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SSD MED/19

Breast Cancer-Related Lymphedema: Prevalence, Risk Factors and Surgical Treatment

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Year 2014/2016 – Cycle XXIX

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Abstract

This study aimed to add some new insight into the epidemiology, aetiology and surgical treatment of Breast Cancer-Related Lymphedema (BCRL). Results demonstrate that about 45% of women will develop BCRL after 3 years from breast cancer treatment. Obese women in advanced breast cancer stages, treated with mastectomy and extensive axillary lymphadenectomy (total number of removed lymph nodes ≥ 20) are at major risk to develop BCRL, thus they should be referred to monitoring programs with the aim to prevent the onset of lymphedema. However, once developed, lymphedema can be treated with customized surgical procedures that allow improvement in the quality of life of selected BCRL patients.

Summary

Purpose: Breast Cancer-Related Lymphedema (BCRL) is a challenging psychophysical disease affecting women after breast cancer treatment. A lack of standardized diagnostic and surgical strategies contribute to the large variations available in literature about the prevalence and identification of risk factors for BCRL as well as on outcomes of its surgical treatment. The aims of this study were: to estimate the long-term prevalence of BCRL by using a standardized diagnostic protocol; to determine risk factors associated to BCRL development; to report the outcomes of a tailored surgical protocol adopted in selected BCRL patients.

Materials and Methods: the study was divided into two phases. *Phase I* (cross sectional study) was designed to evaluate the prevalence and risk factors of upper-limb lymphedema in a cohort of breast cancer survivors 3 years after unilateral mastectomy or breast-conservative surgery with axillary lymph node dissection. A questionnaire was administered to each patient to assess demographic, lifestyle, clinical and pathological factors associated with BCRL. Presence of lymphedema was determined by using a combination of three diagnostic modalities: circumferential tape measurement, self-reported lymphedema symptoms and lymphoscintigraphy. Lymphedema patients were classified for staging and severity according to the International Society of Lymphology system classification. Univariate and multivariate statistical analyses were used to evaluate risk factors for lymphedema.

Phase II (prospective study) was conducted to evaluate the effectiveness of a surgical protocol applied for the treatment of selected BCRL patients recruited from phase I. Preoperatively, each patient underwent physical examination and Indocyanine Green (ICG) lymphography in order to evaluate the presentation of lymphedema (pitting or no-pitting edema) and the functionality of the lymphatic vessels. Patients with active lymphatic channels were candidates for linfatico-venular anastomosis (LVA). Patients with non-functioning lymphatic channels and non-pitting lymphedema were candidates for circumferential liposuction (CL). Postoperatively each patient underwent upper limbs circumferential measurements at 1, 3, 6 and 12 months after surgery. Post-treatment measurements were compared to

the preoperative circumference values to evaluate limb volume reduction.

Results: in *Phase I*, a total of 80 breast cancer survivors were enrolled. The overall prevalence of lymphedema was 45% (CI 95% 0.3385; 0.5653). The univariate analysis showed significant association between lymphedema and BMI ≥ 30 Kg/m2 (OR = 2.96, p = 0.035), mastectomy (OR = 4.32, p = 0.021), number of excised lymph nodes ≥ 20 (OR= 2.96, p = 0.035) and advanced TNM stages of breast cancer (OR = 2.63, p = 0.042). Smoke was found to be a protective factor for development of lymphedema (OR = 0.18, p = 0.031). At the multivariate analysis only a number of excised lymph nodes ≥ 20 (OR = 1.09, p = 0.044) and mastectomy (OR = 3.93, p = 0.047) remained significantly associated to the occurrence of lymphedema.

In phase II, six patients were selected. Three showed early II stage lymphedema with pitting edema and active lymphatic channels, thus they underwent lymphatico-venular anastomosis (LVA group). The remaining three patients with late II stage lymphedema, no pitting edema and non-functioning lymphatic vessels underwent circumferential liposuction (CL group). At 12 months follow-up, upper limbs circumferential measurements demonstrated an average reduction of limb volume excess of 53.3% and 88.7% in LVA and CL groups respectively.

Conclusions:

The current study demonstrate that the standardization of diagnostic and surgical protocols employed in the management of Breast Cancer-

Related Lymphedema allows to define accurately the entity of the disease, the classes of patients considered at major risk and those who would benefit from surgical treatment.

CHAPTER 1

Introduction

Breast Cancer-Related Lymphedema (BCRL) is defined as a chronic swelling syndrome due to obstruction or disruption of the lymphatic drainage system in patients following breast cancer surgical treatment.[1]

It represents a challenging psychophysical disease associated with different symptoms such as heaviness, stiffness, discomfort, paraesthesia and pain. In patients with long-standing untreated lymphedema, infections are the most common complications and in rare cases a lymphangiosarcoma may develop.[2]

Currently, little is known about risk factors and the real prevalence of BCRL. In addition, different surgical treatments are described in the literature ranging from functional therapeutic techniques to palliative solutions. However, despite large series are available and these procedures are becoming more popular, there is still a huge variability in reported outcomes.[3-6]

This inconsistency in the data can be attributed to the lack of standardization of modalities employed for the assessment of risk factors and diagnosis of BCRL, and to the variability in the indications and outcome measures used in the surgical treatment of the disease.

The main objectives of this study were: to estimate the prevalence and risk factors for lymphedema in a cohort of breast cancer survivors by using a standardized protocol; to report our preliminary experience and outcomes with the use of lymphatico-venular anastomoses and circumferential liposuction in the surgical treatment of selected breast cancer-related lymphedema patients.

CHAPTER 2

Materials and Methods

This study was approved by local Ethics Committee (N°8/2016) and was performed in accordance with the ethical guidelines of the Declaration of Helsinki. It was divided into two phases.

2.1. Phase I: cross-sectional study

In this phase, the study was designed to determine the prevalence and risk factors for upper-limb lymphedema in a cohort of breast cancer survivors 3 years after unilateral mastectomy or breast-conservative surgery (lumpectomy/quadrantectomy) with axillary lymph

node dissection (ALND) for clinically or histologically [after sentinel lymph node biopsy (SLNB)] node-positive breast cancer.

Sample size of this study was determined a priori to be about 80 patients using the Open Source Epidemiologic Statistics for Public Health (OpenEpi, version 3.01). Sample size calculation was based on an estimated prevalence of the outcome factor in the population (lymphedema) of 21,4%, according to previous studies.[7] Two sided significance level (alpha error) was set at 5% and desired precision of the estimate was set at 9%.

The study started on June 1, 2013 and concluded on December 31, 2015, date on which all patients were examined at a distance of 3 years after surgery.

2.1.1. Patients' recruitment

Initially, n=220 women that underwent breast cancer surgery and ALND performed by the same surgeon in the period between January 1, 2010, and December 31, 2012 were considered consulting the registry of the Department of Oncology of the University Hospital "P. Giaccone" of Palermo, Italy. A trained research assistant performed a pre-screening of the sample by analysis of medical records to select women who met the following inclusion criteria: age ranged between 18 and 85 years on the date of surgery, unilateral breast cancer diagnosis, unilateral breast and axillary surgical treatment, no history of primary lymphedema. A unilateral diagnosis and treatment allowed using the contralateral limb as a control for lymphedema. Among these patients, n=1 was excluded because of a history of bilateral breast cancer surgical treatment. All eligible women (n=219) were contacted by

telephone to participate in the study. Of these, n=8 died due to non-cancer causes, n=51 were not contactable and n= 80 refused to participate. Finally, 80 women were enrolled and gave informed, written consent prior to participation. Figure 1 shows patients' recruitment flow chart.

2.1.2. Data collection and risk factors assessment

Each patient was interviewed by the same research staff member. A questionnaire was administered to assess potential risk factors for development of lymphedema. The following data were recorded:

- demographic, clinical and lifestyle characteristics of patients at time of breast and/or axillary surgery [age, body mass index (BMI), side of dominance/handedness, history of tobacco, alcohol and caffeine use];
- past medical history (comorbidities such as diabetes, hypertension, chronic heart failure, renal failure, thyroid disease, familiarity for lymphedema and history of infection, musculoskeletal or osteo-articular disorders, venous incompetence, surgery or trauma in both upper limbs);
- tumour characteristics (histological type, disease stage by using AJCC TNM staging);[8]
- characteristics of breast surgery {treated side, type of surgery [breast conservative surgery (lumpectomy/quadrantectomy) or mastectomy]};
- characteristics of axillary surgery (treated side, number of

removed lymph nodes, number of metastatic lymph nodes);

- types of breast cancer adjuvant therapies (radiotherapy, chemotherapy, hormonotherapy, immunotherapy).

