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# Dual Fluorescent Tracers for Surgical Guidance: Preventing Donor-site Lymphedema in Vascularized Lymph Node Transfer

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**Introduction:** Vascularized lymph node transfer (VLNT) restores physiological lymphatic function. Although effective, postoperative impairment of donor-site lymphatic function and iatrogenic lymphedema following lymph node transfer remains a pressing concern.

**Methods:** Prospective analysis of VLNT patients undergoing dual fluorescent tracers-assisted harvest was performed at our institution from September 2013 to April 2022. Reverse lymphatic mapping of the lower extremity was performed with indocyanine green (ICG). Blue dye was utilized in both white light and near-infrared spectra for visualization of donor-site lymphatic structures. Demographics, intraoperative details, and surgical outcomes were recorded.

**Results:** Twenty-five patients were included. Median age was 52.9 years with a body mass index of 29.1 kg/m$^2$ and mean follow-up of 44 months (range 24 to 90 months). Lymphedema stage ranged from Campisi 2 to 4. Inguinal VLNT was performed in 13 patients, and 12 patients received combined VLNT and free flap breast reconstruction. No patients required change in lymph node donor site intraoperatively. All ICG stained nodes were preserved in situ. No cases of iatrogenic lower extremity lymphedema were observed. Postoperative bioimpedance spectroscopy, circumferential, and volumetric measurements of the donor-site limb did not show evidence of subclinical or clinical lymphedema. The donor site healed appropriately in 92% of patients; one patient developed methylene blue-induced skin necrosis.

**Conclusion:** Reverse lymphatic mapping and surgical guidance with dual ICG and blue dye fluorescent tracers provides surgeons with real-time surgical guidance without radioisotope, improves surgical visualization in both white light and near-infrared spectra, and avoids iatrogenic lymphatic dysfunction in the donor limb.
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## INTRODUCTION

Lymphedema is a chronic, debilitating condition that may arise from the disruption of lymphatic channels due to radiation, trauma, or idiopathic causes. Although conservative therapies are considered the mainstay methods of treatment, there is currently no cure, with many patients affected by lifelong progression of the disease.[1,2] This has prompted advances in surgical approaches to treat lymphedema. Vascularized lymph node transfer (VLNT) involves microvascular transplantation of functional lymph nodes to restore physiological lymphatic function. Although effective, studies have reported impaired donor-site lymphatic function postoperatively and iatrogenic lymphedema following lymph node transfer from the groin.[3–6] Moreover, variations in harvest technique of vascularized groin lymph node transfer and anatomical lymphatic drainage pattern further complicate donor-site lymphatic function.[7]

To address this, Thompson et al[8] reported that preserving axillary reverse mapping nodes during axillary lymph

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node dissection could reduce the incidence of postoperative upper extremity lymphedema. Dayan et al[9] further applied this concept to vascularized lymph node flap harvest and proposed further modification by using a dual-tracer approach to visualize lymphatic drainage pathways from individual anatomic regions. Classically, radioisotope is injected into the distal extremity and blue dye is injected in the trunk at the region corresponding with a potential lymph node harvest site. Blue lymph nodes are selected for removal and transplantation, whereas those that are emitting radioactivity are avoided. More recently, Aliotta and Schwarz[10] were the first to replace radioisotope with the fluorescent tracer indocyanine green dye (ICG) in VLNT, as it provides a safe and cost-effective radioisotope-free technique with similar accuracy to technetium-99 isotope scanning.

The combination of fluorescent-guided surgery with high sensitivity near-infrared (NIR) imaging has allowed advances in immediate visualization of lymphatic anatomy and flow without special material handling.[11] Previous studies have demonstrated its advantages in the visualization of lymphatic channels in axillary sentinel lymph node biopsy and axillary reverse mapping in breast cancer.[11–14] Furthermore, the combination of ICG with other fluorescent tracers has shown promising results for greater differentiation and selection of lymph nodes in axillary reverse mapping.[15] However, no studies have yet investigated the benefits or donor-site outcomes of dual fluorescent tracer reverse lymphatic mapping in patients receiving VLNT surgery.

