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ORIGINAL ARTICLE – BREAST ONCOLOGY

Surgical Prevention of Arm Lymphedema After Breast Cancer Treatment

Francesco M. Boccardo, MD[1], Federico Casabona, MD[2], Daniele Friedman, MD[3], Maria Puglisi, MD[3], Franco De Cian, MD[4], Filippo Ansaldi, MD[5], and Corradino Campisi, MD[1]

[1]Department of Surgery, Unit of Lymphatic Surgery, S. Martino Hospital, University of Genoa, Genoa, Italy; [2]Department of Obstetrics and Gynecology, S. Martino Hospital, University of Genoa, Genoa, Italy; [3]Department of Surgery, Breast Unit, S. Martino Hospital, University of Genoa, Genoa, Italy; [4]Department of Surgery, Unit of Oncologic Surgery, S. Martino Hospital, University of Genoa, Genoa, Italy; [5]Department of Health Science and Statistics, S. Martino Hospital, University of Genoa, Genoa, Italy

ABSTRACT

Purpose. To prospectively assess the efficacy of the lymphatic microsurgical preventive healing approach (LYMPHA) to prevent lymphedema after axillary dissection (AD) for breast cancer treatment.

Methods. Among 49 consecutive women referred from March 2008 to September 2009 to undergo complete AD, 46 were randomly divided in 2 groups. Twenty-three underwent the LYMPHA technique for the prevention of arm lymphedema. The other 23 patients had no preventive surgical approach (control group). The LYMPHA procedure consisted of performing lymphatic-venous anastomoses (LVA) at the time of AD. All patients underwent preoperative lymphoscintigraphy (LS). Patients were followed up clinically at 1, 3, 6, 12, and 18 months by volumetry. Postoperatively, LS was performed after 18 months in 41 patients (21 treatment group and 20 control group). Arm volume and LS alterations were assessed.

Results. Lymphedema appeared in 1 patient in the treatment group 6 months after surgery (4.34%). In the control group, lymphedema occurred in 7 patients (30.43%). No statistically significant differences in the arm volume were observed in the treatment group during follow-up, while the arm volume in the control group showed a significant increase after 1, 3, and 6 months from operation. There was significant difference between the 2 groups in the volume changes with respect to baseline after 1, 3, 6, 12, and 18 months after surgery (every timing P value < 0.01).

Conclusions. LYMPHA represents a valid technique for primary prevention of secondary arm lymphedema with no risk of leaving undetected malignant disease in the axilla.

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F. M. Boccardo, MD
e-mail: francesco.boccardo@unige.it

The incidence of arm lymphedema after sentinel lymph node (SLN) biopsy varies from 0% to 13%, but lymphedema after axillary lymph node dissection varies from 7 to 77%.[1] This wide variability in lymphedema prevalence is due to the definition and method to determine lymphedema, the different length of follow-up, the different number of positive lymph nodes, postoperative irradiation, and body habitus.[2–4]

There exist so-called arm derivative lymphatic pathways, among which the main ones are represented by the cephalic bundle running to the supraclavicular nodes through the deltopectoralis way (the Mascagni pathway) and the posterior bundles that run to the posterior scapular nodes through the tricipital way (the Caplan pathway).These derivative paths are one of the possible explanations of why lymphedema does not always develop after axillary resection and radiotherapy for breast cancer treatment.

It is possible to identify afferent lymphatics and nodes coming from the lymphatic pathway draining the arm. In the blue node draining the arm, the absence of cancer cells was confirmed both by frozen sections and definitive histological findings. Nevertheless, the identification of the efferent lymphatics, which is mandatory to truly preserve the lymphatic flow of the arm, is almost impossible because the lymphatics departing the blue nodes join the common lymphatic pathway draining the breast.

Elsewhere, we have reported some cases of use of the lymphatic microsurgical preventive healing approach (LYMPHA) technique and demonstrated the feasibility of the technique in patients referred to undergo complete AD.[5] The aim of this study was to evaluate the effectiveness of this technique in a prospective study using objective clinical and lymphoscintigraphic (LS) assessment.

