Original Article

Prophylactic lymphatic surgery: the T-LAR approach

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Abstract

Aim: Breast cancer-related lymphedema (BCRL) is the most significant lasting morbidity among breast cancer survivors. Targeted-lymphatic axillary repair (T-LAR) is a novel surgical approach we proposed to reduce the risk of BCRL in patients undergoing an axillary lymph node dissection (ALND) or sentinel lymph node biopsy (SLNB). This study evaluated the effectiveness of T-LAR approach as a lymphedema preventive Surgery.

Methods: A retrospective analysis of a prospective maintained database was performed to evaluate patients with breast cancer who underwent ALND or SLNB with T-LAR approach

between January 2017 and December 2018. Patient and tumor characteristics, oncologic and reconstructive operative details, complications and lymphedema development were analyzed.

Results: T-LAR approach was performed in 55 patients with a mean age of 51.05 ± 9.42, mean body mass index (BMI) was 25.1 ± 3.63 and median of lymph nodes removed were 13 (10-17.50) during ALND. The identification rate of arm lymphatics was 100%. The number of lymphovenous anastomosis (LVA) for each patient ranged from 0-3, 15 patients (27.3%) had 1 LVA and 26 patients (48.1%) had more than 1 LVA while in 14 patients (25.5%) no need for immediate lymphatic repair. Two patients developed lymphedema (3.6%) with median follow-up was 2.3 years.

Conclusion: The T-LAR approach is a novel, safe and reliable prophylactic intervention that significantly can decrease the incidence of BCRL as it provides maximal preservation of lymphatic continuity, identification of transected lymphatics, and reestablishment of upper extremity lymphatic drainage pathways.

Keywords: Axillary lymph node dissection, axillary reverse mapping, breast cancer, lymphedema prevention

INTRODUCTION

Approximately 200 million worldwide and 3 to 5 million people in the United States suffer from extremity lymphedema; the incidence is particularly high in cancer survivors[1-3].

Breast cancer-related lymphedema (BCRL) affects approximately 20-45 % of breast cancer survivors after surgical intervention[4,5]. Axillary lymph node dissection (ALND) and radiotherapy are considered the main factors that increase the risk of lymphedema development[6-8].

In recent decades, techniques for the treatment of peripheral lymphedema, including lymphovenous anastomosis (LVA) and vascularized lymph node transfer (VLNT), were associated with improved quality of life, discontinued use or decreased need for compression

therapy and significant limb volume reduction[9,10]. Nevertheless, none of these treatments were proven to be curative for lymphedema, and preventive measures have to be considered[11,12].

The approach of axillary surgery had modified over time to lower the risk of lymphedema. Sentinel lymph node biopsy (SLNB) had significantly decreased the risk of lymphedema, however, still many patients with breast cancer are indicated for ALND[13,14]. Axillary reverse mapping (ARM) represents an important modification in the approach of axillary surgery aiming at identification and preservation of arm lymphatics to minimize unnecessary arm morbidity from lymphadenectomy without compromising the oncologic safety. Klimberg group was first to provide detailed description of ARM using blue dye and isotope contrast in ALND and SLNB[15,16]. The continuous evolution and modification in the ARM resulted in three kinds of tracers, blue dye, radionuclide and fluorescent dyes currently used in the identification of ARM with variable identification rate[17,18]. An innovative approach to surgically prevent lymphedema was first reported in patients undergoing ALND by Boccardo *et al.*[20], the Lymphatic Microsurgical preventative healing approach (LYMPHA) where the divided arm lymphatics were identified at the time of ALND, then lymphovenous implantation was performed immediately[19]. The follow-up studies reported a lymphedema rate of 4.34% after ALND combined with LYMPHA[20]. Similar study was reported by Feldman *et al*.[21] with a significant reduction in lymphedema rates after ALND combined with LYMPHA to 12.5%. However, the LYMPHA technique is not real LVA, it is performed through implantation of isolated blue lymphatics to a nearby vein and this technique was reported to be associated with a higher rate of thrombosis compared with true end to end LVA[22].

Targeted-lymphatic axillary repair (T-LAR) is a novel approach based on ARM using combined indocyanine green(ICG) lymphography and blue dye to enhance lymphatic visualization following axillary surgical intervention. Surgical decision was guided according to the intraoperative axillary ICG lymphography, if there was preserved continuous fluorescent lymphatic flow through axilla, no lymphatic repair was performed. However, if there was axillary fluorescence interruption, immediate true lymphatico-venous anastomosis (LVA) of transected arm lymphatics was performed to preserve lymphatic continuity and reestablish physiologic upper extremity lymphatic drainage pathways.