2.1.3. Lymphedema assessment

Determination of lymphedema was based on objective (circumference measurements) and subjective (patient perception of lymphedema) assessment clinical methods in combination with instrumental investigation (lymphoscintigraphy).

Specifically, each patient underwent circumference measurement of upper limbs. In the absence of a baseline measurement, the upper limb ipsilateral to axillary lymphadenectomy was defined as “treated side” and the contralateral limb was defined as “untreated side” and used as control assuming that it was functionally intact. Patients were asked to sit with the arms supported on a table. Measurements were taken keeping both upper limbs in a similar position with 90° elbow flexion and hand palm up. On the volar aspect of the limbs, an imaginary line joining the apex of the third finger of each limb (point 0) with the acromioclavicular joint was drawn. Several points placed at 10 cm intervals from the point 0 up to the armpit were marked along the drawn line using a skin-marker pencil. Circumferences on treated and untreated limb were measured and compared at each marked point, placing the top edge of a flexible, non-stretching measuring tape just below the mark. Measurements were photographed and recorded on a database (Figure 2). Difference

between two-limb circumferences (L) at any level of more than 2 cm was considered as clinical sign of lymphedema.[9-10]

Indirect volume for each limb was calculated on the basis of the measurements using a truncated cone volume (Vtc) formula for the forearm and the arm, as follows: $Vtc = \frac{1}{3}\pi h\,(R^2 + r^2 + Rr) = \frac{(C^2+c^2+\mathrm{Cc})\,\mathrm{h}}{12\pi}$; and a cylinder volume (Vc) formula for the hand, as follows: $Vc = \pi R^2 h = \frac{C^2 h}{4\pi}$. *R* and *r* are radius of two consecutive circumference measurements, *C* and *c* are circumferences of two consecutive measurements and *h* is height. Giving a fixed value to the height (10 cm), the total Limb Volume (LV) was calculated as follows: $\left(\frac{10}{12\pi}\sum_{i=2}^{n-1} + C_i^2 + C_{i+1}^2 + C_i C_{i+1}\right) + \frac{10}{4\pi} C_1^2$ (Figure 3). This method demonstrated excellent inter- and intra-observer reproducibility in comparison to water displacement which is considered the gold standard.[11-13]

Then, patients were asked if they noted the presence of heaviness and/or swelling on the treated limb. These two subjective symptoms are reported to be highly predictive of lymphedema and were used in this study to proceed to the instrumental investigation.[14-16]

Patients that experienced swelling or heaviness and did not show clinical features of lymphedema at the circumference measurements, were invited to underwent lymphoscintigraphy to recognise subclinical forms of lymphedema. All lymphoscintigraphies were performed according to the following protocol: with the patient in the supine position and the upper limbs positioned alongside the body, 1mCi (37 MBq) of 99 mTc-labeled nanocolloidal albumin (Nanocoll, Ge

Healthcare Srl, Milan, Italy) in a volume of 0.2 ml was simultaneously injected intradermally in the second web space of both hands, by two experienced nuclear radiologists. Resistance to injection, blanching and a visible raised bleb confirmed the intradermal location. Images were acquired on a dual-head gamma camera equipped with ultra high-resolution low energy collimators and recorded with a 10% energy window centered on a 140-kV photopeak of 99mTc. Anterior and posterior partial whole body images (128x128 matrix) were taken at rest from the injection site to the axilla starting at 2 time points, 20 and 60 minutes after the injection. Thereafter, patients were asked to squeeze a soft ball simultaneously with both hands for 20 minutes and then imaging was repeated at 120 minutes. Absent visualization of supraclavicular or infraclavicular lymph nodes and/or presence of dermal backflow were considered lymphoscintigraphic signs of lymphedema (Figure 4).[17-19]

After clinical and instrumental evaluation, patients were categorized into two groups according to the presence (cases) or absence (non-cases) of unilateral lymphedema. Figure 5 shows the diagnostic algorithm used in this study.

Lymphedema patients (cases) were classified using the staging and severity system of the International Society of Lymphology (ISL). The staging system is based on details about the amount of swelling and the condition of the skin and tissues at each stage. Currently the ISL lymphedema staging system consists of four levels being numbered from 0 to III (Table 1). **Stage 0** lymphedema refers to a latent or sub-clinical condition where swelling is not yet evident despite

impaired lymph transport. Patients may report a feeling of heaviness in the limb, but many patients are asymptomatic in this latency stage. It may exist months or years before overt oedema occurs. **Stage I** lymphedema is referred to as “reversible lymphedema”. In this stage, the patient presents with very soft, pitting edema with no fibrosis due to an early accumulation of fluid relatively high in protein content. Prolonged elevation of the limb leads to complete resolution of the clinically evident swelling. **Stage II** lymphedema, also called “spontaneously irreversible lymphedema,” presents with intradermal fibrosis that decreases tissue suppleness and reduces the ability of the skin to indent (“pit”) with pressure. Applying firm pressure into the tissue for at least 5 seconds assesses pitting edema. If an indentation remains after the pressure is released, pitting edema is present. In this stage resolution of clinically evident lymphedema is rarely possible with elevation. Late in Stage II, the limb may or may not pit as excess fat and fibrosis supervenes. **Stage III** is also called “lymphostatic elephantiasis”. It is associated with a significant increase in the severity of the fibrotic response, tissue volume, and other skin changes such as papillomas, cysts, fistulas, and hyperkeratosis. Skin folds on the wrists and ankles deepen, the patient may present with slight or no pitting edema. Within each stage, severity of lymphedema based upon volume differences between the lymphedematous limb and the contralateral normal limb was defined as **mild** (<20 percent increase), **moderate** (20 to 40 percent increase), or **severe** (>40 percent increase) (Table 2) .[14,20]

2.1.4. Statistical Analysis

Statistical analysis was conducted using the statistical software R (R version 3.1.2). Descriptive statistics (mean ± SD; range, frequency and percentage) were calculated for subject characteristics. Considering the presence of lymphedema as outcome of interest, population was divided into two groups: cases (lymphedema patients) and non-cases (no lymphedema patients). The marginal effect of each variable on lymphedema occurrence was studied through univariate analysis. The association between discrete/categorical variables and lymphedema occurrence was studied through Odds Ratios. Fisher Exact Test was used to evaluate any statistically significant difference in the two groups. The association between continuous variables and lymphedema occurrence was studied through mean differences. Welch-Satterthwaite T-Test was used to evaluate any statistically significant difference in the two groups. Therefore, a multivariate analysis was conducted. A logistic regression model was used to examine the correlation between statistically significant variables and the outcome of interest (lymphedema occurrence).

Age and BMI were examined respectively at a cut-point of 60 years and 30 Kg/m2 because it is expected that lymphatic function should be altered over these values.[17,21-24]

Breast cancer stages III and IV were considered advanced according to the AJCC TNM staging system.[8, 25-27]

Number of excised and positive (for metastasis) lymph nodes were examined as continuous variables and at a cut-point of 20 and 4 lymph nodes respectively.[28-29] Significance was set at P 0.05.

2.2. Phase II: prospective study

In the second phase, the study was designed to evaluate the effectiveness of surgical treatment of lymphedema.

Lymphedema patients recruited from phase I who met the following inclusion criteria were invited to undergo lymphedema surgical treatment: a) age ranged between 18 and 70 years, b) no breast cancer residual disease or recurrence; c) ASA ≤3; d) past history of lymphedema conservative therapy (at least 6 months) with poor results. Exclusion criteria were: a) ongoing chemo/radiotherapy; b) venous insufficiency and thrombosis in the affected limb.

Patients who accepted to participate gave informed, written consent prior undergoing the surgical protocol described below.