PATIENTS AND METHODS

Study Design

Among 49 consecutive women from March 2008 to September 2009 referred to undergo complete AD, performed by surgeons of the same breast unit who used the same technique, 46 were randomly divided in 2 groups; the other 3 patients were not analyzed because they refused to consent to LS before surgery. Twenty-three underwent the LYMPHA technique, performed by a surgeon skilled in lymphatic microsurgery, for the prevention of arm lymphedema. The other 23 patients had no preventive surgical approach (control group). No wrapping or compression therapy was used in any of the patients of both groups.

The average age was 57 years (range 39–80 years). To be included in this prospective study, patients with unilateral breast cancer had to be referred to undergo complete AD as a result of clinically or ultrasonographic positive axillary lymph nodes or positive SLN. Exclusion criteria were cases in whom only SLN biopsy technique was performed and SLNs were negative.

In the treatment group, 16 patients had lymph node metastasis, and therefore lymphatic-venous anastomosis (LVA) was performed during the primary surgery, together with breast cancer treatment, SLN biopsy, intraoperative frozen sections (showing the metastasis), and axillary dissection (AD). In the other 7 patients, there was no lymph node metastasis demonstrated by intraoperative frozen sections, and therefore the LYMPHA technique was planned after finding micrometastasis after immunohistochemical investigations. Thus, in this last group of patients, we could perform LYMPHA during the complete lymph node dissection at second-time surgery (Table 1).

Operative Technique

Patients signed a specific consent form indicating the kind of operation, possible risks, and complications of participating in the LYMPHA procedure. Blue dye (Lymphazurin) was injected in the volar surface of the upper third of the arm in a quantity of about 1–2 ml intradermally, subcutaneously, and under muscular fascia. Usually after 5–10 min it is possible to visualize arm lymphatics. Axillary nodal dissection was performed, usually starting far from the upper lateral part of the axilla, which was removed nearly at the end of the dissection so as not to damage the lymphatic pathways coming from the arm. These lymphatics were temporally clipped near their afference to the nodal capsule and thus prepared for anastomosis.

During lymph node dissection, one or two collateral branches of the axillary vein were prepared with a length suitable for reaching the lymphatic vessels. Axillary lymph node dissections were performed by surgeons (not residents) of the same breast unit, and there was no difference in the way the AD was done in the 2 groups. The microsurgical technique of LVA has already been described.[5,6] Lymphatic bypass procedures were performed by the same surgeon, skilled in lymphatic microsurgery, who was different from the surgeons who performed lymph node dissection. The vein was an average of 2 mm in diameter, and lymphatics about 0.5 mm in diameter. The number of lymphatics anastomosed ranged from 2 to 4. The “sleeve” technique was used, with lymphatics being put into the vein’s cut end. A collateral of the axillary vein is used for anastomoses. In some cases, a large gap in between the vein and the lymphatics can be found, but in these cases, it is usually enough to dissect the vein and above all the

TABLE 1 Patient baseline characteristics

Variable	Control group	Treatment group	*P* value
Age, median (25th–75th percentile)	67 (53–73)	68 (52–74)	NS
Body mass index, median (25th–75th percentile)	26 (23–32)	29 (24–32)	NS
Preoperative LS, median (25th–75th percentile)	8 (6–13)	9 (5–12)	NS
Lymph nodes retrieved, median (25th–75th percentile)	18 (12–22)	17 (14–24)	NS
Metastatic lymph nodes, median (25th–75th percentile)	2 (0–4)	2 (0–4)	NS
Volume, median (25th–75th percentile)	2299 (1900–3308)	2896 (1979–3309)	NS
Type of surgery (mastectomy/tumorectomy)	11/12	12/11	NS
Radiotherapy (yes/no)	12/11	11/12	NS
Cellulitis (yes/no)	5/18	4/19	NS

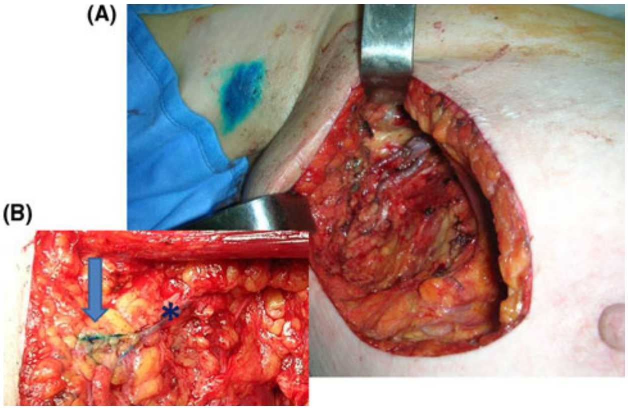

FIG. 1 LYMPHA operative technique at a lower (**a**) and higher (**b**) magnification, showing the LVA between arm lymphatics (*arrow*) and a collateral branch of axillary vein (*)

