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PRS GLOBAL OPEN

ORIGINAL ARTICLE

Reconstructive

Immediate Lymphatic Reconstruction Using a Handheld Fluorescence Imaging Device

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Background: Immediate lymphatic reconstruction (ILR) has traditionally required a fluorescent-capable microscope to identify lymphatic channels used to create a lymphaticovenous bypass (LVB). Herein, a new alternative method is described, identifying lymphatic channels using a commercially available handheld fluorescence imaging device.

Methods: This was a single-center study of consecutive patients who underwent ILR over a 1-year period at a tertiary medical center. Intradermal injection of fluorescent indocyanine green dye was performed intraoperatively after axillary or inguinal lymphadenectomy. A handheld fluorescent imaging device (SPY-PHI, Stryker) rather than a fluorescent-capable microscope was used to identify transected lymphatic channels. Data regarding preoperative, intraoperative, and outcome variables were collected and analyzed.

Results: The handheld fluorescent imaging device was successfully able to identify transected lymphatic channels in all cases (n = 15). A nonfluorescent-capable microscope was used to construct the LVB in 14 cases. Loupes were used in one case. In 13 cases, ILR was unilateral. In two cases, bilateral ILR was performed in the lower extremities. All upper extremity cases were secondary to breast cancer (n = 7). Lower extremity cases (n = 8) included extramammary Paget disease of the penis, ovarian cancer, vulvar squamous cell carcinoma, squamous cell carcinoma of unknown origin, soft tissue sarcomas, cutaneous melanoma, and porocarcinoma.

Conclusions: ILR, using indocyanine green injection with a handheld fluorescent imaging device, is both safe and effective. This method for intraoperative identification of lymphatic channels was successful, and LVB creation was completed in all cases. This approach makes ILR feasible when a fluorescent-capable microscope is unavailable, broadening access to more patients. *(Plast Reconstr Surg Glob Open 2023; 11:e5480; doi: 10.1097/GOX.0000000000005480; Published online 18 December 2023.)*

INTRODUCTION

Lymphedema is a chronic medical condition characterized by the retention of lymphatic fluid within the body, leading to swelling, which may result in changes to the skin and adjacent tissues.[1,2] Lymphedema can be classified as primary or secondary, depending on the etiology and cause. Primary lymphedema is a congenital or inherited condition stemming from developmental errors in the lymphatic network.[1,2] This predominantly affects children and may be secondary to conditions like Noonan or Turner syndrome.[1,2] Secondary lymphedema is caused by disruption to normally functioning lymphatic channels and is often a result of infection, surgery, trauma, or radiation therapy. In the United States, secondary lymphedema is most often a chronic and potentially debilitating sequela of oncologic care, secondary to lymphadenectomy and/or radiotherapy. Historically, rates of lymphedema after axillary lymph node dissection (ALND) have been commonly reported between 20% and 40%, with reports as high as 77%.[3–7] Initially, lymphatic treatments (operative and nonoperative) were aimed at controlling or resolving symptoms after secondary lymphedema had already developed.

In 2009, the lymphatic microsurgical preventive healing approach (LYMPHA) for intraoperative immediate lymphatic reconstruction (ILR) was introduced.[8] In this technique, the lymphatics draining the upper extremity are identified during axillary dissection by intradermal injection of isosulfan blue.[8] This allows the surgeon to identify lymphatic channels as the blue dye is drained.

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Received for publication June 15, 2023; accepted October 12, 2023.

DOI: 10.1097/GOX.0000000000005480

Disclosure statements are at the end of this article, following the correspondence information.