2.2.1. Preoperative assessment

Each patient underwent physical examination and Indocyanine Green (ICG) lymphography in order to determine an appropriate surgical therapeutic strategy.

Physical examination was performed to differentiate between pitting and non-pitting edema. Pitting edema is characterized by lymph fluid collection in the adipose tissue and is mainly recognized in the early stages of lymphedema (stage I to early II). Non-pitting edema argues for an advanced stage of the disorder (late stage II to III), characterized by severe fibrosis and hypertrophy of adipose tissue.[14,30]

ICG lymphography was conducted to assess the functionality of the lymphatic vessels. ICG is a water-soluble fluorescent dye that has been used mainly to map blood flow in the heart, liver and eye when administered intravenously. In assessment of the lymphatic system,

ICG is injected subcutaneously where it binds to albumin and is taken up by the lymphatic system where it can be detected using near infra-red range camera system deep in the tissue.[31-38]

In this study, ICG lymphography was performed as follows. With the patient in supine position, 0,2 ml of ICG (Indocyanine Green Pulsion, PULSION Medical System AG, Munich, Germany) was injected subcutaneously in the second web space of the affected limb. Immediately after ICG injection, an infrared camera system [Photodynamic Eye (PDE); Hamamatsu Photonics K.K., Hamamatsu, Japan], composed of a camera unit, near-infrared–emitting diodes, and a controller unit that operates the camera, was used in order to illuminate with near infrared light the skin of the affected limb and to image the fluorescence emitted by ICG absorbed in subcutaneous lymph vessels. Functional and active lymphatic vessels were visualized on a display as fluorescent channels.

Patients with active lymphatic channels were considered candidates for linfatico-venular anastomosis (LVA). In cases of non-functioning lymphatic channels and non-pitting lymphedema, patients were candidates for circumferential liposuction (CL). Patients with non-functioning lymphatic channels and pitting lymphedema, were invited to perform intensive physical rehabilitation therapy and then they were revaluated for the possibility to undergo circumferential liposuction.[30]

2.2.2. Lymphatico-venular anastomosis technique

LVA is a derivative surgical procedure. The main objective is to redirect the lymph to the venous system directly, without going through

the thoracic duct. This procedure can be performed only in presence of functioning lymph vessels.[30]

In this study the procedure was performed as follows. Preoperatively, 0,2 ml of ICG were injected in the second web-space of the affected hand. PDE system confirmed that ICG was flowing up through the lymphatic vessels in the adipose tissue. Then the location and paths of active lymphatic channels were traced on the skin using a marker pencil.

Under general anaesthesia, after disinfection of the affected limb, an incision of about 2 cm in length was made over the proximal side of the fluorescent active lymphatic vessels. After skin incision, venules (with a diameter of 0.5 to 1 mm) that lie beneath the dermis or in the superficial fat layer and adjacent lymphatic vessel (with a diameter of 0.5 to 1 mm) were exposed and separated by using an operative microscope. Once isolated, lymphatic vessel and adjacent venule were transected and, depending on the vessels diameter, an end-to-end (distal stump of the lymphatic vessel with proximal stump of the venule) or end-to-side anastomosis was performed with four to eight interrupted stitches using nylon 10/0 or 11 /0. Number of anastomoses depended on the number of active lymphatic vessels visualized by using ICG lymphography. Finally, patency of anastomosis was tested by injecting 0,2 ml of Patent Blue 2 cm distal the skin incision. Lymph fluid was seen flowing through the anastomosis along the vein. Skin incision/s was/were closed with interrupted stitches using nylon 4/0 (Figure 6).

In the immediate postoperative period (the first 48 hours) patient was invited to elevate the affected limb. On postoperative day 3, patient started muscular activation by squeezing a rubber ball. At day 21, patient was invited to begin physical activity (swimming). Compression garments were not prescribed.

2.2.3. Circumferential liposuction technique

Circumferential liposuction is an ablative surgical procedure. The main objective is to reduce the volume of the affected limb by removing the hypertrophied adipose tissue. This technique can be performed only in absence of functioning lymph vessels as it destroys the remaining lymphatic channels. Of note, it should be reserved only for compliant patients who are committed to wearing lifelong compression garments.[30,39]

In this study, the procedure was performed according to the technique described by Brorson.[39] Specifically, Made-to-measure compression garments (two sleeves with gauntlets) were measured and ordered 2 weeks before surgery, using the healthy upper limb as a template. Under general anaesthesia, a tourniquet was placed at the proximal part of the affected limb. Ten to fifteen, 3-mm-long incisions were made circumferentially on the entire affected limb until the tourniquet and a tumescent saline solution (1 to 2 L) containing low-dose adrenaline and lignocaine was injected in the adipose tissue to reduce blood loss. Tourniquet was inflated and power-assisted liposuction was performed circumferentially from the wrist to the shoulder using 15 and 25 cm long cannulas with diameter of 3 and 4 mm. After this phase a variation in the technique described by Brorson

was introduced. Specifically, when the arm distal to the tourniquet was treated, a multilayer bandage (deep layer: sterile gauze pads; middle layer: absorbent batting bandage fibre bonded; superficial layer: elastic bandage) instead of sterilized made-to-measure compression sleeve and glove was applied in order to absorb bleeding and reduce edema. The tourniquet was removed and the most proximal part of the upper limb was treated using the tumescent technique. Finally, the multilayer bandage was continued proximally to cover the shoulder. The incisions were left open to drain in to the multilayer bandage (Figure 7). An isoxazolyl penicillin was given intravenously for the first 24 hours and then in tablet form until incisions were healed (10 to 14 days after surgery).

On postoperative day 2, the multilayer bandage was removed and the first set of garments was applied. On postoperative day 3, the first set was removed and replaced with the second set while the first was washed and dried. This routine was repeated every 2 days for two weeks. After the 2-week control, the garments were changed every day.

2.2.4. Postoperative assessment

Upper limbs circumferential measurements were performed at 1, 3, 6 and 12 months postoperatively. Post-treatment measurements were photographed, recorded on a database and compared to the preoperative circumference values to evaluate the effectiveness of the surgical treatment.

CHAPTER 3

Results

3.1. Phase I: cross sectional study

Eighty right-handed breast cancer women with age ranging between 37 and 83 years (mean ± SD: 58.16 ± 9.63 yr) and body mass index (BMI) ranging from 18.3 to 46.6 kg/m2 (mean ± SD: 28.1 ± 5.84 kg/m2) were studied. Of these, 33.75% and 88.75% reported alcohol and coffee consumption respectively, 16.25% were current smokers, 81.25% had co-morbidities, 11.5% had a past history of upper limb trauma. Only 1 patient had familiarity for lymphedema. Demographical and anamnestic characteristics of examined patients are shown in Table 3.

Primary breast cancer was located on the right breast in 57.50% (46/80) of patients and on the left breast in 42.50% (34/80). 86.25% (69/80) of patients had a ductal carcinoma and 13.75% (11/80) had a lobular carcinoma. Mastectomy was performed in 18.75% (15/80) of patients and breast conserving surgery (BCS) in the remaining 81.25% (65/80). Axillary lymphadenectomy was performed in all cases. The average number of excised lymph nodes and positive lymph nodes were 17.27 (SD: ± 6.13) and 4 (SD: ± 5.41) respectively. Adjuvant chemotherapy was given in 68.75% (55/80) of patients, hormone therapy in 78.75% (63/80), immunotherapy in 11.25% (9/80) and radiotherapy in 88.75% (71/80). Early breast cancer (Stage I, II) was found in 48 patients (60%), advanced breast cancer (stage III, IV) in 32 patients (40%). Clinical and pathological characteristics of patients are shown in Table 4.

At the circumferential measurements, 37.5 % (30/80) of patients had a clinically manifested lymphedema (L > 2cm). Eighteen patients (22.5%) with not measured lymphedema, reported subjective symptoms (heaviness and swelling) of lymphedema and were considered eligible for lymphoscintigraphy. Only 7/18 accepted to undergo lymphoscintigraphy and 6 of them showed lymphoscintigraphic features of lymphedema. Thus, the overall prevalence of lymphedema was 45% (CI 95% 0.3385; 0.5653). Specifically, 36 patients (45%) were classified as lymphedema patients (cases) of which 37.5% (30/80) showed clinical lymphedema and 7.5% (6/80) had a sub-clinical lymphedema. Forty-four (55%) patients had no diagnosis of lymphedema and were considered as non-cases. Table 5

shows number and percentage of lymphedema and no-lymphedema patients recognized in the study population.