Here, we propose a lymphographic method to allow for more precise visualization and differentiation of lymphatic channels using dual fluorescence reverse lymphatic mapping. Our aim is to evaluate this approach and its ability to allow for more robust differentiation and visualization of lymphatic drainage pathways. This refinement of reverse lymphatic mapping allows for highly selective incorporation of lymphatic tissue within the lymph node flap, thereby improving postoperative outcomes and reducing iatrogenic donor-site–related lymphedema.

## METHODS

Analysis of a prospective database of patients undergoing lymphatic reconstruction at our institution was conducted from September 2013 to December 2021. Only VLNT patients who had undergone radioisotope-free dual fluorescent tracers-assisted harvest were included. All procedures were performed by the senior author. Patient demographics, intraoperative characteristics, postoperative outcomes, complications, and follow-up were recorded. Reverse lymphatic mapping of the lower extremity was performed with ICG ($\lambda_{ex}$ = 808 nm, $\lambda_{em}$ = 822 nm). Blue dye, methylene blue or isosulfan blue ($\lambda_{ex}$ = 665 nm, $\lambda_{em}$ = 686 nm), was utilized for visualization and localization of donor-site lymphatic structures. In this study, blue dye was used as both a tracer visible under white light conditions and as a fluorophore excited in the NIR spectrum. ICG angiography was also used to assess for flap and lymph node perfusion. Postoperative lymphedema was defined by patient reported subjective symptoms, physical examination, circumferential leg measurements, or abnormal bioimpedance measurements as defined by a lymphedema index (L-Dex) value greater than 10 or less than −10.

### Takeaways

**Question**: Can blue dye fluorescence enhance surgical visualization and minimize donor-site morbidity during-vascularized lymph node transfer (VLNT) harvest when used in conjunction with indocyanine green (ICG) for reverse lymphatic mapping?

**Findings:** Prospective analysis of 25 patients undergoing groin-based VLNT with reverse lymphatic mapping using blue dye and ICG resulted in no cases of postoperative lymphedema and a 92% donor-site healing rate.

**Meaning**: Immediate visualization and differentiation of lymphatic structures is enhanced with reverse lymphatic mapping using ICG and blue dye fluorescent tracers in the near-infrared and white light spectra. Safety is further optimized without the need for radioisotopes.

## TECHNIQUE

Patients with breast cancer–related lymphedema underwent groin VLNT based on the superficial circumflex iliac artery. In patients requiring breast reconstruction, VLNT was performed in conjunction with deep inferior epigastric perforator (DIEP) or muscle sparing transverse rectus abdominis myocutaneous microsurgical free flaps (Fig. 1).

### Reverse Lymphatic Mapping of the Donor Site

Preoperatively, four 0.5 mL aliquots of blue dye were injected adjacent to the lymph node basin into the lower abdominal wall. Blue dye was used at the primary nodal donor site instead of ICG, as ICG tissue staining obfuscated perfusion assessment[18]

A total of 1.6 mL of ICG was injected in 0.2 mL each of the dorsal web spaces of the foot and in a circumferential pattern at the medial thigh. ICG movement into the lymphatics of the lower extremity was facilitated by manual massage and observed with NIR fluorescence multispectral imaging Quest Spectrum Device (QMI, the Netherlands). Imaging was performed periodically throughout flap harvest to continually monitor for evidence of ICG fluorescence in the deep and superficial inguinal lymph node basin. This allowed for maximal preservation of extremity lymphatic drainage pathways.