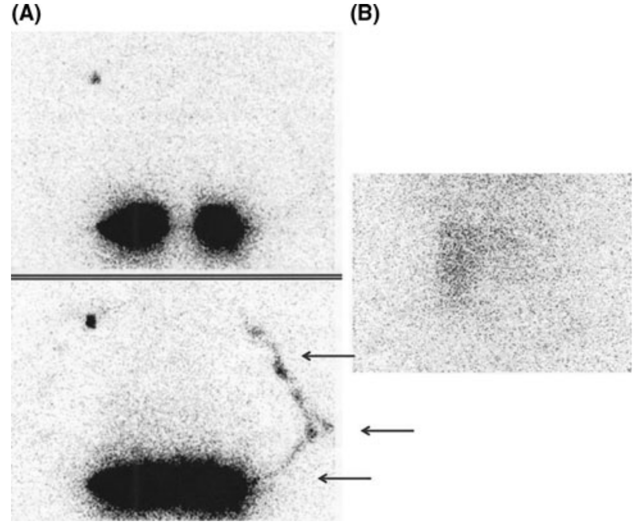

FIG. 2 LS postoperative control after LYMPHA technique, showing a good arm lymphatic draining pathway (*arrow,* **a**), and the early liver uptake (**b**)

lymphatics from the surrounding tissues. If necessary, one of the subscapular or thoracodorsal veins, which are usually long enough, can also be used. Particular attention must be paid in placing the drain tube so as not to damage the anastomosis (Fig. 1). LVA takes only 15–20 min to perform, and in our study, the procedures were performed by a surgeon skilled in lymphatic microsurgery. There is no increased rate of blood loss, wound infection, or seromas compared to standard axillary lymph node dissection.

Clinical and LS Assessment

All patients in the 2 groups were studied clinically before surgery by volume measurements (using the formula of a truncated cone according to Kuhnke method) and by LS.[7,8] Lymphedema was defined as a difference in excess volume of at least 100 ml compared to preoperative volume measurements. Patients usually realize the amount of increased volume, mostly describing an increased hardness of tissues in a specific area, either the wrist or the forearm. The follow-up included volumetry at 1, 3, 6, 12, and 18 months after surgery in both groups.

LS was carried out in 21 cases in the treatment group and in 20 cases of the control group by 18 months after surgery (Fig. 2).

Statistical Analysis

Nonparametric tests were used to explore the variable relationships between groups and between timing. The comparison between groups of quantitative variables age, body mass index, preoperative LS, lymph nodes retrieved, metastatic lymph nodes, and volume at baseline was performed by the Wilcoxon test. Nominal baseline variables surgical procedure, radiotherapy, and presence of cellulitis were compared by Chi-square or Fisher's exact tests.

The comparison of difference between baseline and volume at 1, 3, 6, 12, and 18 months after surgery in the treatment and control groups was performed by the Wilcoxon test (between groups) and matched pair test (between timing). The volume difference between baseline and different timing in treatment and control groups was represented by box plots showing 10th, 25th, 75th, and 90th percentiles. The number of patients with lymphedema, defined as a difference in excess volume of at least 100 ml, at 18 months in the treatment and control groups were compared by 2-sided Fisher's exact test.

RESULTS

Lymphedema appeared in 1 patient in the treatment group after 6 months from the operation (4.34%) and persisted until 18 months later. It occurred in a patient who underwent radiotherapy and who became stable with time without any inflammatory complications. In the control group, lymphedema occurred in 7 patients (30.43%) and appeared mostly after 3 months from operation. Beginning from month 3, the proportion of patients with lymphedema was statistically higher in the control group ($P = 0.047$). Table 1 summarizes baseline characteristics of all participants according to treatment group. There were no statistically significant differences between the 2 groups in the baseline values of measures of demographic and anthropometric data, in disease characteristics and in type of surgery, and in the proportion of women who undertook to radiotherapy and had cellulitis.