Of the 36 lymphedema patients, 16.7% had stage 0 lymphedema, 25% had stage I lymphedema, 52.8% had stage II lymphedema and 5.5 % had stage III lymphedema. According to the lymphedema severity system classification of the ILS, 63.9% (23/36) of patients had mild lymphedema, 30.6% (11/36) had moderate lymphedema and 5.5% (2/36) had severe lymphedema.

Univariate analysis showed significant association between the occurrence of lymphedema and the following variables: BMI ≥ 30 Kg/m^2 (OR = 2.96, p = 0.035), mastectomy (OR = 4.32, p = 0.021), number of excised lymph nodes ≥ 20 (OR= 2.96, p = 0.035) and advanced TNM stages of breast cancer (OR = 2.63, p = 0.042). Smoke was found to be a protective factor for development of lymphedema (OR = 0.18, p = 0.031). Only 1 patient had familiarity for lymphedema thus this variable was excluded from statistical analysis. The marginal effects of each variable on lymphedema occurrence are shown in Tables 6 and 7.

Multivariate-adjusted analysis showed that a number of excised lymph nodes ≥ 20 (OR = 1.09, p = 0.044) and mastectomy (OR = 3.93, p = 0.047) were positively associated with lymphedema. Table 8 shows the selected logistic regression model.

3.2. Phase II: prospective study

A total of six lymphedema patients accepted to underwent lymphedema surgical treatment according to the inclusion and

exclusion criteria established in this phase. Of these, three showed early II stage lymphedema and the remaining 3 showed late II stage lymphedema. At the physical examination and ICG lymphography, patients with early II stage lymphedema had pitting edema and active lymphatic channels respectively, thus they underwent lymphatico-venular anastomosis (LVA group). Patients with late II stage of lymphedema had non-pitting edema and non-functioning lymphatic channels, thus they were considered for circumferential liposuction (CL group).

In LVA group, the mean percentage of postoperative reduction of volume excess between the threated limb and the contralateral control side was of 53.3% (range: 51 to 55%) at a follow period of 12 months. The mean postoperative value of reduction of the maximum preoperative circumferences difference between the threated limb and the contralateral control side was 1.5 cm (range: 1.2 to 1.7 cm). In the CL group, the mean percentage of postoperative reduction of volume excess between the threated limb and the contralateral control side was of 88.7% (range: 87 to 90%) at a follow period of 12 months. The mean postoperative value of reduction of the maximum preoperative circumferences difference between the threated limb and the contralateral control side was 3.7 cm (range: 3.5 to 4 cm). In the two groups, none of patients showed postoperative complications. Lymphedema patients' characteristics, surgical treatment details and postoperative results are shown in table 9.

CHAPTER 4

Discussion

Results from this study demonstrate that the overall prevalence of upper limb lymphedema among breast cancer survivors is 45% (36/80) 3 years after breast cancer treatment. This study showed also a pyramidal arrangement of lymphedema presentation. Specifically, 63.9% (23/36) of women had early stages of lymphedema (0 to early II ISL stages) with a mild severity, 30.6% (11/36) of patients were classified to have late in stage II lymphedema with a moderate severity and 5.5% (2/36) of patients had a severe stage III lymphedema.

The prevalence of lymphedema found in this study is higher than the prevalence rates between 9% and 40% reported by other studies. [26,40-42]

The explanations why our results disagree with those of other studies may be as follows.

First, prevalence of lymphedema is lower when relies only on clinical criteria and increases if multiple diagnostic techniques are applied. Many studies may underestimate the real prevalence of the disease because the estimation is achieved by using only one diagnostic modality.[7,26,43-46] In our study, circumferential tape measurements and lymphoscintigraphy in patients with self-reported symptoms were used. This standardized protocol allows to diagnose lymphedema even in a subclinical phase, revealing the submerged portion of the “lymphedema iceberg”.

Second, several studies report that there is an increase in the prevalence of lymphedema by the lengthening of the surgical follow-up. The risk of developing lymphedema increases persistently until 20 years after surgery, although most cases occurred within 3 years. Thus, studies reporting the prevalence of lymphedema with less than 3 years of follow-up would underestimate the true prevalence.[7,28,47-48] We studied our patients at 3 years, supporting the acquisition of the long-term prevalence of lymphedema.

Third, the lack of pre- or immediately post-operative measurements could lead to an overestimation (or underestimation) of the prevalence of the disease, because the assumption of a preoperative equivalence between the healthy and the affected limb in

order to perform a comparative assessment at the follow-up could not be true due to pre-existing muscular hypertrophy.[49]

However, if we consider the prevalence of clinical lymphedema (37.5%) revealed in this study, the resulting value can be comparable to that of other studies that evaluated the prevalence of the disease in patients with similar characteristics (ALND, TNM stage I-III) at a similar follow-up time and with similar diagnostic techniques and criteria (L > 2cm).[26,50-52]

Our study showed also that BMI, mastectomy, total number of excised lymph nodes and TNM stage are important risk factors in order to predict the onset of lymphedema.

Many studies have described the association between BMI and lymphedema.[26,48,53-57] This study demonstrated that a BMI ≥ 30 kg/m^2 increases the odds of lymphedema by approximately three times (OR = 2.96). More than one hypothesis has been introduced to explain the association between obesity and lymphedema. Foldi et al. believe that obesity acts in synergy with lymphedema, boosting up his negative effects. In addition, a high body weight is linked with a reduced diaphragmatic excursion, that impairs the mechanism of lymphatic suction allowed by negative intrathoracic pressure.[58] According to Shahpar et al. obesity, especially in advanced age, could worsen the severity of lymphedema because it is associated with decreased mobility, reduced levels of physical activity and failure of the muscular pump.[50]

As described in literature, type of breast surgery is considered as an important predictive factor for development of lymphedema.[50,54-

[55,59-61] Hayes et al. found that the risk of lymphedema is six fold higher in patients who underwent a more extensive surgery.[28] A possible explanation is that an aggressive breast surgery could be responsible of a greater damage to lymph system compared to the effect of a more conservative surgery.[62] The present study further supports these findings. Specifically, both univariate (OR = 4.32) and multivariate (OR = 3.93) analysis showed an increased probability to develop lymphedema in patients that underwent mastectomy compared to those that received breast conservative surgical treatment.

It is generally accepted that more extensive axillary lymph nodes dissection (number of removed lymph nodes) results in more extensive disruption of lymphatic vessels and, consequently, is associated with an increased risk of lymphedema.[26,47,50,54-56,63-66] Axillary lymph node dissection seems to decrease lymphatic drainage from the upper limb producing an accumulation of protein-rich fluid into the interstitial space. A large number of removed lymph nodes increases the risk of postoperative sequelae like seroma that could lead to tissue fibrosis and necrosis. In addition, seroma evacuation triples the probability to develop lymphedema.[67] In this study, a number of removed lymph nodes greater than 20 was associated to a significantly higher risk of swelling (OR = 2.96). Statistical analysis revealed that the odds of lymphedema increased by 9% for each additional lymph node removed (OR = 1.09).

