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Combination of lymphovenous anastomosis and lymph node transfer for breast cancer-related lymphedema

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Abstract

With the remarkable advancement of microsurgery, surgical treatment for lymphedema has been increasing, and its good results are well established. However, surgical treatment for advanced-stage lymphedema is still a challenging task. We reviewed several methods of combining lymphovenous anastomosis (LVA) and vascularized lymph node transfer (VLNT) in breast cancer-related lymphedema (BCRL) patients. Representative VLNT flap options for BCRL patients include the omental flap, superficial circumflex iliac perforator (SCIP) flap, and deep inferior epigastric artery (DIEA) flap combined with inguinal lymph nodes performed simultaneously with breast reconstruction. The surgical outcome, technical details, and donor site morbidities of each surgical option were reviewed. While all three options show significant surgical benefits, each has its clear advantages and disadvantages. The decision on the surgical method may vary according to the needs of each patient and the clinical situation.

Keywords: Breast cancer, lymphedema, advanced stage BCRL, omental flap, DIEP flap, SCIP flap, lymphovenous anastomosis, vascularized lymph node transfer

INTRODUCTION

With the advancement of microsurgical and supermicrosurgical techniques, new surgical methods for breast cancer-related lymphedema (BCRL) have been introduced. Since the introduction of supermicrosurgery-based lymphovenous anastomosis (LVA) and microsurgery-based vascularized lymph node transfer (VLNT), surgeons worldwide have utilized these techniques with promising results[1-3].

Furthermore, new imaging modalities, including lymphoscintigraphy, indocyanine green (ICG) lymphography, high-frequency ultrasonography, and magnetic resonance (MR) lymphangiography, have been applied to the field of lymphedema, allowing more accurate and sensitive detection of lymphatic vessels and lymphatic fluid collection[4-7]. While LVA has previously been performed predominantly in early-stage lymphedema patients, based on these advanced images, the indications for LVA have been widened to include advanced lymphedema patients as well[8,9].

However, some researchers have postulated that LVA alone may not be effective in chronic lymphedema patients[10,11], particularly patients in the late 2 and 3 stages of The International Society of Lymphology (ISL) lymphedema stage. As previously shown in pathophysiological studies, chronic inflammation and lymphatic fluid stasis cause deterioration of the pumping mechanism of the lymphatic vessels along with programmed cell death of lymphatic endothelial cells[12]. Together, they cause tissue fibrosis and progressive pathological changes in the lymphatic lumen until the lymphatic vessel becomes sclerotic and nonfunctioning. In these cases, providing a bypass through LVA at the distal lymphatic system where there is insufficient lymphatic flow may not be effective in the long run.

In these advanced BCRL patients, providing healthy lymphatic vessels and lymph nodes (lymphatic complex) through VLNT has effectively reduced arm volume and improved the patient's quality of life[3,13,14]. Compared to lower extremity lymphedema patients, BCRL patients have the advantage of having an anatomical recipient candidate for lymph node transfer, the axilla. Therefore, in theory, utilizing both of these methods with very different fundamental mechanisms can maximize the outcome for these patients. More recently, the combination of LVA and VLNT has been introduced to combine the effects of these procedures in treating BCRL patients[15-17]. This paper will discuss our protocol and techniques for performing combined LVA and VLNT in BCRL patients.

FLAP OPTIONS, PATIENT SELECTION, AND OPERATIVE DETAILS

Decision-making of surgical methods in late-stage lymphedema

Aside from radical debulking procedures, there are three main options for advanced BCRL: LVA, VLNT, and suction-assisted lipectomy(SAL). While technical details and indications of each procedure vary between different surgical centers, selecting the most suitable surgical method or a combination of techniques to maximize the outcome and patient satisfaction is the common goal for all surgeons.