### Vascularized Lymph Node Transfer

Flap design was guided by both preoperative computed tomography angiography and doppler ultrasound to ensure both lymphatic structures and blood supply was captured. Several 0.1 mL aliquots of blue dye were injected subcutaneously in an oblique linear fashion at the lower lateral abdomen at the margin of the planned flap. Meticulous dissection was performed in the inguinal region

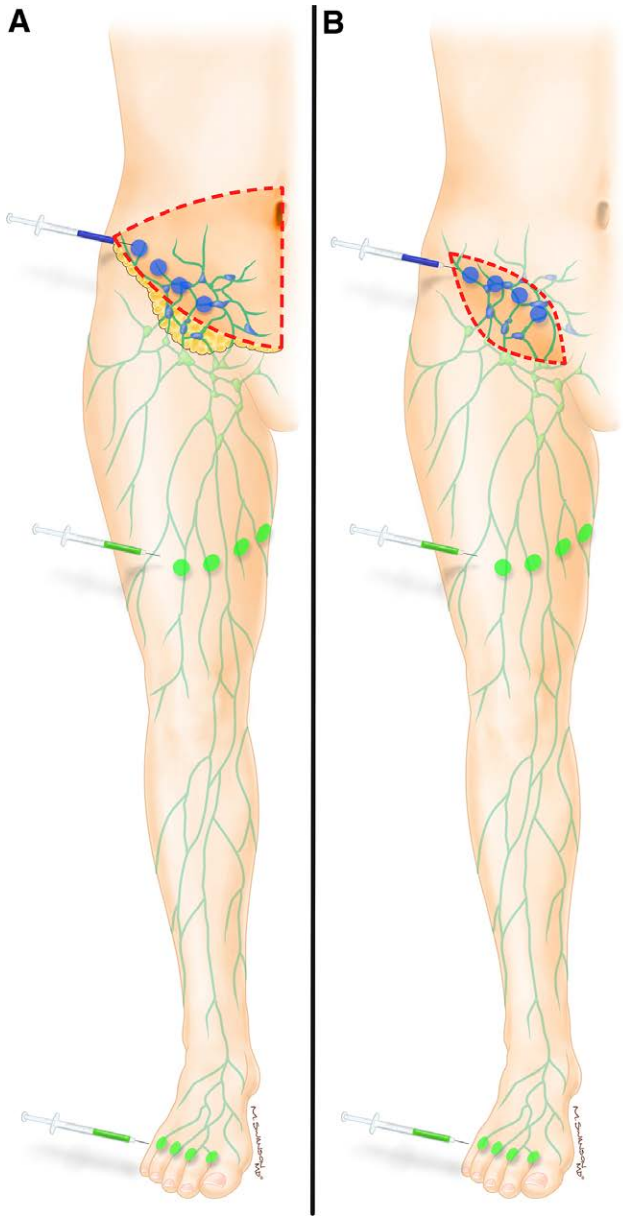


**Fig. 1.** Schematic demonstrating respective injection sites for ICG and blue dye. The combined DIEP and VLNT flap. The left demonstrates the combined DIEP and VLNT flap, and the right shows the inguinal and superficial circumflex iliac artery perforator flap.

to identify and preserve blue-stained lymphatic channels, lymph nodes and associated vascular structures. (**See figure, Supplemental Digital Content 1**, which displays the view of VLN flap in continuity with the right hemiabdominal DIEP flap. The anterograde pathway of blue dye can be traced from the injection site at the lower lateral DIEP flap through the superficial groin lymphatic collectors and lymphatic tissue for targeted lymph node harvest. Orientation is as follows: bottom of the image is cranial, top is caudal, and right is the right lateral lower abdomen, **http://links.lww.com/PRSGO/C67**.) As dissection proceeded inferomedially toward the femoral vessels, lymph nodes without connection to the lymphatic drainage of the lower limb were harvested. These nodes and associated lymphatic collectors were often visualized in the ambient light conditions of the operating room containing blue dye. [**See figure, Supplemental Digital Content 2.** The ICG channel cannot be seen well in white light unlike blue dye. Top row: Blue dye visualization of inguinal lymphatic tissue for harvest with planned VLNT and DIEP flap. Bottom row: ICG dye visualization of lymph nodes draining the lower extremity medial to the convergence of SIEV and SCI vessels. Blue arrows point to the SCIV. Green arrows point to lymphatic tissue draining the lower extremity. **http://links.lww.com/PRSGO/C68**.] The blue dye-associated NIR fluorescence signal was detected in those buried within the adipose substance of the flap.