A lymphaticovenous bypass (LVB) is then performed to an axillary vein tributary to prevent the development of lymphedema postoperatively.[8] ILR, using this blue dye technique for lymphatic channel identification, has demonstrated reduced rates of secondary lymphedema development compared with historical controls, with postoperative lymphedema rates after ALND noted to be 5% over a 4-year period.[9] Although effective, this method is not always feasible because some breast surgeons prefer to use this same blue dye to identify sentinel lymph nodes of the breast, obscuring identification of the axillary lymph nodes draining the arm.[10]

For this reason, an alternative method to identify lymphatic channels transected during lymphadenectomy has been used, namely using fluorescent dye. Both indocyanine green (ICG) and fluorescein isothiocyanate (FITC) have been described. Currently, ICG is the most common dye used for lymphatic vessel mapping. However, ICG fluorescence is only excitable in the nonvisible spectrum, meaning the dye is displayed as a white signal on a black background. Until recently, this has not allowed for concurrent visualization of the ICG dye and visible light in the operative field through the microscope.[10] Only recently, the newest generation of fluorescent-capable microscopes offer an overlaid image of ICG signal with simultaneous visible light.

More recently, Spiguel et al described a method of identifying lymphatic channels intraoperatively using a fluorescent-capable microscope with 560-nm filter and FITC.[10] FITC is excitable in the visible spectrum.[10] This allows the lymphatic surgeon to use a fluorescent-capable microscope to clearly visualize lymphatic channels and surrounding tissues under microscope magnification. This facilitates lymphatic mapping, dissection, and reconstruction all in the same surgical field.[10] This technique, however, requires a fluorescent-capable microscope, which may not be widely available at all institutions.

This case series reports a novel method for intraoperative identification of lymphatic channels using ICG injection with a commercially available, handheld fluorescence imaging device. The use of this technology, therefore, makes ILR feasible if a fluorescent-capable microscope is not available. We aimed to demonstrate the safety and efficacy of this technique for application in ILR. We hypothesize that ICG visualized through handheld fluorescent imaging would be a safe and effective alternative to microscope-visualized FITC or ICG for lymphatic mapping and dissection during ILR.

Takeaways

Question: Microscope-visualized fluorescein isothiocyanate is an effective method for lymphatic mapping but may not be readily available. We hypothesize that indocyanine green (ICG) visualized through a handheld fluorescent imaging device would be an effective alternative for lymphatic mapping during immediate lymphatic reconstruction (ILR).

Findings: In a retrospective review of 15 patients undergoing lymphadenectomy for an upper or lower extremity malignancy, ILR with the proposed technique was 100% successful. In an average follow-up period of 11.9 months, two patients developed lymphedema.

Meaning: ICG visualized through a handheld fluorescent imaging device is a safe and effective method for intraoperative mapping of lymphatic channels for ILR.

METHODS

This is a retrospective review of a prospectively maintained database of all patients who consecutively underwent attempted ILR at a single tertiary care medical center from June 2020 to June 2021. During the period, ILR was performed by identifying lymphatic channels using ICG injection with a portable handheld fluorescent imaging device (SPY-PHI, Stryker, Kalamazoo, Mich.). During the study period, one ILR case was excluded because it was performed using a trial/loaner fluorescent-capable microscope. Lymphatic localization with this alternative technique was not attempted or performed during that case. A single surgeon, who has completed fellowship-training in microsurgery, performed all the attempted ILR procedures. The medical records were reviewed, and data regarding demographic information (age, gender, BMI), diagnoses, procedures, LVB construction, and additional surgical/oncological characteristics were collected. Additionally, the number of lymph nodes removed, the number of LVBs constructed per patient, and the size of lymphatic vessels were collected.

Surgical Technique

ILR was performed by the creation of one or more LVBs at the time of the nodal extirpation. Immediately after completion of the ablative portion of the procedure, the surgical site was explored for potential recipient veins. Thereafter, ICG 2.5% solution was injected intradermally in four aliquots (2 mL total injected) over the medial and anterior aspects of the limb, approximately 6–8 cm distal to the surgical site. The SPY-PHI handheld fluorescent imaging device was then used to visualize divided lymphatic channels. These were marked with ink (gentian violet). A nonfluorescent surgical microscope was then used to create one or more LVBs, based on the number of available veins and transected lymphatic channels. For LVBs, a single lymphatic channel was anastomosed with a single vein in an end-to-end fashion. The surgical site's incision was closed in a standard, multilayer fashion, and a no. 15 Blake drain was placed exiting the dependent portion of the surgical site away from the LVB.