Our protocol for lymph node donor selection

At our institution, we primarily use three donor sites for VLNT: right gastroepiploic artery-based omental flap, deep inferior epigastric perforators (DIEP) flap with the superficial inferior epigastric artery (SIEA) or superficial circumflex iliac artery (SCIA) based lymph node flap, and superficial circumflex iliac artery perforator (SCIP) flap [Figure 1].

The donor selection depends mainly on two factors: the need for breast reconstruction and the contracture level of the axilla [Figure 2]. If the patient wants simultaneous breast reconstruction, the DIEP flap harvested with groin lymph node is our preferred choice. Patients who do not need or desire breast
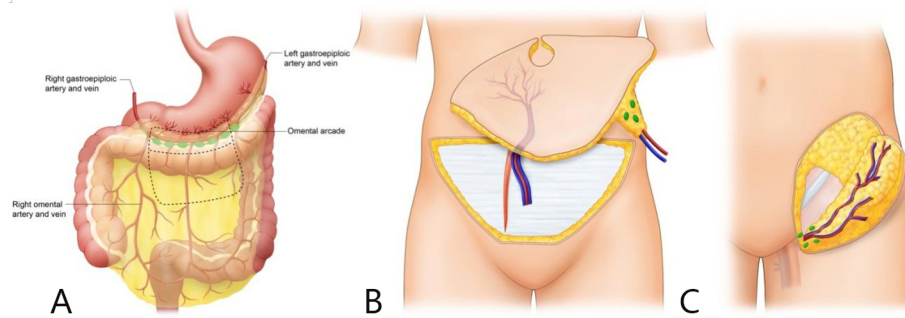
Figure 1. (A) omental lymph node flap based on the right gastroepiploic artery; (B) DIEP and SIEA or SCIA-based lymph node flap. Either contralateral or ipsilateral lymph nodes can be used; (C) SCIP flap. The lateral portion of the flap is elevated superficial to Scarpa's fascia, while the medial flap is elevated deeper to incorporate superficial inguinal lymph nodes. DIEP: deep inferior epigastric perforators; SIEA: superficial inferior epigastric artery; SCIA: superficial circumflex iliac artery; SCIP: superficial circumflex iliac perforator.
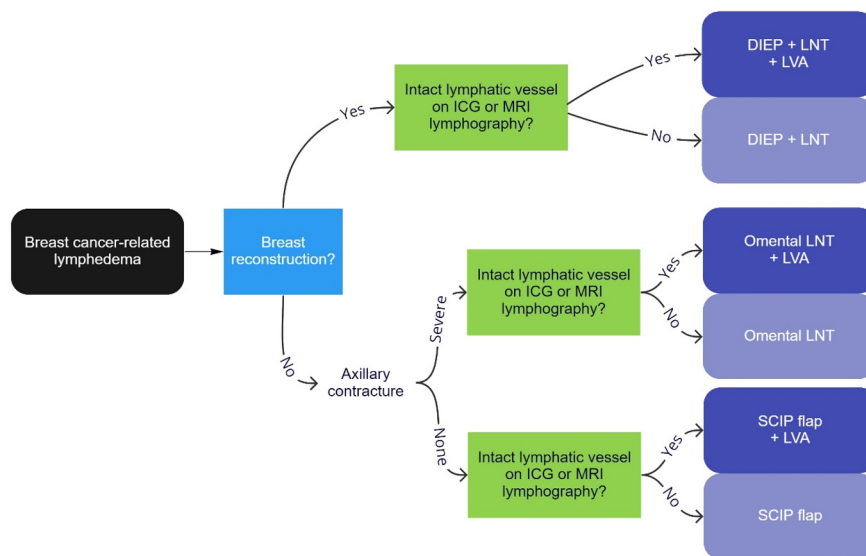
Figure 2. Flow chart of the operative plan decision-making. The flap selection depends on whether the patient needs breast reconstruction and whether the axilla is severely contracted or not. In addition, in patients with intact and functional lymphatic vessels on preoperative imaging, LVA is concurrently performed. ICG: indocyanine green; DIEP: deep inferior epigastric perforators; LNT: lymph node transfer; LVA: lymphovenous anastomosis; SCIP: superficial circumflex iliac perforator.