The majority of studies didn't find any significant association between TNM pathological stage of breast cancer and BCRL. Only few works reported that an advanced stage of breast cancer is positively

related with the onset of lymphedema.[25-27] The present study showed that an advanced TNM stage is associated with an almost threefold increase of the probability of lymphedema (OR = 2.63). This is maybe due to metastatic involvement of axillary lymph nodes, that is common in advanced stages of disease and could lead to lymphostasis and lymph accumulation in the interstitium.[68]

Radiation therapy, especially if involves the armpit, could cause lymphedema or worsen a pre-existing disease. It could cause tissue fibrosis, vasoconstriction of lymph vessels, sclerosis of lymphatic vessel walls, resulting in an impaired drainage of the axilla.[25-27,50,63,66] Despite previously researches reported the radiation therapy as a predictive factor for lymphedema[53,56,61,64-66,69-70], this study didn't show any significant association between radiotherapy and BCRL. As described by Hayes et al. it could be related to recent improvements in radiation techniques.[28] However, it should be emphasized that almost the totality of patients enrolled in the present study (71/80) received radiation therapy and the majority of them (64/80) underwent BCS as a part of the tumorectomy/quadrantectomy, axillary lymphadenectomy and radiotheraphy (TART/QUART) protocol. For these reasons, our probabilistic sample could be too much homogeneous and then inadequate to show the effect of radiation therapy as a risk factor for lymphedema. In fact, in the population studied the isolated contribution of radiotherapy on lymphedema could be masked by its frequent association with quadrantectomy, that is associated with a lower risk of lymphedema in comparison with mastectomy.

Surprisingly, this study showed that smoking is a protective factor against lymphedema (OR = 0.18). Such a striking association is supported in literature by only one study referred by Bedi et al.[71] Nicotine, one of the main components of tobacco smoke, is a potent vasoconstrictor: it reduces blood flow, inhibits endothelium-dependent vasodilation and impairs responses to vasoactive substances.[72-74] For these reasons smoking reduces the rate of capillary filtration into the interstitium and so it could diminish the accumulation of lymph fluid in the third space. Angiogenesis is another factor involved in the determinism of lymphedema. Smoking inhibits the production of HIF-1 and VEGF-A: this means that it blocks hypoxia-induced angiogenesis leading to minor lymphatic leakage into the interstitial space.[71,75]

Currently, once BCRL develops, it is considered as a chronic disease that cannot be cured; it can only be managed, with the aims of reducing limb size, preventing progression and complications, and improving limb function and quality of life. Different therapeutics strategies are available in literature ranging from conservative therapy, pharmacotherapy, and surgery. [76-77]

Conservative therapy is the primary method currently used to treat lymphedema. It includes manual lymph drainage, pneumatic pumps, exercise, non-elastic wrapping, use of compression garments, and skin care. Treatment effects for conservative therapy are reported to be in the range of 8% to 66%. However, a lack of accuracy in studies design (absence of case-control groups, small sample size, variability in follow-up measures) severely influence the strength of these findings.[76-78]

The use of medications such as benzopyrones and selenium compounds to manage secondary lymphedema is currently emphasized. However, systematic reviews of the literature evaluating the effectiveness of these compounds report that there is no evidence in support of their use.[76-80]

Surgery for lymphedema is typically recommended when conservative treatment is unsuccessful or impractical. Different techniques ranging from reconstructive to ablative procedures are described in literature for the management of BCRL. However, there is still a wide variation in reported outcomes probably due to a lack of standardization in the indications and post-operative follow-up measures.[5-6,76-78] As described by Masià et al., excellent results in terms of reduction of excess of limb volume, improvements in limb function and quality of life could be achieved with the use of lymphatico-venular anastomosis and liposuction if a meticulous preoperative assessment and a customized surgical approach are performed in selected BCRL patients.[30] Our results, even if obtained in a small series (6 patients) and for a short follow up period (12 months), further support these findings. Specifically, lymphatico-venular anastomosis technique applied in lymphedema patients with pitting edema and functioning lymphatic vessels allowed an average reduction of limb volume excess of 53.3%; circumferential liposuction technique allowed to obtain an average limb volume reduction of 88.7% in patients with no-pitting edema and non-functioning lymphatic vessels.

CHAPTER 5

Conclusions

Results from this study highlight that Breast Cancer-Related Lymphedema is an emergent complication affecting breast cancer survivors with a long-term prevalence of 45%. This means that about one in two women will develop lymphedema after breast cancer treatment. Specifically, obese women in advanced breast cancer stages, treated with mastectomy and extensive axillary lymphadenectomy (total number of removed lymph nodes ≥ 20) seem to be at major risk. These patients should be referred to educational programs and monitoring service with the aim to prevent or recognize

the early onset of lymphedema. Once developed, lymphedema is difficult to manage. If it is not promptly diagnosed and treated in early period, treatment may be unsuccessful. Thus, early detection of lymphedema is mandatory to allow the application of early conservative therapy that represents the primary strategy of care. However, even though prevention programs and conservative treatments should fail, surgical treatment could promise satisfactory results enabling to improve the quality of life of BCRL patients.

CHAPTER 6

Tables and Figures

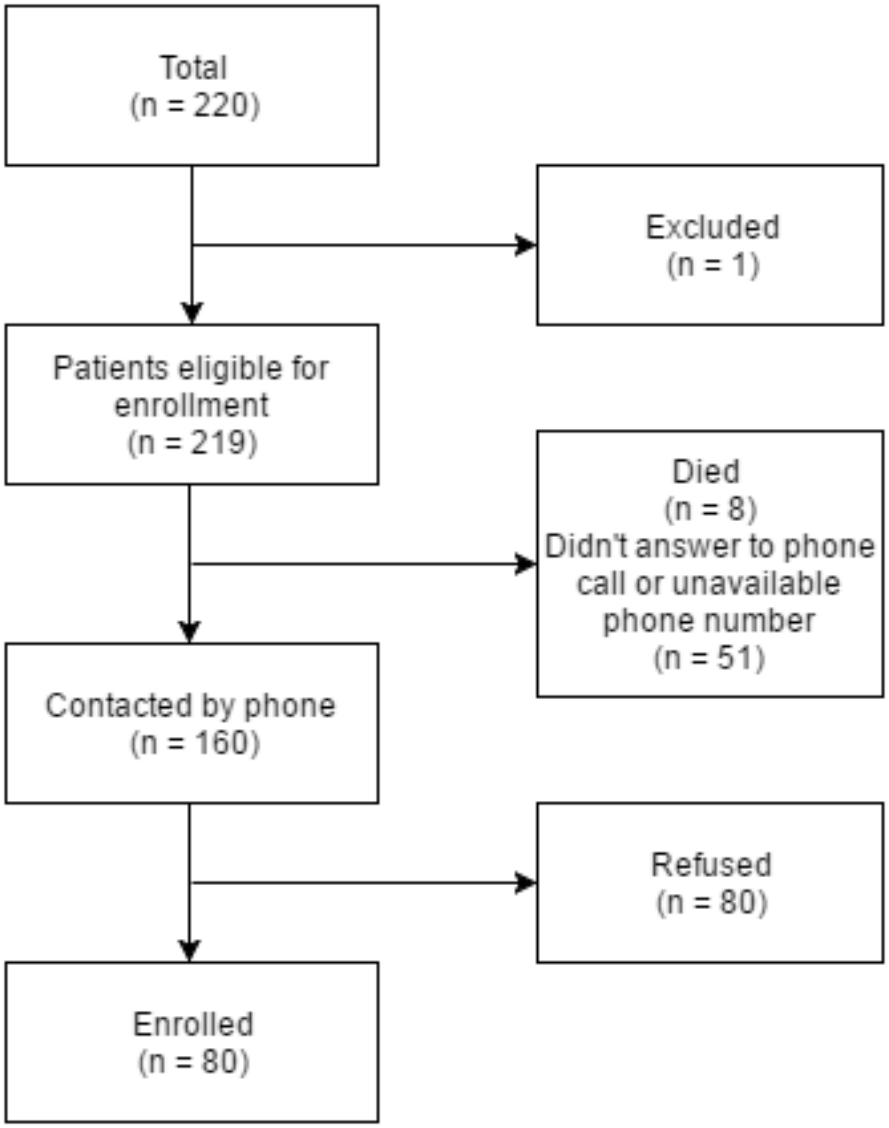
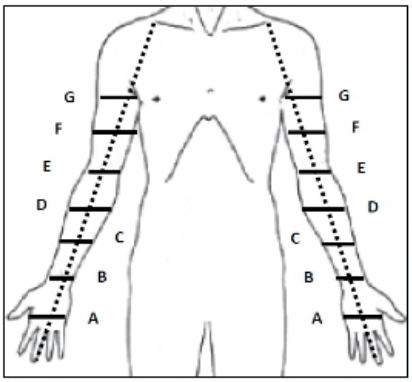


