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# Lymphatic venous anastomosis (LVA) for treatment of secondary arm lymphedema. A prospective study of 11 LVA procedures in 10 patients with breast cancer related lymphedema and a critical review of the literature

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**Abstract** *Objective* The incidence of breast cancer related lymphedema (BCRL) varies between 7–35% depending on the combination of treatment modalities. Early detection of BCRL is crucial in order to start an effective non-operative treatment program. Because of the lack of prospective research on this topic, this study was undertaken to prospectively determine the effect of Lympho Venous Anastomosis (LVA) on BCRL and to review the current literature. *Study design and methods* Ten patients who were previously treated for breast cancer by surgery, radiotherapy, and chemotherapy, and were unresponsive to 12-weeks of non-operative treatment, underwent an LVA procedure (Degni-Cordeiro). Objective measurements were gathered for circumferential measurement and water volumetry, and quality of life. Various types of lymphoscintigraphy were carried out pre-operatively and post-operatively at 3 and 12 months. Treatment was embedded in a multidisciplinary setting. *Results* Post-operative volume measurements initially showed a 4.8% reduction of lymphedema at 3 months

and a 2% reduction after one year. Various scintigraphic parameters showed some improvement. Quality of life questionnaires reported minimal improvement. Reviewing the literature, only retrospective studies were found; these reported varying results for LVA procedures. The selection of patients, classification of lymphedema, indications and types of LVA, and additional therapeutic options were heterogeneous, not comparable, and lacked a validated method of effect-assessment. *Conclusions* Our results showed a minimal reduction in volume of lymphedema following LVA; in the literature, there was no convincing evidence of the success of LVA. Non-operative treatment and elastic stockings are still preferred by most patients with lymphedema, especially in early stages with few irreversible changes.

**Keywords** Lympho-venous anastomosis (LVA) · Microsurgery · Evidence-based medicine · Lymphoscintigraphy · Inverse water volumetry · Review · Breast cancer related lymphedema

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## Introduction

Lymphedema is a chronic disease caused by impairment of the lymphatic transport capacity, resulting in edema, excess of tissue proteins, and in latter stages, inflammation and irreversible changes such as fibrosis and excess of adipose tissue [1]. Lymph transport impairment and clinical signs of lymphedema can be acquired (secondary) or congenital (primary). Treatment of lymphedema is challenging. Therapeutic approaches consist of both non-operative and operative methods. The overwhelming majority of patients can effectively be treated by non-operative means such as complex decongestive therapy (CDT) in combination with

manual lymphatic drainage, bandaging, physical exercises, skin care and elastic stockings. In the long lasting maintenance phase, therapeutic elastic stockings are mandatory. The goal of all non-operative treatment modalities is to reduce capillary filtration, improve drainage of interstitial fluid and macromolecules, and therefore reduce swelling, inflammation, recurrence of erysipelas, and improve quality of life [2]. Operative treatment is only indicated in a few cases as a last resort.

Many reconstructive techniques have been described, such as lymphovenous anastomosis (LVA) [3], lymphovenous-lymphatic (LVL) transplant (especially in the presence of venous hypertension [4]), and forms of lymph vessel transplantation [5]. LVA has been the most frequently used type of operation.

So far, most studies on LVA have both demonstrated a lack of significant volume reduction and considerable heterogeneity in the study populations. Therefore, we decided to evaluate the effectiveness of LVA in the treatment of one-sided breast cancer related lymphedema in a limited prospective study using objective, validated measurement methods with very strict inclusion criteria. These results will be discussed along with a review of the literature.

## Patients, materials and methods

### Study design and population

The study was conducted in the Lymphedema Department of Nij Smellinghe Hospital in Drachten, The Netherlands, from 1999 to 2002. A systematic review of English and German language literature retrieved from MEDLINE, COCHRANE and Cinahl databases up to April 2007 was performed. The articles were classified in levels of scientific evidence according the criteria for evidence-based medicine.