reconstruction can benefit from either the omental flap or the SCIP flap. In patients with severely scarred axilla, the soft tissue of the omental flap can provide the volume and cushion in the axilla. On the other hand, if no additional bulk is needed, the thin SCIP flap can deliver the benefits of lymph node transfer without altering the contour of the axilla or the limb. The lymph node flap is anastomosed to the thoracodorsal artery or a branch after the axilla's scar release. If intact and functional lymphatic vessels are identified on preoperative imaging, LVA is also performed at two to three sites, usually in the forearm region.

In all patients, ICG lymphography and MR lymphangiography are performed to identify intact and functional lymphatic vessels. In patients with lymphatic ducts suitable for LVA, LVA is performed. In patients undergoing breast reconstruction, CT angiography is performed to identify perforators, pedicle paths, and the location of supra-inguinal lymph nodes. In patients undergoing omental LNT, abdomen-pelvis CT is performed only if the patient has a history of abdominal operation. In patients undergoing SCIP flap, the use of ultrasound can help in the identification of SCIA and nearby lymph nodes.

These three donor sites are primarily used due to minimal donor-site complications and reduced operation time. Other studies have proposed that LVA and VLNT be performed in a staged or staggered fashion due to the long operation time. However, the aforementioned donor sites allow lymph node harvest to be performed simultaneously with LVA since the operative fields do not overlap[18]. As a result, the addition of LVA does not significantly elongate the operation time compared to VLNT alone.

Omental flap
The omental flap's biggest advantage is the low possibility of iatrogenic lymphedema. Compared to supraclavicular, submental, or groin flaps that can cause iatrogenic lymphedema or chyle leak, iatrogenic lymphedema has not been reported after the omental flap harvest[19]. However, some disadvantages are the need for intra-abdominal surgery, its associated complications, and possibly conspicuous abdominal scars. Additionally, harvesting lymph nodes in a relatively unfamiliar area can be a hurdle for plastic surgeons. At our institution, we overcome these pitfalls by cooperating with general surgeons specializing in laparoscopic gastrointestinal surgery. After harvesting the flap through a single port in the umbilicus, the flap is inset in the scar-released axilla [Figure 3].

Another benefit of the omental flap is its abundance of lymph nodes. Along the omental arcade, numerous lymph nodes exist. In their cadaveric study of ten adults without gastric disease, Borchard *et al.* reported an average of 14.9 ± 14.1 lymph nodes along the greater curvature[20]. This contrasts with 6.2 ± 1.3 lymph nodes found in 10 × 5 cm groin flaps in another cadaveric study by Cheng *et al.*[21].

Combined breast reconstruction with DIEP and lymph node transfer
Early reports have shown the benefit of immediate breast reconstruction in reducing the occurrence of BCRL[22]. However, the lymphedema-reducing benefit of autologous tissue-based breast reconstruction without concurrent lymph node transfer has been debated[22-24]. On the other hand, simultaneous VLNT and breast reconstruction have shown promising results[25-28].

Therefore, in BCRL patients seeking delayed breast reconstruction, combined breast reconstruction using DIEP flap and SIEA-based lymph node flap can be an excellent option to restore the breast and improve BCRL symptoms.

Similar to omental harvest, LVA can be performed in the arm while DIEP and lymph node flap is harvested in the abdomen to reduce operation time. While DIEA is used as the feeding vessel for the perforator flap, SCIA is used as the feeding vessel for the groin lymph nodes. DIEA is anastomosed to the internal mammary artery (IMA), and SIEA/SCIA is anastomosed to the thoracodorsal artery. SCIA and the lymph node can be harvested either ipsilateral or contralateral to the DIEA[29]. In our experience, using the contralateral SIEA minimizes kinking of the DIEA pedicle. If the inset proves difficult, the SIEA/SCIA-based lymph node can be separated from the DIEP flap for easier anastomosis and inset.