Figure 1. Patients' recruitment flow chart



Circumferential tape measurement	RIGHT ARM (cm)	LEFT ARM (cm)
A: [Point 0] 10 cm from the tip of the middle finger	21.5	25.5
B: [Point 1] + 10 cm from A	22.5	31.5
C: [Point 2] + 20 cm from A	30.5	39.5
D: [Point 3] + 30 cm from A	31.5	40.5
E: [Point 4] + 40 cm from A	37.5	42
F: [Point 5] + 50 cm from A		
G: [Point 6] + 60 cm from A		

Figure 2. Upper limbs circumferential measurement with flexible tape

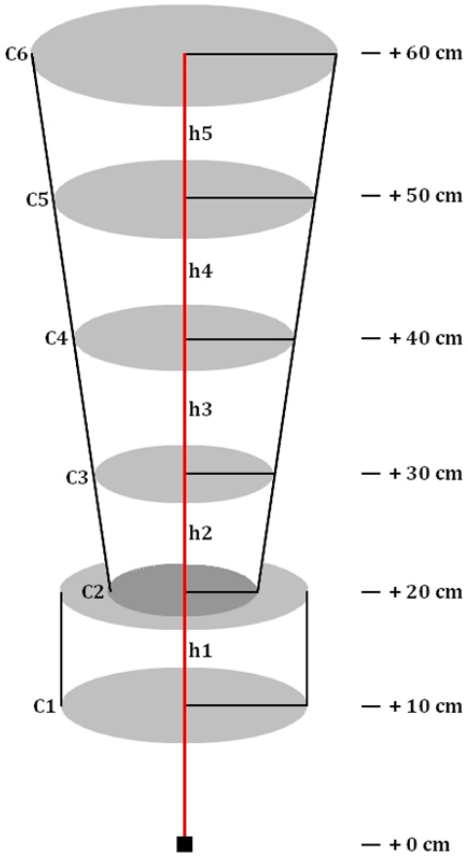


Figure 3. Geometrical model to estimate limb volume.

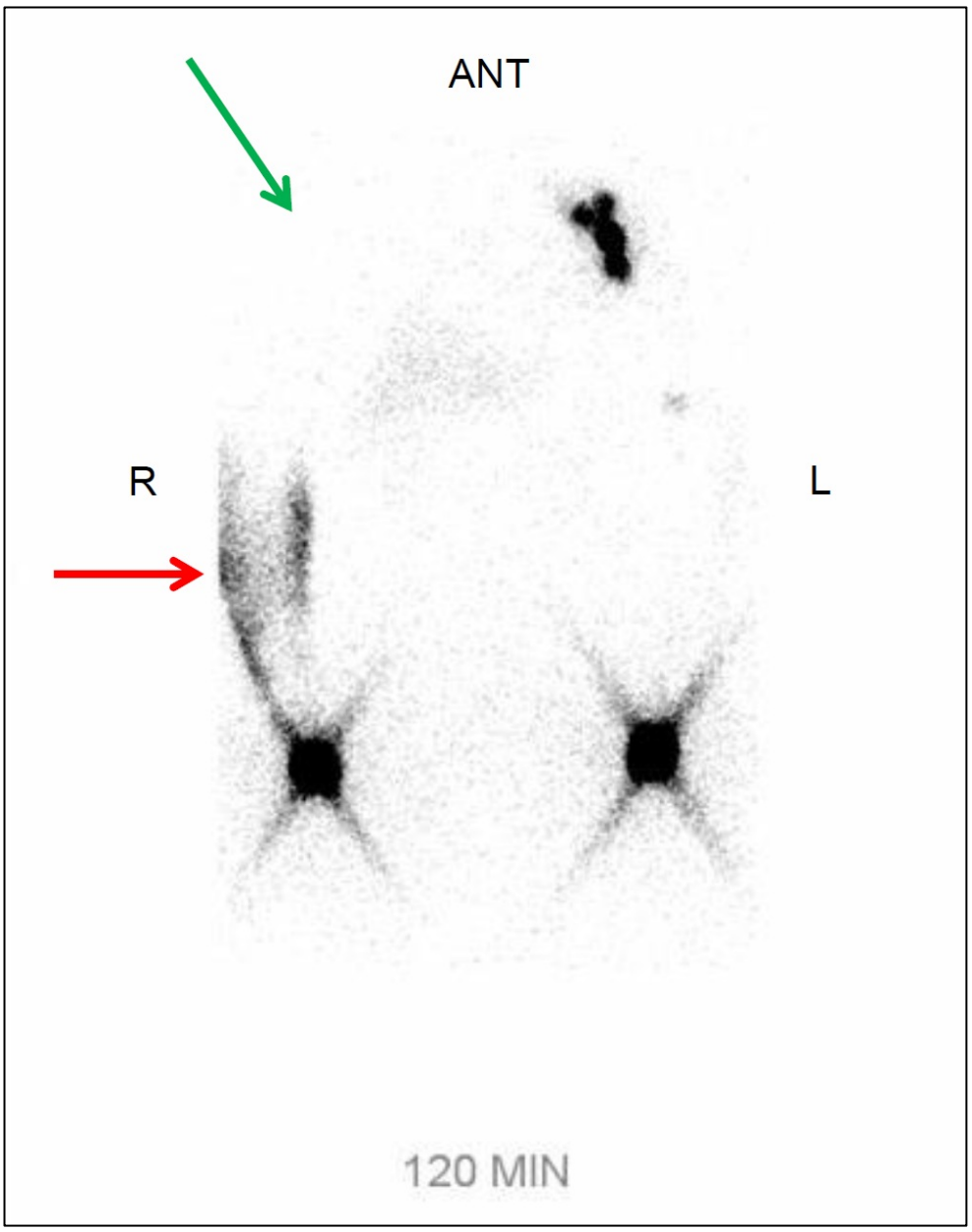


Figure 4. Anterior projection *(ANT)* of lymphoscintigraphic image taken at 120 minutes after injection of the radiotracer in the second interdigital web space of both hands). This patient shows absent visualization of supraclavicular or infra-clavicular lymph nodes *(green arrow)* and dermal back flow *(red arrow)* on the right *(R)* upper limb.

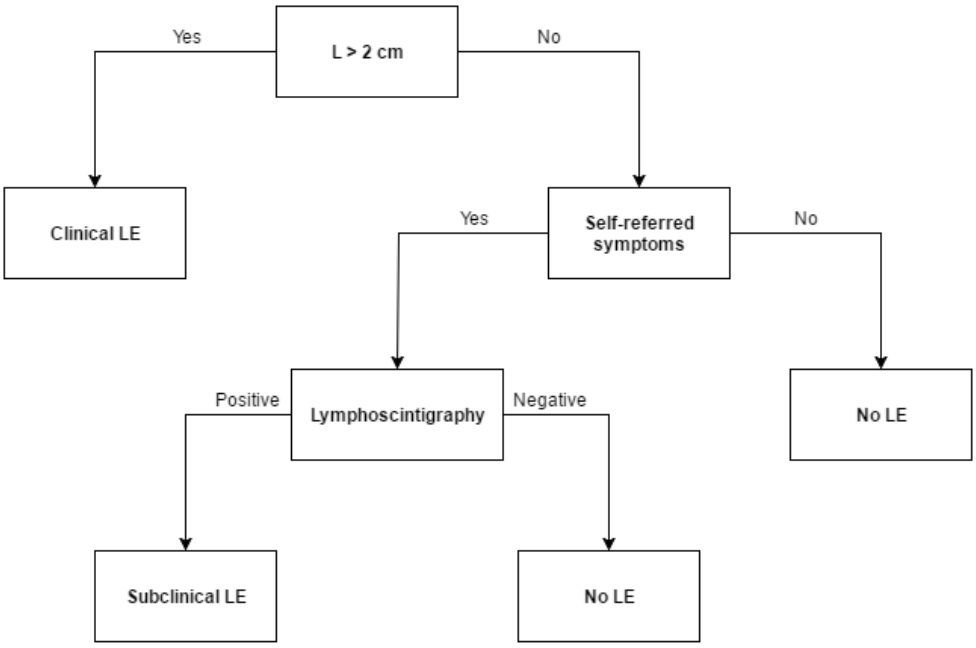


Figure 5. Diagnostic algorithm of upper limb lymphedema.