The study population consisted of 10 BCRL patients with severe lymphedema and persistent complaints, not responsive to maximal non-operative lymphedema treatment and who met the inclusion criteria for operative treatment. The patients were hospitalized in the lymphedema clinic to undergo a LVA according to our protocol.

### Inclusion and exclusion criteria

In order to be included in this prospective study, patients with unilateral breast cancer related lymphedema had to meet the following criteria:

- No volume reduction after 3 months of complex decongestive treatment including manual lymph

drainage, compression therapy, and physiotherapy, with persistent complaints such as heaviness, pain, shoulder function impairment, and recurrent attacks of erysipelas

- Persistent volume excess of more than 800cc measured by inverse water volumetry
- Proven scintigraphic signs of obstruction by absence of liver uptake and highly pathological transport index
- No recurrent malignancy
- Good patient compliance and willingness to wear therapeutic elastic stockings
- Operability.

### Data collection and lymphoscintigraphy

All patients underwent objective measurements with validated methods. The quality of life was measured pre-operatively and 6 months postoperatively using the validated SF-36 quality of life assessment questionnaire [6]. Volume measurements were performed prior to LVA and at 3, 6, 12, and 24 months after LVA. Volumetry was performed with the inverse water volumetry method (gold standard) [7]. Furthermore, indirect circumferential measurements were taken according the Herpertz method [8] for unilateral swelling, correlating the difference between the lymphedemic limb and the normal one.

The following clinical classification [9] (Campisi) was used:

Stage 1a: no edema, in spite of the presence of lymphatic circulation anomalies (e.g. due to mastectomy and axillary/inguinal lymphadenectomy; no difference in volume and consistency between limbs).

Stage 1b: same as stage 1a with mild edema, returning to normal after night rest.

Stage 2: permanent edema, spontaneously regressing only with antideclivous position and night rest

Stage 3: permanent edema, not spontaneously regressing with antideclivous position, and ingravescens (erysipelas/cellulitis)

Stage 4: fibrolymphedema (initial lymphostatic verrucosis) with “column” limb

Stage 5: elephantiasis with severe limb deformation (including sclero-indurative pachydermitis and lymphostatic verrucosis)

### Scintigraphic protocol

Unilateral lymphoscintigraphy was performed with focus on the liver uptake. On the anterior and posterior images,

counts were determined in the liver and in the total field of view respectively. Subsequently, geometric means were calculated for the liver and the total field of view. The liver fraction was calculated. In cases of very early detection of liver uptake, the possibility exists for technical failure resulting from unintentional intravenous injection of radioactive tracer: the fast venous transport causes the tracer to show up in the liver very early. In the case of correct subcutaneous administration of the radioactive tracer, the liver can be visualized after some time through uptake via blood vessels. The radioactive tracer reaches the blood stream either via the thoracic duct or, in the case of a functioning lymphatic venous anastomosis, via this shunt. We defined any uptake at 120 and 180 minutes as sign of lymphatic drainage from the arm, which was preoperatively absent. Results were analyzed preoperatively and one year postoperatively.

In unilateral lymphoscintigraphy,  $^{99m}\text{Tc}$ -Nanocolloid was administered subcutaneously in the second interdigital space of the edematous arm. A dose of 80 MBq and a volume of 0.1 ml were used. Mobilization was standardized by asking the patient to make a fist repetitively during a fixed period of time. During the first 40 min following the injection, dynamic images were taken, including the entire arm, the axilla and the liver. Then images were made 60, 120, and 180 min after the injection.

The images were interpreted in three ways: visual (qualitative) interpretation, semi-quantitative interpretation using the Transport Index, and quantitative interpretation through calculation of the liver fraction after 60, 120, and 180 min.

In clinical practice, visual interpretation is the method most often used, as it is easy to perform; however, small differences between pre and postoperative studies may be difficult to recognize.

Kleinhans et al. have described the Transport Index [10]. In this index, five parameters describe the lymph flow: lymphatic transport kinetics (K), distribution pattern (D), time lapse to appearance of lymph nodes (T in minutes, multiplied by 0.04), assessment of lymph nodes (N), and assessment of lymph vessels (V). Each parameter can be given a score from 0 to 9, where 0 means that there are no abnormalities and 9 indicates that the condition for a given parameter could not be worse. The five scores are then added, resulting in the Transport Index, which can vary from 0 (normal) to 45 (most abnormal).