SCIP flap
In patients who do not want delayed breast reconstruction and are at increased risk of complications from abdominal surgery (e.g., previous surgery, peritonitis, *etc.*), SCIA-based VLNT flap is another possible option. The main advantages of SCIP flap are inconspicuous scar, well-known anatomy of the vasculature and the lymphatic drainage, and the ability to provide a large skin paddle when needed[30].

SCIP flap has limited donor site morbidity and is a familiar free flap for most microsurgeons. One major disadvantage of the SCIP flap is the possibility of iatrogenic lymphedema, which will be discussed in the
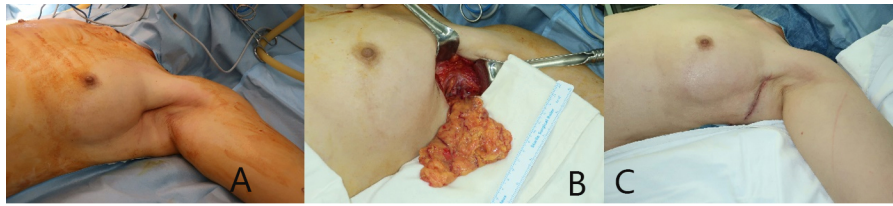
Figure 3. (A) Left BCRL patient with severe contracture of the axilla; (B) Omental lymph node flap after anastomosis to a branch of the thoracodorsal artery. In severely scarred axilla, extra omental tissue is harvested as shown and inset into the axilla; (C) Postoperative axilla. BCRL: breast cancer-related lymphedema.

next section.

To incorporate only the superficial groin lymph nodes and to minimize the bulkiness of the flap, we start the lateral elevation of the flap superficial to Scarpa's fascia. As the dissection approaches the femoral vessels, dissection continues deep to the Scarpa's fascia to harvest the lymph nodes superficial to the femoral vessels. Reverse lymphatic mapping using Technetium (deep lymph nodes) and ICG (superficial lymph nodes) is performed to accurately identify the superficial lymph nodes to be incorporated into the flap [Figure 4][30]. These nodes are usually located "within a 3 cm radius of a point 3cm inferior and perpendicular to a point 1/3 the distance from the pubic tubercle to the anterior superior iliac spine"[30].

Donor site morbidity
As with all operations, combined LVA and VLNT have their risks. While complications associated with LVA are minor and easily manageable, donor site morbidity after VLNT can perplex the patients and the surgeons. The potential morbidities of each of the mentioned donors are as follows.

Omental flap
Omental flap harvest can be performed through a conventional laparotomy, multiport laparoscopic approach, a single port approach, or a robotic approach[31,32]. In a retrospective comparative study of 177 patients, gastroepiploic lymph node flap harvest was performed through laparoscopic (126) or open approach (51)[33]. In the laparoscopic approach group, there was 1 case of acute pancreatitis and 2 cases of ileus. Complication rates were higher in the open approach group with 3 cases of ileus, 1 case of small bowel obstruction, 2 superficial surgical site infection, and 1 wound dehiscence. Furthermore, postoperative pain was significantly less in the laparoscopic, with the additional benefit of a shorter hospital stay. At our institution, the omental flap is harvested through a multiport laparoscopic or single-port laparoscopic approach to minimize complications, decrease scarring, and improve patient recovery [Figure 5].

SIEA or SCIA-based lymph node flaps
A possible detrimental complication in harvesting groin lymph nodes is iatrogenic lymphedema of the lower limb. To reduce the risk, reverse lymphatic mapping using Technetium and ICG is necessary[30]. Groin lymph nodes are composed of deep and superficial nodes, where the deep nodes manage the lymphatic flow from the leg. The flap must be elevated to incorporate the superficial node while preserving the deep nodes [Figure 4]. Several studies have reported such complications[34]. While rare, it is very difficult to manage and should be avoided at all costs through careful dissection and reverse lymphatic mapping.