Postoperative Surveillance

Patients were seen in the clinic at 1 week, 3 weeks, and 6 weeks after discharge from the hospital, and then every 3 months. During each visit, patients were assessed for symptoms or signs of lymphedema, and objective circumference limb measurements were taken. Lymphedema was defined similarly as reported by Johnson et al.[11] Lymphedema was diagnosed if both (1) a 7% volume increase in the operated extremity compared with the contralateral extremity was detected and (2) symptoms (ie, tightness, heaviness, swelling) consistent with lymphedema were present. Lymphedema was categorized using the four-stage system designated by the International Society of Lymphology (stage 0, stage I-III). Bioimpedance measurements were not available or performed. If the patient met these criteria while undergoing adjuvant treatment, with the exclusion of hormone therapy and immunotherapy, or within 6 months of their last oncologic treatment, lymphedema was classified as transient (ie, "transient lymphedema"). A diagnosis of lymphedema was given if the patient met the above-specified criteria 6 months or more after their last oncologic treatment (surgery, adjuvant radiation therapy, or chemotherapy).

Statistical Analysis

Descriptive statistics of the collected data were performed. Continuous numerical data were characterized by means and SDs or median and interquartile range (IQR). Categorical variables were represented as frequencies and percentages. All statistical analysis was performed using SPSS (SPSS Statistics for Mac, Version 28.0; IBM Corp., Armonk, N.Y.).

RESULTS

Fifteen patients underwent attempted ILR after oncologic nodal resection. In all cases, ILR was successfully completed with the creation of one or more LVBs. The patient cohort included two men (13.3%) and 13 women (86.7%). The average patient age was 56.4 ± 15.7 years, and the average body mass index (BMI) was 27.0 ± 5.3 kg/m². Two patients died of progressive disease within 6 months of surgery. The average follow-up time was 11.9 months ± 262 days. One patient (6.7%) received neoadjuvant radiotherapy, and eight patients (53.3%) received adjuvant radiotherapy. Eight patients (53.3%) received chemotherapy. Additional patient information is listed in Table 1.

The 15 patients in this series had a total of 27 LVB constructions and an average of 2.0 ± 1.0 LVBs performed per patient. ILR was performed in the upper extremity in seven cases (46.7%) and in the lower extremity in eight cases (53.3%). All seven of the upper extremity cases were secondary to breast cancer. Lower extremity cases included a diversity of pathologies. Pathologies included extramammary Paget disease of the penis (n = 1, 6.7%), ovarian cancer (n = 1, 6.7%), vulvar squamous cell carcinoma (n = 1, 6.7%), squamous cell carcinoma of unknown origin (n = 1, 6.7%), soft tissue sarcoma (n = 2, 13.2%), cutaneous melanoma (n = 1, 6.7%), and porocarcinoma (n = 1, 6.7%).

Unilateral ILR was performed in 13 cases (86.7%), and bilateral ILR was performed in two cases (13.3%). Both bilateral ILR cases were in the lower extremities. An average of 13.7 ± 8.0 lymph nodes were removed per patient. The average lymphatic channel size used for ILR was 0.5 ± 0.2 mm. Additional surgical/oncological characteristics are listed in Table 2.

Table 1. Patient Characteristics

Variable	Value
Sex, n (%)	
Female	13 (86.7%)
Male	2 (13.3%)
Average Age, y (SD)	56.4 ± 15.7
BMI, n (%)	
Healthy (18.5–24.9 kg/m²)	6 (40%)
Overweight (25.0 to <30.0 kg/m²)	4 (26.7%)
Obese (>30 kg/m²)	5 (33.3%)
Average BMI, (SD)	27.0 ± 5.3
Diagnosis, n (%)	
Breast cancer	7 (46.6%)
Extramammary Paget disease of penis	1 (6.7%)
Ovarian cancer	1 (6.7%)
Vulvar squamous cell carcinoma	1 (6.7%)
Metastatic squamous cell carcinoma	1 (6.7%)
Lower Extremity Malignancies	
Sarcoma	2 (13.2%)
Cutaneous melanoma	1 (6.7%)
Porocarcinoma	1 (6.7%)
Comorbidities, n (%)	
Active smoker	0 (0.0%)
Cerebrovascular accident	1 (6.7%)
Chronic obstructive pulmonary disease	0 (0.0%)
Congestive heart failure	0 (0.0%)
Coronary artery disease	0 (0.0%)
Diabetes mellitus	0 (0.0%)
Hyperlipidemia	4 (26.7%)
Hypertension	7 (46.7%)
Follow-up, months ± days (SD)	11.9 ± 262