This study aims to investigate the effectiveness of the T-LAR approach as an immediate lymphatic reconstruction technique in the prevention of Lymphedema development in a cohort of newly diagnosed breast cancer patients.

MATERIALS AND METHODS

After institutional review board approval, a retrospective review of prospectively maintained data base of all patients newly diagnosed with unilateral breast cancer who underwent T-LAR approach during axillary surgery at our institution between January 2017 and December 2018. Patients with lost long-term follow-up or not compliant to the standard postoperative protocol were excluded from our study. The same breast plastic surgery team in our institution performed oncological breast surgery and immediate reconstruction.

Surgical technique

ALND was performed in all patients in the standard fashion including level I and II lymph nodes using the anatomic landmark technique previously described. ALND was performed under loupe magnification using Plasmablade ^{R} (Medtronic, Fridley, Minnesota) to minimize thermal injury.

Axillary Reverse Mapping (III-ARM)

III-ARM was performed using combined Intraoperative Isosulfan blue and Indocyanine Green(ICG) lymphography. Starting with intradermal injection of 0.2 mL of Isosulfan blue dye 2.5% (Blue Patent V Sodique, Guerbet. Le Raincy, France) along medial aspect of proximal ipsilateral arm to facilitate intraoperative identification and dissection of afferent arm lymphatics [**Figure 1**]. Level I and II ALND was approached through upper axillary incision then meticulous dissection was performed to visualize blue stained afferent lymphatics coming from the arm. Once identified, those blue stained arm lymphatics that connected with lymph nodes were dissected as long as possible distally and transected after placing vascular clips. In contrast, those blue lymphatic channels that crossed the axilla, normally located at the upper axillary area, mostly around the axillary vein, without connection with axillary lymph nodes, were carefully preserved.

After ALND completion, Intradermal injection of 0.2-0.4 mL of ICG (5 mg/mL) (PULSION Medical Systems, Feldkirchen, Germany) in the interdigital web spaces of the ipsilateral hand. Few minutes after injection, ICG lymphography (Fluoptics, Grenoble, France) was performed. If arm lymphatic drainage was maintained adequately by the preserved lymphatics with no connection to resected lymph nodes, then no need for LVA. The immediate axillary LVA was indicated when isolated main arm lymphatics were transected during the ALND, with significant interruption of the arm lymphatic drainage that confirmed by post-dissection ICG lymphography. If so, 2-3 competent LVA were performed to neighboring small veins, usually tributaries of lateral thoracic or thoraco-dorsal veins. LVA technique was based on supermicrosurgery technique using non-absorbable 10-0 or 11-0 sutures. After LVA procedure, ICG lymphography by the microscope (Pentero 800, Zeiss, Germany) is done to confirm adequate arm lymphatic flow with no fluorescent leak at the axilla [**Figure 2**].

For SLNB, we used ICG and Isosulfan Blue dye in the same way described for ALND.
If the fluorescent lymphatics coming from the arm were communicated with the SLN, so arm lymphatic drainage could be affected after SLNB, then isolation and microscopic dissection of this afferent lymphatic and anastomosis to a nearby vein with matching caliber (LVA) was performed after excision of the SLN.
Operative details of the T-LAR approach were documented including the number of III-ARM performed either with or without LVA, number of LVA, and the operative time for each procedure.

Follow up

Immediately postoperatively the upper limb was wrapped in a lightly compressive dressing for 10 days to limit postoperative swelling. Gradual postoperative limb exercises were initiated especially the abduction of the arm to avoid any tension at the site of anastomosis.

Patients were evaluated during the follow-up by a blinded specialized lymphedema therapist at 3, 6, 12 months after surgery then once every 6 months. Patients with less than a 12-month follow-up were excluded. BCRL diagnosis was based on the following subjective and objective elements: (1) When the signs and symptoms of (i.e., tightness, heaviness, swelling) consistent

with lymphedema as determined by a certified lymphedema therapist continued more than 6 months after completion of cancer management, (2) More than 2cm persistent increase in limb circumference using tape-measuring at predetermined sites on the ipsilateral limb (3) ICG lymphography for checking the interruption of lymphatic flow through the axilla or any signs of dermal backflow at 1-year follow-up. A diagnosis of lymphedema was given if the patient met the above-specified criteria 6 months after their last oncologic treatment (surgery, radiation therapy, or chemotherapy).