**OUTCOMES**
Proper postoperative management is crucial in maximizing the benefits while reducing complications of these operations. In all patients undergoing LVA, a compression garment is applied immediately after the
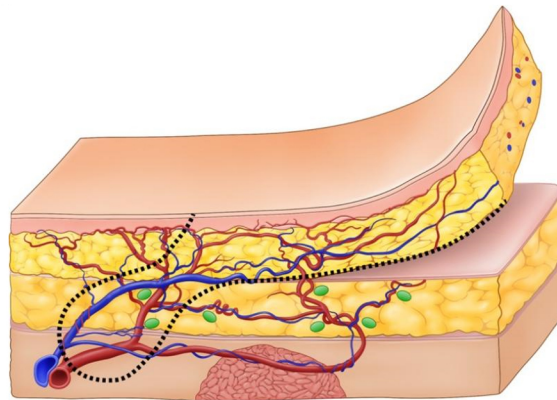
Figure 4. Superficial lymph nodes should be accurately harvested with thin flap elevation in order to minimize iatrogenic lymphedema risk.
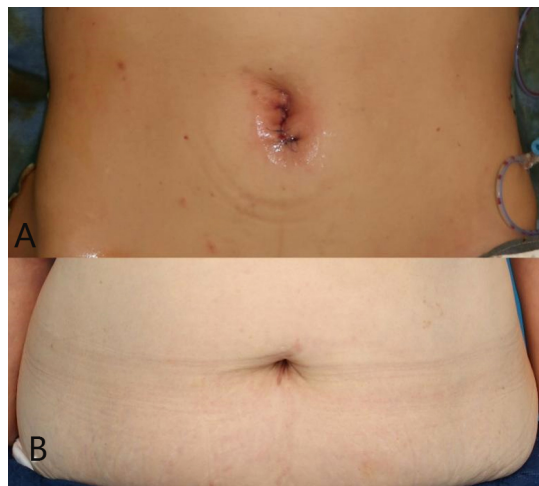
Figure 5. (A) Immediate postoperative photograph of the umbilicus after single-port laparoscopic harvest of the omental flap; (B) 12-month photograph of the umbilicus.

operation to maintain the positive pressure gradient from the lymphatic duct to the anastomosed vein. In patients undergoing breast reconstruction with DIEP and LNT, the patient is encouraged to maintain absolute bed rest for three days. After this period, the patient is allowed for light mobilization to minimize the potential of anastomosis-related complications. In patients undergoing omental LNT, the patient is closely monitored for any abdominal discomfort and pain with daily abdomen x-rays. In patients undergoing SCIP flaps, the routine postoperative free-flap protocol involves minimal ward ambulation, intravenous Prostaglandin E1 injection, and a low-residue diet for three days.

Di Taranto *et al.* reported a significant reduction in lower limb circumference and tonicity in both VLNT and VLNT and LVA groups at 1-year follow-up[15]. However, there was no significant difference between the two groups, possibly due to the short follow-up. Garza *et al.* also reported similar improvements in volume and quality of life as reported by the Lymphedema Life Impact Scale (LLIS)[17]. Their long-term study on both upper and lower extremities analyzed limb volume changes for combined VLNT and LVA procedures.

Interestingly, limb volume change showed V-shaped improvements where the volume reduction effect diminished during postoperative six months through 12 months and then improved dramatically at 24 months follow-up. This can be explained by the initial benefit of LVA immediately postoperatively due to the diversion of the excess lymphatic fluid through the bypass. The effects of VLNT were evident at 24 months of follow-up after sufficient lymphangiogenesis.

It is important to note that both limb volume reduction and LLIS scores were best at 2~3-year follow-ups, even more so than at 3-month postoperative follow-ups, where the benefit of LVA would be in effect. This study provides evidence that combined LVA and VLNT may provide better outcomes than each operation on its own.