#### Operating technique

All LVA procedures were carried out under general anesthesia. A skin incision was made in the upper arm, about 7–10 cm above the elbow. No pneumatic tourniquet was

used for exsanguination. Intradermal and subcutaneous injections of Methylene Blue were used 1 to 2 cm distal to the skin incision lines to outline the lymphatic system. All operative procedures were carried out by an experienced micro-vascular surgeon (BvdL) using an operating microscope. After skin incision, careful dissection was performed to identify small-sized veins (1–3 mm in diameter). After identifying a suitable vein, and collecting lymphatics (including some lymphatic vessels), lymphatic capillaries were dissected in the surrounding area. The diameters of these lymphatic vessels were 0.3 mm or less. With micro instruments, end-to-side anastomoses were made according to the Degni-Cordeiro procedure [11] using 11–0 micro sutures; at least 3–4 anastomoses were made. Average completion time of the LVA procedure was about 60 min. Antibiotics were used perioperatively; the extremity was bandaged and elevated at night. Elastic stockings were continued permanently during the follow-up.

#### Results

A total of 11 LVA procedures in 10 female patients were included in our study in the period from 1998–2002. The mean age of the patients was 58.7 years ( $\Delta$  46–68). All patients had stage 3 breast cancer related lymphedema according to Campisi, and were treated with mastectomy, axillary lymph node dissection, radiotherapy, and chemotherapy. Lymphedema was present for a mean period of 5.3 years ( $\Delta$  3–14 years) before LVA. None of the patients had responded sufficiently to our standardized conservative treatment program over 3 months. After removal of any pitting component, no further volume reduction could be achieved.

#### Quality of life

After 6 months, 5 of 10 patients had subjective relief of their complaints according to the SF-36 questionnaire.

#### Volumetry (See also Table 1)

After 3 months, there was a slight but insignificant reduction of volume. After one year this reduction diminished to almost zero (Table 1). The preoperative volume difference between both arms was 988cc.

After one year, the mean volume difference was 1075cc ( $\Delta$ 500–1856).

The Herpertz circumferential measurement demonstrated improvement of 4.8% after one year. The initial

**Table 1** Summary of results

|   |  |
|---|--|
| Mean age ( $n = 10$ )                                   | 58.7 Years ( $\Delta$ 46–68)                                       |
| Duration of lymphedema                                  | 5.4 years ( $\Delta$ 3–14)   |
| Clinical classification by Campisi                      | Stage 3: $n = 10$  |
| <i>Inverse water volumetry</i>                          |  |
| Total volume pre OP                                     | 4253 cc ( $\Delta$ 2817–6456)                                      |
| Volume difference normal side pre OP                    | 988 ( $\Delta$ 532–1400)   |
| Volume difference normal side at 3 months               | 841 ( $\Delta$ 232–1256)   |
| Volume difference normal side at 6 months               | 994 ( $\Delta$ 500–1789)   |
| Volume difference normal side at 12 months              | 1075 ( $\Delta$ 500–1856)  |
| <i>Herpertz method at 0–12 months: (at four points)</i> |  |
| Mean Volume difference pre OP                           | 35.2% ( $\Delta$ 20–50%)   |
| Mean volume difference 12 months                        | 33.5% ( $\Delta$ 18–49%)   |
| <i>Visual signs lymphoscintigraphy</i>                  |  |
| Dermal back flow  | 10   |
| Lymph vessels   | 0  |
| Lymphnode in the elbow                                  | 1  |
| <i>Kleinhans transport index at 0–12 months</i>         |  |
| TI pre OP   | 43.0 ( $\Delta$ 28–45)   |
| TI post OP  | 42.2 ( $\Delta$ 30–43)   |
| Liver uptake at 0–12 months                             |  |
| LC pre OP (after 120 and 180 min)                       | 0  |
| LC post OP (after 120 and 180 min)                      | 0  |
| SF 36 questionnaire 0–6 months                          | Slight subjective improvement in 5 patients who felt less disabled |

volume reduction with water displacement of 16% at three months was lost after one year, when no more than 2% volume difference was observed.