When compared with previous volume measure, no significant differences in arm volume were observed in the

TABLE 2 Postoperative lymphedema rate in the 2 groups

Follow-up	Control group ($n = 23$)	Treatment group ($n = 23$)
1 month	1 (4.34%)	0
3 month	1 (4.34%)	0
6 month	4 (17.39%)	1 (4.34%)
12 month	1 (4.34%)	0
18 month	0	0

P value < 0.05

TABLE 3 Transport index (TI)

TI = K + D + (0.04 × T) + N + V
K = transport kinetics
0 normal
3 mild delay
5 marked delay
9 no transport
D = distribution of the tracer
0 normal
3 mild dermal diffusion
5 marked dermal diffusion
9 absent visualization
T = appearance time of lymph nodes (min)
N = visualization of lymph nodes
0 normal
3 mild
5 poor
9 absent
V = visualization of lymph vessels:
0 normal
3 mild
5 poor
9 absent
Normal TI < 10
Pathological TI ≥ 10

treatment group during follow-up, while the arm volume in the control group showed a significant increase after 1 (mean difference 11.61 ml, SE 3.87, $P < 0.01$), 3 (mean difference 22.82 ml, SE 5.9, $P < 0.01$), and 6 months (mean difference 31.56 ml, SE 5.78, $P < 0.01$) after operation. No significant changes in arm volume were observed at months 12 and 18, compared to data registered at months 6 and 12, respectively, in the control group. Significantly higher volume with respect to baseline after 1, 3, 6, 12, and 18 months from operation (every timing $P < 0.01$) was detected in the control group compared to the treatment group (Table 2, Fig. 3).

Duplex scanning allowed us to exclude a venous pathology in all patients. LS allowed us to confirm the lymphostatic nature of the edema. To quantify visual findings in LS, the Kleinhans transport index (TI) was used.[4,9,10] The TI includes the following parameters: transport kinetics (K), distribution of the tracer (D), appearance time of lymph nodes in minutes (T), visualization of lymph nodes (N), and visualization of lymph vessels (V): $TI = K + D + (0.04 \times T) + N + V$ (Table 3). Normal LS pattern corresponded to a TI value of <10. An impaired LS pattern in our study had a mean TI of 16 (range 12–19).

Preoperatively, LS had a statistically significant predictive value (TI) in terms of risk of lymphedema appearance. In this regard, LS proved to be an instrumental criterion in selecting patients at risk for secondary lymphedema.

Postoperatively, LS demonstrated the patency of micro-LVA (patency rate 95.6%), both through direct (visualization of preferential lymphatic pathway, disappearance of the tracer passing into the bloodstream) and indirect (early liver uptake of the tracer) parameters in the treatment group. In the control group, on the other hand, LS allowed us to find lymphatic drainage impairment in patients with secondary lymphedema.

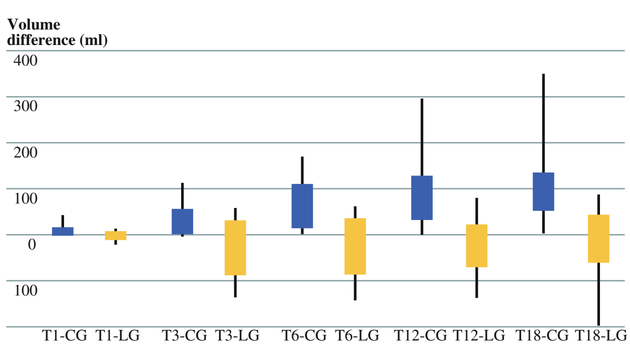

FIG. 3 Volume difference between baseline and different timing in treatment group (*LG*) and control group (*CG*), represented by box plots showing 10th, 25th, 75th, and 90th percentiles

DISCUSSION

Notwithstanding the wide variability in lymphedema prevalence, the incidence of secondary arm lymphedema is high. SLN biopsy was introduced and carried out to prevent lymphedema, but recent studies have demonstrated that even with SLN biopsy alone, lymphedema rates are not negligible.[11,12] Therefore, prevention is of key importance to avoid lymphedema occurrence.