Lower extremity draining nodes containing ICG and crossover lymph nodes with both blue dye fluorescence and ICG fluorescence were noted and preserved outside the resection borders. The lymph node flap was then transplanted to the axillary recipient site (Fig. 2). Anastomosis was most commonly performed to the thoracodorsal vessels. Both axillary and inguinal surgical sites were closed over drains.

## RESULTS

Our study included 25 patients. Patients had a median age of 52.9 years (range 34–77 years) and a median body mass index of 29.1 kg/m$^2$ (range 22.2–36.9 kg/m$^2$) with a mean follow-up of 44 months (range 24–90 months) (Table 1). Long-term follow-up of at least 2 years postoperatively was achieved in all patients. Clinical evaluation of lymphedema according to Campisi staging indications ranged from 2 to 4.[16] Inguinal VLNT was performed in 13 patients, and 12 patients received combined VLNT and free flap breast reconstruction. One patient reported slight bilateral lower extremity edema preoperatively.

No patients required change in lymph node donor site intraoperatively. All ICG stained nodes were able to be preserved in situ. Additional verification that the desired lymph nodes and lymphatic tissue were contained within

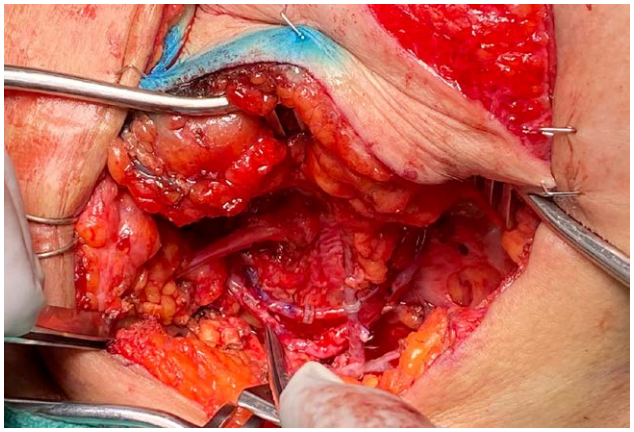

**Fig 2.** Inset flap with microanastomoses at the recipient site in the axilla. The SCIV of the lymph node flap is coupled to the retrograde thoracodorsal vein. DIEP vessel anastomoses to the anterograde thoracodorsal vessels.

**Table 1. Differences in Lower Extremity Circumference and Volume with Follow-up**

| Patient | Circumferential Difference between Ipsilateral and Contralateral Lower Extremity (cm) | | | | Volumetric Difference (%) | Follow-up, mo |
|---|---|---|---|---|---|---|
| | Thigh | Knee | Calf | Ankle | | |
| 1 | 0 | −0.1 | −0.2 | −0.6 | −1.1 | 27 |
| 2 | −0.2 | −0.6 | −0.4 | 0 | −0.5 | 117 |
| 3 | 0 | 0 | 0 | 0 | 0 | 73 |
| 4 | 0.8 | 0.3 | 0.2 | 0 | 1.9 | 69 |
| 5 | 0.1 | 0.5 | 0.5 | 0.3 | 0.8 | 25 |
| 6 | 0.7 | 1.5 | 0.7 | 0 | 1.7 | 24 |
| 7 | 0.3 | 0 | 0.6 | 0 | 0.7 | 44 |
| 8 | −0.1 | −0.2 | −0.1 | 0 | −0.2 | 54 |
| 9 | −0.8 | −0.5 | 0 | 0 | −1.9 | 42 |
| 10 | 0.5 | 0 | 0.1 | 0.1 | 1.4 | 93 |
| 11 | 1 | −0.9 | −0.5 | −0.1 | 2.2 | 65 |
| 12 | 1 | 0.6 | 0 | 0 | 2.4 | 52 |
| 13 | 0.1 | 1.5 | 0.6 | 0.1 | 0.4 | 36 |
| 14 | 0.5 | 0.6 | 0.6 | 0.3 | 1.7 | 24 |
| 15 | −0.2 | −0.2 | 0 | 0 | −0.5 | 59 |
| 16 | −0.9 | −0.9 | 0 | −0.1 | −2.3 | 27 |
| 17 | 1 | 0.5 | 0.5 | 0 | 2.4 | 24 |
| 18 | −0.2 | −0.1 | −0.5 | 0 | −0.5 | 33 |
| 19 | −0.4 | 0.2 | 0.1 | 0 | −1 | 40 |
| 20 | −0.8 | 0.1 | 0 | 0 | −1.9 | 26 |
| 21 | 0.8 | 0.8 | 0.7 | 0.1 | 2.1 | 28 |
| 22 | 0 | 0.3 | 0.1 | 0 | 0 | 34 |
| 23 | −1 | −0.8 | −0.5 | −0.1 | −2.6 | 24 |
| 24 | −0.2 | 0 | 0 | 0 | −0.5 | 27 |
| 25 | 0.6 | 0.6 | 0 | 0 | 1.4 | 24 |