DISCUSSION

While the exact mechanism behind the synergistic effects of LVA and VLNT has not been elucidated, several possible explanations exist. First, the initial volume reduction induced by LVA can improve patient compliance. In a study by Yang *et al.*, liposuction allows chronic patients to apply compression garments more easily, improving patients' compliance with complete decongestive therapy[35].

Secondly, LVA's physiological changes can improve the effectiveness of VLNT. Histological evidence shows decreased hyperkeratosis, local inflammation, and dermal fibrosis[36]. As Rustad and Chang pointed out, LVA can reduce local tissue inflammation and promote better lymphangiogenesis from the VLNT[37].

Di Taranto *et al.* previously compared VLNT alone with LVA and VLNT in patients with secondary lower limb lymphedemas[15]. In all the patients, suction-assisted lipectomy (SAL) was also performed two weeks after the initial lymphedema operation. Both groups showed a significant reduction in limb volume and skin tonicity. Although not statistically significant due to the small sample size (*P*-value of 0.08), the addition of LVA showed greater volume reduction above the knee.

In their preliminary report of 12 patients who underwent simultaneous supraclavicular VLNT and LVA for lower limb lymphedemas, Chung *et al.* showed a significant reduction in both mean limb circumferences and lower extremity lymphedema index[38]. These findings can also be applied to BCRL patients.

Most BCRL patients have undergone axillary lymph node dissection, which causes fibrosis of the axilla. Postmastectomy radiotherapy (PMRT) can further aggravate this fibrosis. In addition to worsening lymphedema by constricting the drainage[39], fibrosis can cause neurologic symptoms such as tingling sensations and neuropathic pain for the patients. While its definitive effect is still debated, releasing the scar tissue and providing new fresh tissue (VLNT) can provide physiological benefits[11,17,40].

Furthermore, LVA and VLNT have different mechanisms for improving lymphedema. LVA forms a shunt between a functioning lymphatic vessel and a vein, allowing drainage of lymphatic fluid into the venous system[41]. On the other hand, VLNT's mechanism is thought to be multifactorial. VLNT acts as a "pump" for lymphatic fluid from the limb to drain through the VLNT after lymphangiogenesis occurs into the surrounding tissue[42]. Because of the difference in the underlying mechanism, LVA's effect is evident almost immediately after the operation, while VLNT shows a delayed effect after successful lymphangiogenesis into the surrounding tissue. By combining these two techniques, synergistic benefits can be gained while overcoming one of the drawbacks of VLNT, the absence of immediate effect, which can deter patient compliance.

Another question to consider is the future roles of old debulking surgeries, such as the Charles procedure, in more advanced BCRL patients. As mentioned previously, performing SAL in conjunction with other methods, such as LVA and VLNT, can improve patient compliance by reducing the volume immediately after the operation[16]. Reducing the volume can ease the elastic stocking application process and motivate patients to comply with CDT. While radical procedures have been considered the last resort for severe cases, they may also be performed in combination with LVA and VLNT either simultaneously or in stages as technology and techniques advance.

As emphasized in this study, patients may have different clinical situations when considering LVA combined with VLNTs for patients in advanced BCRL. Patients may or may not want breast reconstruction, and each patient's degree of axillary fibrosis and contracture can differ. In addition, the availability of laparoscopic or robotic surgery for omental flap harvest in the institution performing the surgery may vary. Considering these various clinical situations, the optimal surgical method should consider the patient's lymphedema pattern, severity, and clinical needs.

CONCLUSION

A further randomized clinical trial is needed to compare the benefits and disadvantages of combined procedures. However, if combined procedures can be performed without increasing overall operation time and complication rates, current evidence does not seem to direct the surgeons away from these combined procedures.

DECLARATIONS

Authors' contributions
Made substantial contributions to the conception and design of the study and performed data analysis and interpretation: Park Jh, Myung Y

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Not applicable.

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Conflicts of interest
All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate
Not applicable. Informed consent was obtained from the patients involved in this manuscript.

Consent for publication
Written informed consent for the publication of the images has been obtained.

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