Standard Deviation.
SPSS: Statistical Package for the Social Sciences.

Statements & declarations

Generative artificial intelligence statement

Generative AI and AI-assisted technologies were not used in the preparation of this work.

Ethical consideration

Documented written consent was gathered from all participants before enrollment. The study procedures was authorized by the Ethics Committee of the Faculty of Medicine, Tanta University Hospital (approval number: 36264MS103/3/23).

Conflict of interest statement

The authors have no conflicts of interest or financial disclosures that could bias or are relevant to the research or information in this paper. The authors have no conflicts of interest to declare.

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Data availability statement

The data supporting this study's findings are not publicly available due to information that could compromise the privacy of research participants, but they are available from K.F. upon reasonable request.

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