#### Scintigraphy (see also Table 1)

According to the Kleinhans transport index, there was no significant difference in transport before and one year after the operation: 43.0 ( $\Delta$  28–45) versus 42.2 ( $\Delta$  30–43).

Qualitative scintigraphic observation demonstrated an absence of lymph transport, dermal backflow and few signs of any organized transport, comparable with longstanding lymph-obstruction. In one patient, a lymph node in the elbow was visualized. After one year, a quantitative scintigraphical evaluation demonstrated no liver uptake after LVA, as compared with an initial lymphoscintigraphy.

#### Long term follow-up

Beyond the initial study design, at long term follow up in 2007 (mean follow-up 8 years), 2 patients had stable lymphedema using elastic stockings, 3 patients had died of metastasis, 4 patients had complete volume reduction after circumferential suction-assisted lipectomy (Brörson method

[12]) and 1 patient was lost to follow up. The main characteristics and results of 10 patients are presented in Table 1.

#### Discussion

This prospective study clearly demonstrates that, although there was an initial period of relief of the subjective complaints in 5 of 10 patients, there were no significant improvements after LVA in our series of patients with chronic lymphedema; neither volume measurements nor scintigraphic measurements showed any effect.

When reviewing the literature of the last decades (see Table 2), there is a striking lack of prospective and comparative studies concerning the effect of LVA on chronic lymphedema. All studies reviewed initially used non-operative treatment by CDT for a period ranging from 3 days up to 6 months. Although this might create a bias when selecting patients for LVA, the alternative is that many patients would have unnecessary operative treatment with perhaps detrimental effects. Most patients with early stages 1–3 of lymphedema can be treated successfully with CDT [22, 23]. Moreover, in many studies information is missing about the follow-up protocol and many do not report whether or not elastic stockings are mandatory after an LVA procedure.