Table 2. Surgical/Oncological Characteristics

Variable	Value
Procedure, n (%)	
Axillary lymphadenectomy	7 (46.7%)
Inguinal lymphadenectomy	8 (53.3%)
No. LVB performed per patient, n (%)	
1	8 (53.3%)
2	3 (20%)
3+	4 (26.7%)
Radiation Therapy, n (%)	
Yes	9 (60%)
No	6 (40%)
Chemotherapy, n (%)	
Yes	8 (53.3%)
No	7 (46.7%)
Intraoperative Details, n (SD)	
Average number of lymph nodes removed	13.7 ± 8.0
Average size of lymphatics vessels used for LVB (mm)	0.5 ± 0.2
Average number of LVB constructed	2.0 ± 1.0

Excluding the two patients who died before 6 months of follow-up, two of 13 patients (15.4%) were diagnosed with lymphedema, as they met the above-specified criteria 6 months or more after their last oncologic treatment.

The first patient with post-ILR lymphedema was diagnosed with extramammary Paget disease of the penis and had preexisting persistent genitourinary and lower extremity lymphedema secondary to at least five prior

Table 3. Patients Diagnosed with Lymphedema

Patient	Age	BMI	Active Smoker	Comorbidities	Risk Factors	Pathology	No. Lymph Nodes Taken	No. LVBs Performed	Radiation	Chemotherapy
1	80	21.83	No	HTN	Preexisting persistent genitourinary and lower extremity lymphedema	Extramammary Paget disease of the penis	27	3	Yes	Yes
2	70	27.44	No	HTN	N/A	Regionally advanced lower extremity cutaneous melanoma	18	1	Yes	Yes

penile and scrotal excisions and reconstructive procedures. After subsequently developing inguinal lymphadenopathy, the patient underwent bilateral inguinal lymphadenectomy and bilateral ILR. At a later date, the patient also underwent bilateral ilio-caval LND as well as adjuvant radiotherapy to the bilateral groins. Throughout this, the patient has experienced lymphedema, which has been stable grade I with the continued use of compression garments and lymphatic physical therapy.

The second patient with post-ILR lymphedema was diagnosed with recurrent cutaneous melanoma from the left leg. Twelve years prior, she had undergone left leg-wide local excision of the primary disease and popliteal sentinel node biopsy. After a 12-year period without evidence of disease, she developed left inguinal lymph node metastases. She underwent inguinal lymphadenectomy and unilateral ILR. The patient received chemotherapy before and after lymphadenectomy as well as adjuvant radiotherapy. She developed left lower extremity lymphedema 165 days after surgery. The lymphedema has also been stable grade I. The individual characteristics of these patients are listed in Table 3.

DISCUSSION

ILR was first introduced in 2009 with a single center's experience in Italy.[8] Since that time, additional centers have adopted and modified the original technique, using blue dye for the identification of the transected lymphatic channels. The initial publication's reported effectiveness has been repeated by multiple previous studies.[8–17] This case series is the first description of using ICG specifically with a portable handheld fluorescent imaging device for ILR and demonstrates its safety and effectiveness.

ICG dye and the commercially available handheld fluorescent imaging system used in this report are commonly used for a variety of other clinical applications (eg, tissue perfusion, hepatobiliary imaging). This system is present in many institutions that do not have a fluorescent-capable microscope. In this report, we demonstrate that this technique for identifying transected lymphatic channels after lymphadenectomy was successful in all cases. ILR with a conventional (nonfluorescent capable) microscope was successfully performed in all cases.