RESULTS

A total of 55 patients (55 upper limbs) with Breast cancer were included in this study. The mean patient age was 51.05 ± 9.42 and mean BMI was 25.1 ± 3.63. The patient's demographics, tumor characteristics, and operative details of our study population were detailed in **Table 1**.

The ARM identification rate of arm lymphatics was 100%, the number LVA performed for each patient ranged from 0-3, 15 patients (27.3%) had 1 LVA and 26 patients (48.1%) had more than 1 LVA while in 14 patients (25.5%) intraoperative ICG lymphography after axillary surgery (20% had SLNB while 80% had ALND) showed intraoperative adequate collateral arm lymphatic drainage through axilla and no LVA was needed [**Figure 3**]. The overall median follow-up was 2.3 years (2.5-5.7), during which the BCRL developed in 2 patients (3.6%). In the two cases that developed lymphedema within the T-LAR group, we were able to do only 1 LVA in the axilla. Nevertheless, the lymphatic vessels had poor quality in these two cases, and we were not satisfied with the LVA performed.

DISCUSSION

Although recent trends recommend reduction in axillary intervention, many patients still benefit from axillary lymph node clearance[23]. Patients who underwent ALND and radiation therapy are particularly at increased risk for lymphedema development and its and psychological and medical implications. Other risk factors associated with the development of lymphedema include the number of nodes removed, number of positive metastatic lymph nodes, taxane-related chemotherapy, postoperative seroma, axillary wound infection and increased BMI[24]. Despite 75% of lymphedema patients develop it within first 3 years, lymphedema can manifest up to 30

years later after cancer treatment[25]. The incidence of BCRL is highly variable ranging from 7%-77% [24,25], variation is likely because of the ALND technical approach, different study designs, lack of standard methods for measurement and the timing of measurement.

Our study found that the T-LAR approach was effective in a high-risk patient cohort with an overall permanent lymphedema rate of 3.6 percent. The rate of transient lymphedema observed in this cohort was 5.4 percent. This rate was relatively lower than that reported by Boccardo *et al*.[20], who found a 10.8 percent rate of transient lymphedema. Among the three cases that were diagnosed with postoperative transient lymphedema, one case resolved completely within 3 months of onset.

The success of T-LAR approach during axillary intervention in minimizing lymphedema development in high-risk population is promising and points to the need to determine appropriate patient selection criteria to broaden its application.

ARM was early described by Klimberg and colleagues in 2007[16], followed by several modifications with different tracers including blue dye, isotopes and ICG fluorescence. However, identification rates of ARM nodes using blue dye alone were variant and relatively insufficient, ranging from 33.7 to 94.7% [17].

Our current approach for ARM using the combined tracers (real-time ICG lymphography and Patent Bleu V) is a reliable combination, 100% identification rate, cost-effective, reproducible, and only a few minutes were required to identify the arm and axillary lymphatic pathways.

Lymphaticovenous implantation between the transected arm lymphatics and collateral branches of the axillary vein is a technique that has been introduced first by Boccardo *et al.*[20], the LYMPHA approach, and achieved a reduction in lymphedema incidence down to 4.34%[21]. However, the LYMPHA technique is not real LVA, it is performed through implantation of isolated blue lymphatics to a nearby vein and this technique was reported to be associated with a higher rate of thrombosis compared with true end to end LVA[22].

Combining ARM using Blue dye with Lympha technique or its modifications has been reported in different studies with different techniques. Variations of these techniques have been reported, most with promising early results[26-28]. However, studies thus far have been heterogeneous. Limitations included the inability to identify transected lymphatic afferents and low-resolution confirmation of intraoperative Lympha patency.

An interesting recent publication reported by Schwarz *et al.*[29], they performed end to end anastomosis in 37 patients and a multiple lymphatic intussusception technique in 21 patients. Patency was confirmed 96.5% of patients, two patients developed LE (4.6%) with overall median postoperative follow-up was 11.8 months.

The T-LAR is not just a technique of immediate lymphatic repair, it is an algorithmic approach [**Figure 4**] through which the decision making following axillary surgery was guided by a reliable ARM combining intraoperative ICG lymphography and patent blue V dye allowing high identification rate of afferent arm lymphatics up to 100%. In a significant number of patients (14 in our study, 25.5%) we can find adequate collateral arm lymphatic drainage that most closely related to the axillary vein after the axillary clearance, using ICG lymphography, in such condition no need for LVA but, in most patients (74.5%), the arm lymphatics were transected following ALND and 1-3 real LVA was indicated using supermicrosurgical technique. Performing Immediate LVA takes the advantage that the arm lymphatics are healthy with a relatively large caliber compared with that performed in LVA for lymphedema cases in which they usually affected to some degree with the pathology and have less diameter at the wrist or forearm. One limitation of our study is that we did not include control group, however, Comparative studies are ongoing to get the evidence and conclude that the procedure has preventive efficacy also, to identify the risk factors for the development of lymphedema even following the T-LAR approach.