**Table 2** Literature on the effects of LVA

| First author      | Study                           | Method of volume measurement  | Lymphoscintigraphy | Intervention                    | N   | Additional treatment             | Follow up (month)        | Results   |
|-------------------|---------------------------------|---|--------------------|---------------------------------|---|----------------------------------|--------------------------|---|
| O'Brien [13]      | Retro SL<br>AVL<br>CTF<br>(0,1) | Volumetry<br>4 point measurement<br>all pre-treatment               | No                 | LVA (10 with reduction surg)    | 40; Follow-up in<br><i>n</i> = 35 32 arm/3<br>leg | No special care                  | 18.6                     | <i>N</i> = 21 32% ↓<br><i>N</i> = 14: 18% ↑   |
| Filipetti [14]    | Retro SL<br>A<br>CTF?           | Class 1: poor<br>Class 2: fair<br>Class 3: good                     | NM                 | LVA arm<br>Some with fasciotomy | 19  | NM                               | Total: 22<br>18 just LVA | 13/22: class 2/3<br>>50% ↓ ( <i>n</i> = 3)<br><50% ↓ ( <i>n</i> = 7)<br>0 ↑↓ ( <i>n</i> = 8)  |
| Van Cruchten [15] | Retro SL<br>A                   | Volume/circumference<br>Staging according to Anderson (AC)          | NM                 | LVA arms                        | 1400  | Some weeks garment               | 60                       | St 1: 81% ↓ <i>n</i> = 792<br>St 2: 69% ↓ <i>n</i> = 413<br>St 3: 57 ↓ <i>n</i> = 120<br>St 4: 31% ↓ <i>n</i> = 75<br>Campisi class: St 1:<br>100% ↓<br>St 2: 98% ↓<br>St 3: 63% ↓<br>St 4: 46% ↓<br>59.2 ± 29.5% ↓ |
| Campisi [16]      | Retro PL/SL<br>AVL<br>CTF(≈)    | Volumetry   | Yes                | LVA                             | 664 adults<br>48 children                         | Elastic stockings                | 60                       | Campisi class: St 1:<br>100% ↓<br>St 2: 98% ↓<br>St 3: 63% ↓<br>St 4: 46% ↓<br>59.2 ± 29.5% ↓   |
| Huang [17]        | Retro PL/SL<br>AVL<br>CTF(0)    | Volumetry   | NM                 | LVA (filariasis + erysipelas)   | 98 (PL/SL)<br>91 leg<br>7 arms                    | NM                               | 26                       | 59.2 ± 29.5% ↓  |
| Yamamoto [18]     | Retro PL/SL<br>AVL<br>CTF(≈)    | 4 point circumference   | NM                 | LV "implant"                    | 8<br>arm: 5<br>leg: 3                             | NM                               | 9–27                     | Wrist: 3–5 cm ↓<br>Underarm: 1–6 cm ↓ (no relative figures)   |
| Vignes [9]        | Pro PL/SL<br>L<br>CTF(≈)        | Volumetry, subjective criteria, visual analog scale (VAS)           | NM                 | LVA                             | 13<br>10 PL<br>3 SL                               | Elastic stockings                | 49–52                    | No volume ±<br>VAS: Bad: 3<br>Intermediate: 5<br>Very good/good: 5<br>82.5% effective ( <i>n</i> = 42)<br>17 from these:<br>>4 cm ↓ lower leg   |
| Koshima [19]      | Retro PL/SL<br>L<br>CTF(6)      | 2 measurements: 10 cm above/under knee staging according to Campisi | Non                | Lymphatico-venular anastomosis  | 52  | Elastic stockings                | 4–24                     | 82.5% effective ( <i>n</i> = 42)<br>17 from these:<br>>4 cm ↓ lower leg   |
| Matsubara [20]    | Retro SL<br>L<br>CTF<br>(1–130) | 2 point circumference   | NM                 | LVA                             | 11  | Elastic stockings +physiotherapy | 21–87                    | >5 cm ↓ ( <i>n</i> = 6)<br>2 cm ↓ ( <i>n</i> = 2)<br>No effect ( <i>n</i> = 3)  |

Table 2 continued

| First author | Study                           | Method of volume measurement  | Lymphoscintigraphy | Intervention   | N  | Additional treatment | Follow up (month)                                 | Results  |
|--------------|---------------------------------|---|--------------------|--|--|----------------------|---|--|
| Campisi [21] | Retro<br>PL/SL<br>A/L<br>CTF(6) | Volumetry<br>Clinical signs<br>Conservative treatment first<br>Staging according to Campisi       | Yes                | LVA arms and legs (arms: n = 231)<br>194 SL<br>37 PL<br>(legs: n = 612) 323 SL<br>289 PL | St 1: n = 25<br>St 2: n = 346<br>St 3: n = 413<br>St 4/5: n = 59 | NM                   | N = 126<br>(>15 years)<br>Total group:<br>N = 843 | Reduction = 126<br>St 1: 0<br>St 2: ≈15% ↓<br>St 3: ≈32% ↓<br>St 3: ≈35%<br>St 4/5: ≈30%<br>>75% (n = 616)<br>50–75% (n = 202)<br><25% (n = 25)<br>No scintigraphic change<br>TI: 2% ↑<br>Circumference: 4.8% ↓ 1 year<br>Volume: 16% ↓ 3 months/<br>9% ↓ after 1 year |
| Damstra      | Pro<br>SLA<br>CTF(3)            | Inverse volumetry<br>Circumference according to herpertz<br>SF-36<br>Staging according to Campisi | Yes + index (TI)   | LVA arms in stadium 3  | 10   | Elastic stockings    | 8 years   |  |

NM = Not mentioned; PL = Primary lymphedema; SL = Secondary lymphedema; Pro = Prospective study; Retro = Retrospective study; A = Arm lymphedema; L = Leg lymphedema; CTF = Conservative treatment first considered unsuccessful (months)

In order to compare treatment options, an adequate classification is necessary. According to stages 1 to 3, conservative treatment of lymphedema is sufficient in most patients [22, 23]. In stage 3 lymphedema, the pitting component can often be treated successfully; however the fibrosis and excess of adipose tissue will remain. Matsubara [20] studied LVA in 9 women with secondary lymphedema of the legs refractory to non-operative management. He obtained the best results when operative procedures were combined with continued postoperative physiotherapy.