Lymphedema Staging System of the International Society of Lymphology (ISL)	
Stage 0	Latent or subclinical condition where swelling is not yet evident despite impaired lymph transport that can be assessed with lymphoscintigraphy (patients who underwent mastectomy and whose arms are equal in volume and consistency). It may exist months or years before overt edema occurs.
Stage I	Early accumulation of fluid relatively high in protein content which subsides with limb elevation. Pitting may occur.
Stage II (early)	Limb elevation alone rarely reduces tissue swelling and pitting is manifest.
Stage II (late)	Limb elevation does not reduce tissue swelling. The limb may or may not pit as excess fat and fibrosis supervenes.
Stage III	Lymphostatic elephantiasis with disappearance of bony landmarks, where pitting can be absent and trophic skin changes such as acanthosis, further deposition of fat and fibrosis, and warty overgrowths have developed.

Table 1. Lymphedema staging system of the International Society of Lymphology (ISL).

Lymphedema Severity System of the International Society of Lymphology (ISL)	
Mild	<20% increase in limb volume (in comparison with the contralateral limb)
Moderate	20-40% increase in limb volume
Severe	> 40% increase in limb volume

Table 2. Lymphedema Severity System of the International Society of Lymphology (ISL)

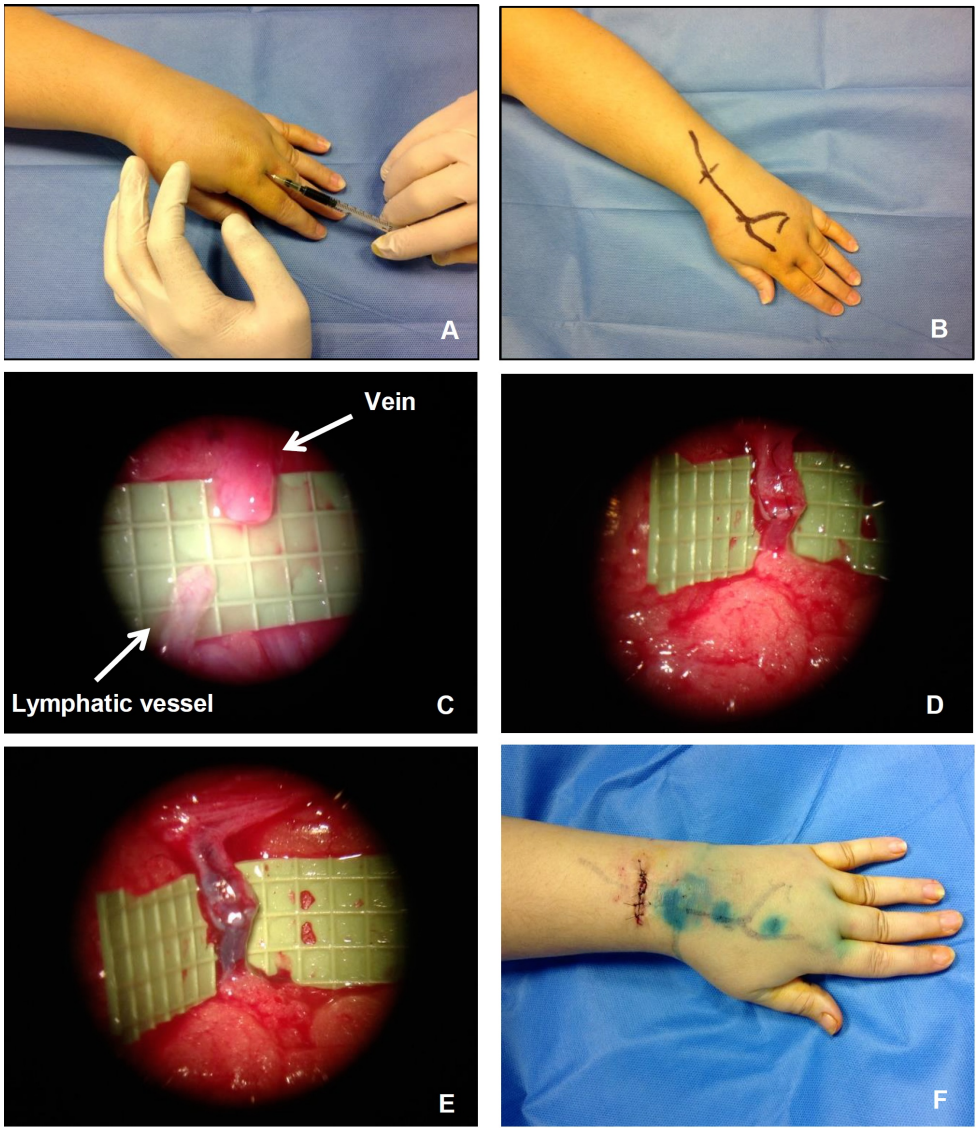


Figure 6. Lymphatico-venular anastomosis technique: (A) Preoperatively, 0,2 ml of ICG were injected in the second web-space of the affected hand. PDE system confirmed that ICG was flowing up through the lymphatic vessels in the adipose tissue. (B) Then the location and paths of active lymphatic channels were traced on the skin using a marker pencil. (C) After skin incision, a small vein that lie beneath in the superficial fat layer and an adjacent lymphatic vessel were exposed and transected by using an operative microscope. (D) An end-to-end (distal stump of the lymphatic vessel with proximal stump of the venule) anastomosis was performed with six interrupted stitches using nylon 10/0. (E) Patency of anastomosis was tested by injecting 0,2 ml of Patent Blue 2 cm distal the skin incision. (F) Skin incision was closed with interrupted stitches using nylon 4/0.

Figure 7. Circumferential liposuction technique: (A) Under general anaesthesia, a tourniquet was place at the proximal part of the affected limb. (B) Ten to fifteen, 3-mm-long incisions were made circumferentially on the entire affected limb until the tourniquet and a tumescent saline solution (1 to 2 L) containing low-dose adrenaline and lignocaine was injected in the adipose tissue to reduce blood loss. (C-D)Tourniquet was inflated and power-assisted liposuction was performed circumferentially from the wrist to the shoulder using 15 and 25 cm long cannulas with diameter of 3 and 4 mm. (E) When the entire arm was treated, (F) a multilayer bandage was applied in order to absorb bleeding and reduce edema.

Variable	Mean (Range, ±SD)	No. (%)
Age at the time of surgery (years)	58.1625 (37 - 83, ±9.6291)	
≥60		29 (36.25)
<60		51 (63.75)
BMI	28.0888 (18.3 - 46.6, ±5.8372)	
≥30		29 (36.25)
<30		51 (63.75)
Dominant side		
Right		80 (100.00)
Left		0 (0.00)
Smoking	1.6750 (0 - 20, ±4.5695)	
Yes		13 (16.25)
No		67 (83.75)
Alcohol		
Yes		27 (33.75)
No		53 (66.25)
Coffee	2.0127 (0 - 5, ±1.2877)	
Yes		71 (88.75)
No		9 (11.25)
Comorbidities		
Yes		65 (81.25)
No		15 (18.75)
Familiarity		
Yes		1 (1.25)
No		79 (98.75)
Past surgery		
Yes		14 (17.50)
No		66 (82.50)
History of upper limb trauma		
Yes		9 (11.25)
No		71 (88.75)
Diabetes mellitus		
Yes		10 (12.50)
No		70 (87.50)
Thyroid disease		
Yes		15 (18.75)
No		65 (81.25)
Venous system disease		
Yes		16 (20.00)
No		64 (80.00)
Hypertension		
Yes		28 (35.00)
No		52 (65.00)
Cardiovascular disease		
Yes		8 (10.00)
No		72 (90.00)
Osteoarticular disease		
Yes		21 (26.25)
No		59 (73.75)
Dyslipidemia		
Yes		6 (7.50)
No		74 (92.50)

Table 3. Demographic, past medical history and lifestyle characteristics of patients enrolled.