In conclusion, the T-LAR approach is a safe and reliable technique for the prevention of BCRL. This technique could improve current health practices, improving patients' quality of life, and decreasing health care expenses. However, further research with multicentric randomized control studies is mandatory to confirm the efficacy and reproducibility of the approach, that necessitates

a learning curve and experience in lymphatic surgery, to develop the evidence and extend the application of the T-LAR concept.

DECLARATIONS

Authors' contributions

Manuscript writing and data collection: Abdelfattah U

Reviewing the manuscript and data analysis: Pons G

Reviewing and editing the manuscript: Masia J

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Figure 1: Clinical demonstration of ARM using ICG lymphography (Marked green color of arm lymphatics) and Isosulfan blue dye injected subdermally at the inner side of the ipsilateral arm. ARM: axillary reverse mapping; ICG: indocyanine green.

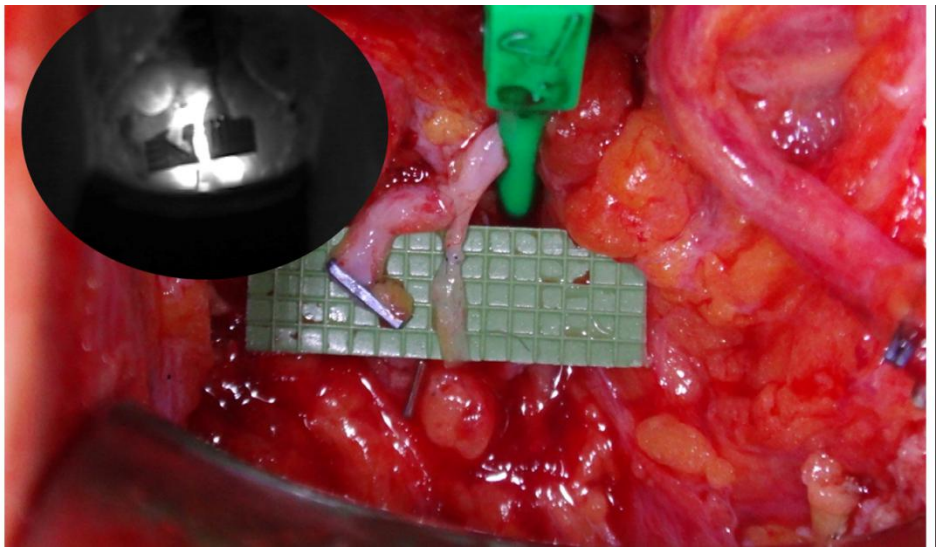

Figure 2: LVA performed immediately after ALND and tested using ICG lymphography to confirm absence of fluorescent leak. ALND: axillary lymph node dissection; ICG: indocyanine green; LVA: Lymphovenous anastomosis.

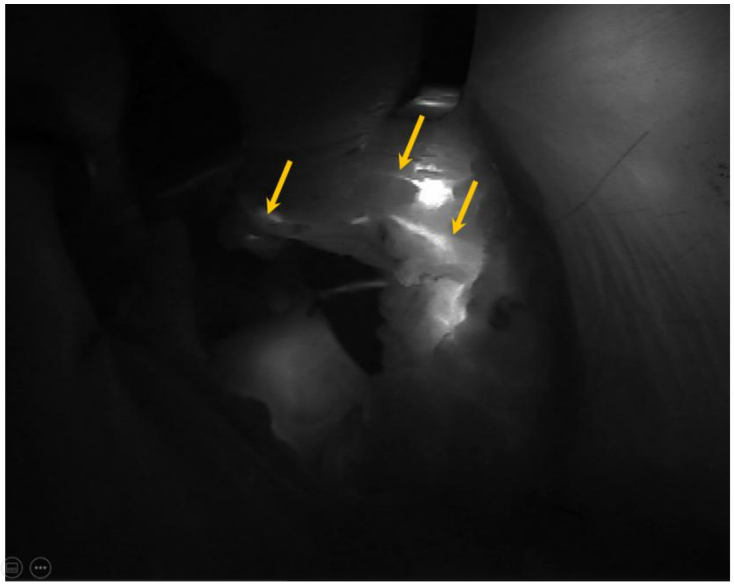

Figure 3: Intraoperative arm ICG lymphography following axillary clearance showing adequate collateral arm lymphatic drainage, in such case, no need for immediate lymphatic reconstruction. ICG: indocyanine green.