The axillary reverse mapping procedure represents an attempt to identify and preserve arm lymphatic drainage. The success of this technique in preventing lymphedema will require ongoing follow-up and studies.[13] Blue-stained nodes were always located in the same position, at the lateral part of the dissection, under the axillary vein and just above the second intercostal brachial nerve.[14] The main issue remains to make sure that the nodes identified are not metastatic and can be preserved during AD. Because the lymphatic pathways from the arm cannot be involved by metastatic process of the primary breast tumor, its preservation should not imply any risk of leaving undetected diseases in the axilla.[9,10] With the axillary reverse mapping technique, the detection rate of blue-stained lymphatics and nodes is 61–71%, and the preservation rate is 47%.[1,10,14] The question is, can we spare what we find? The identification of afferent lymphatics and nodes belonging to the arm lymphatic pathways appears feasible. Nevertheless, the identification of the efferent lymphatics, which is mandatory to truly preserve the lymphatic flow of the arm, is almost impossible because the lymphatics departing from the blue nodes join the common lymphatic pathways draining the breast. Therefore, the preservation is practically impossible. That is why we conceived and carried out the LYMPHA technique, which consists of performing LVA between the arm lymphatics and collateral branches of the axillary vein at the same time as AD. LVAs are performed at the upper lateral part of the axilla and are thus somehow protected from the negative effect of postoperative radiation. In fact, postoperative radiation did not cause any relevant problem in the patients who underwent LVA in this study. In 2 patients, a transitory (for 3 and 5 days, respectively) slight arm edema was observed, which disappeared spontaneously.

There are no relevant costs for this procedure because it is performed during axillary lymph node dissection and takes only 15–20 minutes to be performed. The operating microscope, microsurgical tools, and surgeon are already available, and the cost of suture material is negligible.

Long-term efficacy and patency of lymphatic-venous (LV) bypasses have been demonstrated both clinically and instrumentally by lymphangioscintigraphy even at more than 15 years after surgery. The effectiveness of LV bypasses depends on the technique: end-to-end sleeve technique is preferred to end-to-side technique; the use of a side branch of the main vein with a well-functioning valve is preferred to veins with valvular and parietal insufficiency; several lymphatics are anastomosed to the same vein to create and maintain a proper lymphatic-venous pressure gradient, and thus the caliber of the vein and the lymphatics fit well. These technical aspects are fundamental for the long-term effectiveness of LV shunts. Venous backflow is avoided by choosing a vein with a good valvular apparatus, which prevents the blood from flowing back toward the lymphatics and anastomosing several lymphatics; with a good flow to the same venous segment, a favorable pressure gradient for the lymphatic system occurs. Lymphatics propel lymph by intrinsic beating, the rate and force of which are automatically adjusted by the prevailing level of filling pressure (preload) and outflow resistance (afterload). Extrinsic forces, on the other hand, have little effect on lymph transport at normal intralymphatic pressures and volumes. The same occurs for the thoracic duct and the subclavian vein.

Patients were followed by volume measurements, which allowed us to demonstrate the absence of any negative effect of postoperative radiation. Furthermore, postoperative LS proved the patency of anastomoses long after surgery and radiotherapy. The preservation of arm lymphatics carries no risk of leaving disease in the axilla undetected, and it permits the prevention of lymphedema.[5] Candidate for LYMPHA are those referred to undergo AD with either clinical axillary node–positive or SLN-positive disease. Before surgery, patient selection for LYMPHA, clinical, and instrumental criteria were evaluated. History and physical examination of the patients, together with body mass index, could allow the selection of patients at risk for lymphedema, and this suspicion could be confirmed by LS via semiquantitative evaluation, which is represented by TI.[15,16] Preoperative LS is useful to select patients at risk for arm lymphedema. LS shows lymphatic impairment (in terms of TI) compared to the contralateral arm already present before surgery.

The mean follow-up time was 18 months; this can be considered an appropriate follow-up period because most arm lymphedemas occur in the first year after breast cancer treatment. Thus, to assess the role of LV bypasses in the primary prevention of arm lymphedema after breast cancer treatment, this period can be reasonably considered fair.

Quality of life is gaining more importance as a result of longer survival brought about by advanced and combined treatments of different tumors. Surgery has to be more conservative to try to maintain organ function and reduce morbility. The LYMPHA technique represents a new treatment strategy to reduce morbility of axillary lymph node dissection when it is not possible to preserve arm lymphatic pathways as a result of the risk of leaving disease behind.

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