Variable	Mean (Range, ±SD)	No. (%)
Histologic type		
Ductal		69 (86.25)
Lobular		11 (13.75)
TNM Stage		
Early		48 (60.00)
1A		6 (7.50)
1B		2 (2.50)
2A		27 (33.75)
2B		13 (16.25)
Advanced		32 (40.00)
3A		18 (22.50)
3B		3 (3.75)
3C		6 (7.50)
4		5 (6.25)
Affected side		
Right		46 (57.50)
Left		34 (42.50)
Type of breast surgery		
Mastectomy		15 (18.75)
Quadrantectomy		65 (81.25)
Surgery in the dominant side		
Yes		46 (57.50)
No		34 (42.50)
No. of excised lymph nodes	17.2727 (2 - 41, ±6.1307)	
≥20		29 (36.25)
1-19		51 (63.75)
No. of positive lymph nodes	4.000 (0 - 24, ±5.4121)	
≥4		30 (37.50)
1-3		50 (62.50)
Radiation therapy		
Yes		71 (88.75)
No		9 (11.25)
Chemotherapy		
Yes		55 (68.75)
No		25 (31.25)
Hormone therapy		
Yes		63 (78.75)
No		17 (21.25)
Immunotherapy		
Yes		9 (11.25)
No		71 (88.75)

Table 4. Clinical and pathological characteristics of patients enrolled.

DIAGNOSIS OF LYMPHEDEMA				
	YEAR			
	2010	2011	2012	2010-2012
	No. (%)	No. (%)	No. (%)	No. (%)
TOTAL	38 (100.00)	12 (100.00)	30 (100.00)	80 (100.00)
ABSENT	18 (47.37)	6 (50.00)	20 (66.67)	44 (55.00)
SUBCLINICAL*	2 (5.26)	2 (16.67)	2 (6.67)	6 (7.50)
CLINICAL**	18 (47.37)	4 (33.33)	8 (26.66)	30 (37.50)
CLINICAL + SUBCLINICAL	20 (52.63)	6 (50.00)	10 (33.33)	36 (45.00)
NOTES: *Diagnosed by lymphoscintigraphy **Diagnosed by circumferential tape measurement				

Table 5. Prevalence of lymphedema: lymphedema and non-lymphedema patients in the study population.

Variable	No. Cases	No. Non-cases	OR (95% CI)	P -value
Age at the time of surgery (years)				
≥60	13	16	0.9893 (0.3565 - 2.7199)	1
<60	23	28		
BMI				
≥30	18	11	2.9568 (1.0582 - 8.6318)	**0.0346***
<30	18	33		
Smoking				
Yes	2	11	0.1799 (0.0180 - 0.9178)	**0.0306***
No	34	33		
Alcohol				
Yes	10	17	0.6146 (0.2094 - 1.7340)	0.3490
No	26	27		
Coffee				
Yes	30	41	0.3705 (0.0555 - 1.9015)	0.2861
No	6	3		
Comorbidities				
Yes	31	34	1.8102 (0.4962 - 7.5295)	0.3942
No	5	10		
Past surgery				
Yes	9	5	2.5685 (0.6830 - 10.8958)	0.1432
No	27	39		
History of upper limb trauma				
Yes	3	6	0.5796 (0.0870 - 2.9730)	0.5035
No	33	38		
Diabetes mellitus				
Yes	4	6	0.7940 (0.1510 - 3.6900)	1
No	32	38		
Thyroid diseases				
Yes	7	8	1.0851 (0.2964 - 3.8888)	1
No	29	36		
Venous system disease				
Yes	9	7	1.7493 (0.5071 - 6.2896)	0.4023
No	27	37		
Hypertension				
Yes	15	13	1.6918 (0.6101 - 4.7686)	0.3466
No	21	31		
Cardiovascular disease				
Yes	4	4	1.2465 (0.2143 - 7.2527)	1
No	32	40		
Osteoarticular disease				
Yes	9	12	0.8902 (0.2840 - 2.7115)	1
No	27	32		
Dyslipidemia				
Yes	2	4	0.5920 (0.0506 - 4.4252)	0.6853
No	34	40		
NOTES: *$p < 0.05$				

Table 6. Demographic and past history characteristics of patients. Univariate analysis: contingency tables, odds ratios, 95% confidence intervals and p-values for discrete variables.

Variable	No. Cases	No. Non-cases	OR (95% CI)	P -value
Histologic type				
Ductal	30	39	0.6446 (0.1410 - 2.8078)	0.5306
Lobular	6	5		
TNM Stage				
Advanced	19	13	2.6312 (0.9657 - 7.4196)	**0.0416***
Early	17	31		
Type of breast surgery				
Mastectomy	11	4	4.3172 (1.1237 - 20.6694)	**0.0207***
Quadrantectomy	25	40		
Surgery in the dominant side				
Yes	21	25	1.0632 (0.3984 - 2.8570)	1
No	15	19		
No. of excised lymph nodes				
≥20	18	11	2.9568 (1.0582 - 8.6318)	**0.0346***
1 - 19	18	33		
No. of positive lymph nodes				
≥4	16	14	1.7026 (0.6239 - 4.7208)	0.2579
1 - 3	20	30		
Radiation therapy				
Yes	29	42	0.2012 (0.0191 - 1.1575)	0.0708
No	7	2		
Chemotherapy				
Yes	27	28	1.7028 (0.5882 - 5.1790)	0.3362
No	9	16		
Hormone therapy				
Yes	28	35	0.9012 (0.2685 - 3.0701)	1
No	8	9		
Immunotherapy				
Yes	3	6	0.5796 (0.0870 - 2.9730)	0.5035
No	33	38		
NOTES: *p < 0.05				

Table 7. Clinical and pathological characteristics of patients. Contingency tables, odds ratios, 95% confidence intervals and p-values for discrete variables.

Variable	β	SE (β)	P -value	OR
BMI	0.9399	0.5351	0.0790	2.5597
Smoking	-1.5162	0.8692	0.0811	0.2196
TNM Stage	0.5458	0.5383	0.3107	1.7259
Type of breast surgery	1.3686	0.6876	**0.0465***	3.9299
No. of excised lymph nodes	0.0888	0.0441	**0.0442***	1.0929
Intercept	-2.3750	0.8594	**0.0057***	
-2Log Likelihood	88.7866			
AIC	100.7866			
NOTES: *p < 0.05				

Table 8. Multivariate analysis of significant risk factors associated with lymphedema.

Pat. (No.)	Age	ISL Stage	ISL Severity (%)	Affected limb	Preop volume of affected limb (mL)	Preop volume of healthy limb (mL)	Postop volume of affected limb (mL)	Postop volume of healthy limb (mL)	Preop volume excess (mL)	Postop volume excess (mL)	% of postop reduction of volume excess (compared to contralateral side)[1]	Maximum preop circumference difference[2] (cm)	Postop circumference difference[3] (cm)	Postop reduction of maximum preop circumference difference	Type of surgery	Follow-up (months)	Postop complications
1	65	Late II	Moderate (24%)	Right	2494.6	2007.4	2128.1	2079.6	487.2	48.5	90%	5	1	4	CL	12	None
2	51	Early II	Moderate (21%)	Left	2110.9	1741.8	1751.8	1585.8	369.1	166.0	55%	3.5	2	1.5	LVA	12	None
3	56	Late II	Mild (8%)	Left	2957.6	2743.2	2778.0	2750.1	214.4	27.9	87%	3.5	0	3.5	CL	12	None
4	43	Early II	Mild (16%)	Right	2292.3	1976.4	2107.5	1952.7	315.9	154.8	51%	3	1.8	1.2	LVA	12	None
5	62	Early II	Mild	Left	3223.1	2948.3	3087.9	2961.5	274.8	126.4	54%	3	1.3	1.7	LVA	12	None
6	51	Late II	Moderate (28%)	Right	3171.2	2469.5	2528.4	2451.2	701.7	77.2	89%	6	2.4	3.6	CL	12	None

Table 9. Lymphedema patients' characteristics, surgical treatment details and postoperative results. [1][(Preoperative volume excess – Postoperative volume excess)/Preoperative volume excess]*100; [2] Measured at any level; [3] Measured at the same level taken in the preoperative phase.

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SCIENTIFIC PRODUCTS

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