Differences between the ipsilateral donor-site limb and the contralateral limb were calculated at the thigh, knee, calf, and ankle [donor site (cm) – contralateral limb (cm)]. Follow-up was recorded for last circumferential measurement and symptom screen.

the substance of the flap was confirmed by the presence of blue fluorescence. Visualization without additional dissection and devascularization of the vascularized lymph nodes was enabled using our approach. Of the 25 VLNT patients, five had crossover lymph nodes draining the abdomen and lower limb that were avoided due to proximity to the pedicle origin or location medial to the superficial inferior epigastric vein. For safety, these lymph nodes were not included in the flap.

The donor site of the lymph node flap healed appropriately in 23 patients (92%). Two patients developed donor-site–related complications: one patient developed methylene blue-induced skin necrosis that required operative debridement and closure, and the other developed an abdominal seroma that was managed by ultrasound-guided aspiration. However, it is unclear if the seroma was a result of VLNT or the combined DIEP procedure. No patients developed cellulitis. No iatrogenic lower extremity lymphedema or symptoms of swelling, heaviness, or impaired mobility were observed in any of our patients within the follow-up period. Circumference lower limb measurements did not show differences between operated and unoperated extremities. Postoperative bioimpedance spectroscopy of the donor-site limb revealed no evidence of subclinical or clinical lymphedema (L-Dex ratio: mean −1.6; range −9.6 to 1.4). No patients had delayed drain removal. Of note, one patient acquired skin necrosis as a result of subdermal methylene blue.

## DISCUSSION

VLNT is an effective technique for the physiological treatment of lymphedema. A number of potential donor sites for vascularized lymph nodes exist; the groin is among the most commonly used donor site for VLNT, largely due to well-described anatomic studies, concealable scar, and feasibility for combined free abdominal tissue transfer for breast reconstruction.[17–20]

In the inguinal and femoral region, major drainage pathways of the lower abdomen and the lower extremity are, by and large, separated by distinct fascial boundaries. The superficial lymph node basin drains the lower abdomen and is the target of the vascularized lymph node harvest; deeper lymph node basins are adjacent to the femoral vessels that drain the thigh and lower extremity.[21] Anatomic studies have shown that the superficial lymph node basin is flanked by the superficial circumflex iliac and superficial inferior epigastric vessels, and is typically located superficially to the deep fascia of the thigh.[22,23] This distinction allows for preservation of the deeper and more inferior lymphatics draining the lower extremity. However, iatrogenic donor-site lymphedema still remains a safety concern.[3,4,6] Anatomical variation in lymphatic pathways is not uncommon, and poses increased risk of disruption to the inguinal nodes that drain the lower extremity.[24] Inguinal-based lymphatic tissue transfers are associated with an average overall complication rate of 10.9% and donor-site lymphedema rate of 1.6% across 24 studies.[20] Necessary precautions are needed to avoid further complications while still providing effective treatment.

Here, we present a novel enhancement to the reverse lymphatic mapping technique that improves visualization and limits donor-site–associated morbidity through the use of dual fluorescent tracers, once of which is also visible in ambient, white light conditions. Real-time navigation of the groin lymphatic system is enabled, ensuring safe harvest of the lymph nodes that drain the lower trunk while preserving those that drain the lower extremity.