In a recent personal communication, Campisi [24] suggested that from his point of view, LVA is most suitable in the early stages 1B, II and early III. No other postoperative therapeutic modalities such as elastic stockings, decongestive treatment or anti platelet clotting medication were mentioned. Campisi advised initial physical treatment for peripheral lymphedema. Additionally, in later stages (3, 4 and 5), in the absence of scintigraphical visualization of lymphatics, it is standard procedure to reduce the lymphedema by non-operative methods first, before considering microsurgery. According to Campisi LVA is further contra-indicated for lymphatic-lymphnodal aplasia and stage 5 lymphedema.

For these stages Brorson [12] described a promising method (circumferential suction-assisted lipectomy) that introduces reductive surgical therapy with good long-term results, demonstrating more than 100% volume reduction. Elastic stockings must be worn to maintain these excellent results. From this perspective, we used this method successfully in 4 of our 10 patients refractory to LVA.

From a pathophysiological perspective, the goal for LVA is to reduce interstitial volume by improving lymphatic drainage. To exemplify the results of LVA, we chose objective outcome parameters for improvement of lymphtransport capacity, volume changes and quality of life. Kleinhans et al. demonstrated the usefulness of the Transport Index to evaluate the results of lymphatic grafting [25–27].

In general, lymphoscintigraphy is performed bilaterally, offering objective evidence to distinguish (late stage) lymphatic pathology from non-lymphatic causes of extremity edema. Criteria for lymphatic dysfunction include delayed (>30 min), asymmetric, or absent visualization of regional lymph nodes, and the presence of “dermal backflow”. Additional findings include asymmetric visualization of lymphatic channels and collateral lymphatic channels. All of these parameters are correlated with a clinical diagnosis of lymphedema [28, 29]. Liver fraction scanning [30] is only of merit when the radionuclide is administered in the edematous extremity. Late uptake in the liver (after 3 h) is an indication of lymphatic transport out of the injected arm. The theoretical advantage

of using the liver fraction as an objective means to judge lymphovenous shunt efficacy is clear.

In the current study, we considered any uptake as a positive result. Therefore, we postulated, with an open and well functioning shunt, in due time the radionuclide would be transported from the arm via the shunt into the veins of the arm, followed by further transport to the reticulo-endothelial system, which is mainly located in the liver. A perceptible liver fraction on the postoperative images, when compared to the preoperative situation, thus should indicate an open, well functioning shunt. In this study we could not find any significant improvement in the objective parameters for volume change or liver uptake of  $^{99m}\text{Tc}$ -Nanocolloid. In the literature, convincing, validated, and objective methods for visualization of the effects of a LVA are missing.

## Conclusions

In this first prospective study on the LVA treatment of unilateral breast cancer related lymphedema, despite the limited number of patients, no effect could be measured using objective validated measurement methods. The effects of LVA in literature are also not proven; there is a lack of standardization of the patient population, and the measurement methods are not validated. Most studies are retrospective and often involve a mix of primary, secondary arm and leg lymphedema in the same study. On top of this, classification of lymphedema varies, and the indications and criteria for LVA are unclear. Therefore we conclude that, considering our results and the literature review, LVA is not effective for the treatment of unilateral breast cancer related lymphedema. Although the LVA has been performed and studied for more than 3 decades, this method still has not had a breakthrough and will never become a treatment of choice in daily practice.

Non-operative, decongestive treatment combined with the regular use of elastic stockings is the corner stone of treatment for most patients with lymphedema, especially in its early stages when it involves few irreversible changes; however, in later stages with more irreversible changes, LVA still does not effectively reduce volume.

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