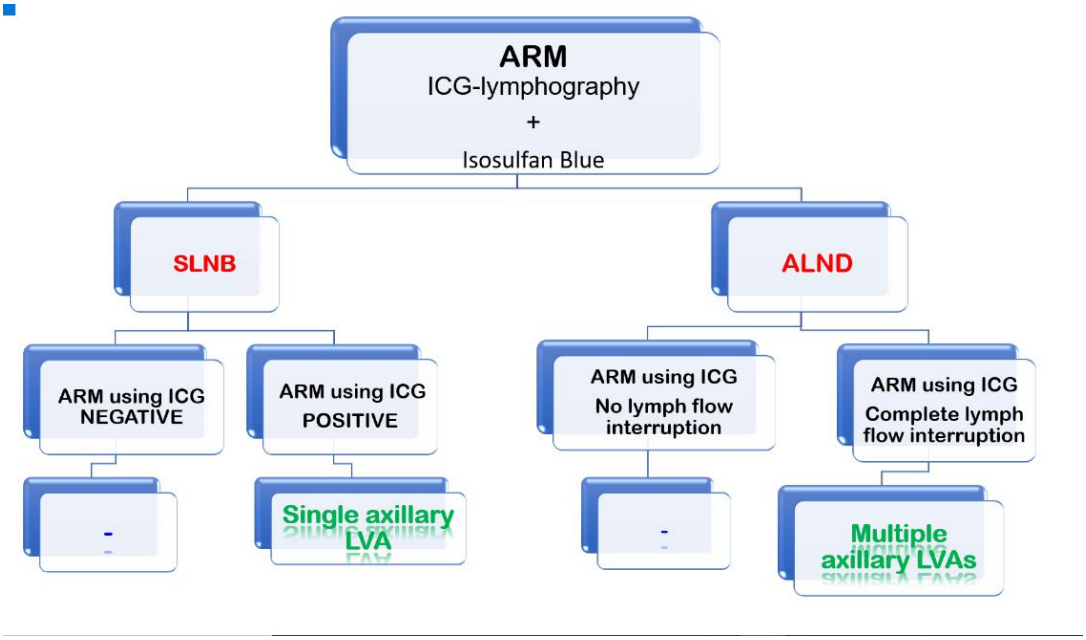

Figure 4: Diagram demonstrating the algorithmic T-LAR approach. ARM： axillary reverse mapping; ICG: indocyanine green; SLNB: sentinel lymph node biops; ALND: axillary lymph node dissection; T-LAR：Targeted-lymphatic axillary repair.

Table 1: Distribution of Patients According to Different Variables, Oncologic and operative details

Variable	**T-LAR group (55 subjects)**
Age mean ± SD	51.05 ± 9.42
< 65 years old	42 (76.4)
> 65 years old	13 (23.6)
BMI mean± SD	25.1±3.63
Side excision- Right	31 (55.5)

Side excision- Left	24 (44.5)
Type of excision- Tumorectomy	12 (21.8)
Mastectomy	43 (78.2)
Adjuvant Radiotherapy	35 (63.6)
Chemotherapy Adjuvant chemotherapy	18 (32.7)
Neoadjuvant chemotherapy	33 (60)
Combined adjuvant and Neoadjuvant	4 (7.3)
N of LN excised median (25-75% percentile)	13 (10-17.50)
N of + LN median (25-75% percentile)	1 (0-2.50)
Axillary intervention-SLNB	11 (20)
Axillary intervention-ALND	44 (80)
Type of reconstruction	
Implant	27 (60)
Autologous	12 (26.7)
Oncoplastic	6 (13.3)
N of LVA performed Median (25-75% percentile)	2 (1-3)
N of LVA (≤ 1)	29 (52.7)
N of LVA (>1)	26 (48.1%)

Visualized lymphatic flow in axilla on follow-up	54 (98.1)
No. of patients diagnosed with transient lymphedema	3 (5.4)
No. of patients diagnosed with ongiong lymphedema	2 (3.6)

T-LAR：targeted-lymphatic axillary repair; LN: lymph nodes; LVA: lymphovenous anastomosis; BMI: body mass index