Intraoperative visualization of donor-site lymphatic channels and extremity sentinel nodes guide a more selective dissection and lymph node harvest. In particular, our technique capitalizes on the discrete optical properties of two dyes detected with NIR imaging, ICG and blue dye, with their distinct fluorescence characteristics to more easily distinguish between lymph node basins. Furthermore, replacement of radioactive tracer with ICG dye allows for direct, precise intraoperative visualization of lower extremity lymphatic drainage pathways.[12] Increasing precision in lymph node differentiation not only has great benefit in reducing postoperative donor-site–related morbidity in this clinical scenario, but also has shown promise to improve outcomes in other applications of reverse lymphatic mapping such as in sentinel lymph node biopsy and lymphadenectomy in treatment of melanoma, breast, and gynecologic malignancies.

Fluorescence-guided surgery has several additional advantages compared to conventional nuclear scintographic methods, such as the combination of transcutaneous and in situ navigation, real-time lymphography, and evaluation of lymphatic transport kinetics. Presently, there are a number of agents available that are commonly used to identify lymphatic channels: ICG, blue dyes, and fluorescein isothiocyanate. Valente et al[12] found that ICG NIR imaging method is an efficient, highly sensitive, and equivalent intraoperative method of sentinel lymph node mapping compared with traditional 99mTc. The radionucleotide tracer is more expensive, poses greater safety risk and discomfort to patients due to radioactive exposure and awake injection, and requires additional preoperative coordination.[28] Spiguel et al[29] demonstrated a dual lymphatic mapping methodology using ICG and fluorescein for the lymphatic microsurgical preventing healing approach procedure. Similar to blue dye, fluorescein excites in the visible spectrum and can therefore be visualized through microscope binoculars with specialized filters or Wood's lamp. The spectral properties of blue dye allow visualization in both white light as well as NIR.

Furthermore, the use of ICG in lymphatic mapping is associated with very few side effects and demonstrates an excellent safety profile. No patients experienced any ICG-related adverse reaction. In addition, blue dyes are widely used and have proven to have an excellent safety profile, with improvements in technical success increasing over time with low complication rates.[25] The reported incidence rate of skin necrosis from methylene blue dye is estimated to be 1.25%,[25] and the incidence of allergic reactions for isosulfan blue is 1.5%–3%.[26,27]

There are particular considerations when using the dual fluorescent tracers technique. First, NIR spectral imaging has a limited penetrance of 1.5–2 cm. Nodes deeply encased within fatty tissue may be more difficult to visualize and require additional dissection of perinodal tissues. This increases the risk of node devascularization, which has a particular importance in VLNT. Interruption of the vascular hilum results in lymph node necrosis and ischemia of the lymph nodes within the flap. Second, ICG tissue staining may complicate perfusion assessment over time, which is why we advocate for blue dye to map the primary nodal donor site, in this case the inguinal region, instead of ICG. Availability of a multispectral or hyperspectral NIR camera, facility with ICG lymphangiography, and proper ICG dye handling to avoid staining of donor and recipient operative fields are necessary logistical considerations for successful mapping. Last, although blue dye is widely used, it is associated with adverse reactions such as skin necrosis and anaphylaxis.[10,30,31] One patient (4%) in our study did require operative treatment for skin necrosis due to methylene blue dye injection. To lower risks of skin necrosis, increased dilution of methylene blue or alternative use of isosulfan blue can be used. For those with known sulfa allergy, a premedication regimen may be used.

## CONCLUSIONS

The novel use of dual fluorescence with ICG and blue dye allows precise, effective, and immediate visualization of distinct lymphatic pathways draining the abdomen and lower extremity. Our technique showed a favorable donor-site morbidity profile and, in particular, prevented iatrogenic donor-site–associated lymphedema. Using this advanced surgical visualization strategy, VLNT flap components can be clearly distinguished while precisely preserving at-risk structures. Reverse lymphatic mapping and surgical guidance with dual ICG and blue dye fluorescent tracers is a safe, efficient innovation for vascularized lymph node flap harvest.

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