ICG holds value in its relatively rapid transit time through lymphatic channels, therefore, providing surgeons with a simple, highly sensitive method of real-time imaging-guided sentinel lymph node mapping.[18] Surgeons can identify divided axillary or inguinal lymphatic channels that may have been incidentally divided during sentinel node excision by injecting the ICG dye intradermally into the affected limb. The lymphatic channels in the field of dissection carry the fluorescent signal in real-time and are visualized using the handheld device. Once identified, the handheld device can be placed aside while the LVB is performed. Importantly, this method can pinpoint lymphatic channels at the millimeter and submillimeter levels. In fact, the average lymphatic channel size used in LVB in this study was 0.5 mm. Therefore, this technique allows surgeons without fluorescent-capable microscopes to identify lymphatic channels for supermicrosurgery and perform repairs with a standard nonflorescent microscope.

Overall, previous studies in the existing literature have reported varying rates of lymphedema after ILR, ranging from 3.10% to 31.3%.[8–17,19] Specifically, Hahamoff et al demonstrated a decrease in their institutional rate of lymphedema from 40% to 12.5%, and Boccardo et al described a lymphedema rate of 4.34% compared with 30.43% in the control group.[8,12,13] Similarly, Cook et al demonstrated a 9.1% rate of lymphedema after ILR for patients having undergone ALND.[20] Interestingly, as surgical centers perform more ILR cases and increase follow-up, there is conflicting data regarding lymphedema rates.[11,12,19] Levy et al have published the largest series to date with the lengthiest follow-up time.[19] This group observed a cohort of 45 women who underwent LYMPHA between 4 and 8 years prior and 45 women who had not undergone ILR. The incidence of lymphedema was not significantly different between the groups, with rates of 31.1% in the LYMPHA group, and 33.3% in the non-LYMPHA group.[19] In their original article published in 2019, Dr. Singhal's group performed ILR in eight patients with a lymphedema rate of 12.5%.[12] A recent update of their prior series published in 2021 included 32 patients who underwent successful ILR with a postoperative lymphedema rate of 3.1% at the end of the study period.[11] The lymphedema rates in our series using a handheld fluorescence imaging device are comparable to those in Dr. Singhal's original series. However, with longer follow-up times, it is becoming evident that ILR may not yield the initially anticipated outcomes, and prospective studies are imperative in determining the true efficacy of ILR.

Only one study to date has reported results for ILR after an inguinal lymph node dissection and showed a lymphedema rate of 8.33% versus 25% in a control group.[14] Like other previously published case series, the current study demonstrates a significant decrease in the incidence of chronic lymphedema (16.7%) after lymph node dissection when ILR is performed. These results are comparable to other similar studies in the literature and demonstrate the overall efficacy of this technique. Adoption of this technique is not only cost-effective but offers access to an intervention empirically proven to reduce the incidence of lymphedema.

Alternative management strategies for secondary lymphedema prevention typically involve multifaceted programs that encompass elements such as active exercise, health education (injury prevention, hygiene, and personal care), and the consistent use of compression garments. Physical activity plays a pivotal role in these lymphedema prevention programs, as it enhances lymphatic and venous flow.[21–25] Compression stockings or sleeves exert controlled pressure on the affected limb, reducing the accumulation of excess lymphatic fluid and preventing reflux.[21,22,26] Lastly, obesity has been identified as a significant risk factor for the development and progression of lymphedema.[27,28] Thus, maintaining a healthy weight through diet and exercise can aid patients in reducing the risk of lymphedema-related complications. Although these strategies can be beneficial, they necessitate behavioral modifications and substantial patient effort. ILR offers a more proactive and potentially less burdensome approach by addressing lymphatic system issues at the source.

Our study is not without limitations. The limitations of this study include the inherent limitations of a retrospective study. Secondly, our sample size was limited, and patients were followed up for a period of 12 months.

CONCLUSIONS

ICG with a fluorescent portable handheld imaging device was found to be a safe and effective method for intraoperative mapping of lymphatic channels for ILR. This provides an alternative method to FITC for visualization of disrupted lymphatic channels when a filter-equipped microscope is not available, and allows for real-time lymphatic visualization with a simple and more commercially available device.

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DISCLOSURE

The authors have no financial interest to declare in relation to the content of this article.

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