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Review

Preoperative planning of lymphaticovenous anastomosis: The use of magnetic resonance lymphangiography as a complement to indocyanine green lymphography

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Abstract *Background:* Lymphaticovenous anastomosis (LVA) is a surgical treatment for lymphedema that requires identification and mapping of functional lymphatic channels. This technique was performed blindly for years because of the lack of suitable methods of study. Progress in imaging techniques and the introduction of Indocyanine green lymphography (ICG-L) represented a significant advancement in lymphedema management. Magnetic resonance lymphangiography (MRL) has also helped improve knowledge about lymphedema anatomy and pathophysiology. We now present our protocol based on both ICG-L and MRL for optimal LVA preoperative planning.
Methods: A prospective study between April 2010 and June 2015 was conducted in 82 patients (77 females, mean age 45.5 years) with stage I (9.8%), II (73.2%), and III (17.0%) lymphedema. All patients underwent lymphedema surgical treatment with LVA. Surgery was planned based on preoperative information from ICG- L and MRL.

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Results: We obtained a mean of 6.87 lymphatic locations per extremity from MRL and selected a mean of 4.04 for LVA. When MRL data coincided with ICG-L data, we found a functional lymphatic vessel in 96.9% of cases and performed LVA successfully in 91.4%.
Conclusions: ICG-L and MRL are noninvasive techniques that provide images of the lymphatic system with sufficient temporal and spatial resolution to depict functional lymphatic vessels. Such knowledge is essential for preoperative planning of LVA microsurgery. We present our protocol for the approach of surgical treatment of lymphedema. This protocol represents a step forward in unifying patient selection criteria and achieving safe, effective, and rational surgery.

Contents

Introduction

Lymphedema is a chronic progressive disease caused by insufficient lymphatic drainage, thereby affecting approximately 250 million people worldwide.[1,2] The main etiology in developed countries is secondary to treatments for malignancy, such as lymph node biopsies and lymph node dissections. For many decades, lymphedema received little attention from the surgical world, mainly because of limited knowledge of lymphatic anatomy and physiology. However, in the past decade, major advancements in the lymphatic imaging and refinement of supermicrosurgery[3] instruments and techniques have rekindled broader interest among surgeons in the pursuit of a definitive surgical treatment for lymphedema.

For many years, lymphoscintigraphy (LS) was the gold standard imaging technique for lymphedema because it provided a reliable global evaluation of lymphatic function. In LS, a radiotracer (Tc-99 m) is injected, and images are captured at 60, 120, and 180 min. Parameters obtained include (1) time-elapsed images to track the radiotracer as it reaches the axilla, (2) the presence or absence of major collectors, (3) lymph node visualization, and (4) the presence of dermal backflow. Although reliable, the main downside of LS is that the resolution is lower than that of other examinations.[4] Other disadvantages include the cost, radiation exposure, and long examination time. LS has now been relegating as a second-line imaging investigation for lymphatic surgery.

Currently, indocyanine green lymphography (ICG-L)[5] is considered the essential diagnostic imaging technique for the lymphatic system. It is simple, minimally invasive, highly sensitive, and accurately reflects the lymphatic system status in real time. It provides information of (1) the precise location of functional lymphatic vessels, (2) the transport capacity of lymphatic vessels, (3) the presence of dermal backflow, and (4) the location of collateral lymphatic vessels (Figure 1). In 2007, Unno et al.[6,7] first introduced ICG-L for preoperative planning of lymphaticovenous anastomosis (LVA), and currently, it is part of the standard approach for lymphatic surgery. Yamamoto et al.[8] demonstrated that ICG-L findings were consistent among patients, and this group defined different patterns associated with different levels of lymphedema severity. Despite the numerous advantages of ICG-L, its major disadvantage is that it cannot detect lymphatic channels deeper than 1.5–2 cm under the skin.

Magnetic resonance lymphangiography (MRL) offers an adjunct imaging technique compared to ICG-L. The images obtained from MRL depict lymphatic anatomy with a high spatial and temporal resolution without radiation exposure.[9-11] Similar to ICG-L, MRL provides data regarding

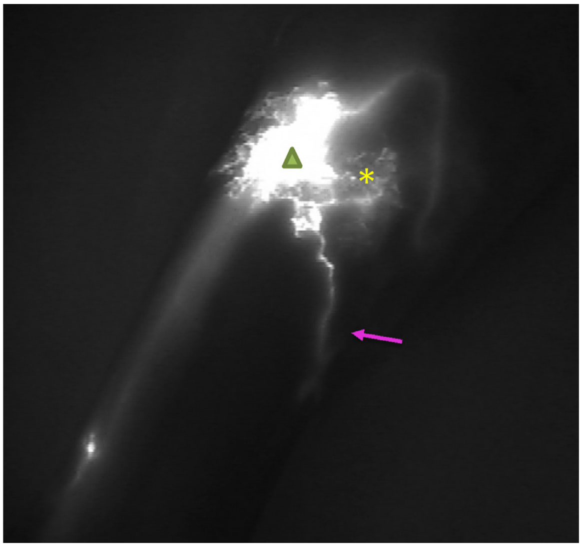

Figure 1 ICG-L of upper limb affected by stage 2 lymphedema demonstrating a linear lymphatic channel (arrow) that ends in an area of dermal back flow (triangle) from where collateral vessels originate (asterisk).

location and transport capacity[12] of lymphatic vessels; however, the added advantages of MRL are that it also provides (1) an image of the entire extremity (2), quantity and quality of both the superficial and deep lymphatic systems, and (3) a three-dimensional image that can be critically reviewed by the surgeon in the preoperative evaluation (Figure 2).

LVA[13] is a surgical treatment described for the treatment of lymphedema. Of utmost importance, the aim of LVA surgery is not only the bypass of lymphatic obstruction into the venous system but also the maximum preservation of remaining lymphatic functionality. Satisfactory results have been demonstrated in well-indicated patients with functional lymphatic vessels[14] and, thus far, ICG-L has been crucial for identifying those patients.

With advancements in imaging, specifically ICG-L with MRL,[15,16] functional lymphatic channels can be identified and mapped preoperatively as suitable targets for LVA. This study evaluates the utility of adding MRL data to thoset of ICG-L for LVA. The aim was to assess the concordance of the MRL with ICG-L and the suitability of MRL selected coordinates for performing successful LVA.

Materials and methods

Patient Selection

We performed a prospective study to analyze the effectiveness of preoperative planning with ICG-L and MRL for identifying suitable functional lymphatic vessels for LVA.

The study included 82 patients with lymphedema (77 females; 5 males) who underwent LVA at Hospital de la Santa Creu i Sant Pau and Clínica Planas in Barcelona, Spain, between June 2010 and June 2015. Only patients with a functional lymphatic system demonstrated by ICG-L were considered for reconstructive surgical treatment. These patients were offered LVA technique combined with other techniques according to the Barcelona Lymphedema Algorithm for Surgical Treatment (BLAST) described by our group.[17]

Figure 2 MRL 3D reconstruction and maximum-intensity projection (MIP) of a patient with lower limb primary lymphedema. A hyperplasic lymphatic system of the right lower limb is visible. The lymphatics reach the lower abdomen where inguinal lymph nodes can also be visualized (arrow).

Briefly, to be considered for inclusion in this study, patientś preoperative ICG-L imaging needed to show the presence of linear functional lymphatic channels. Patients without substantial compromise of the axillary region were offered LVA only. However, if the axillary region showed significant compromise such as lack of lymph node function or axillary vein compression from scarring or fibrosis, a lymph node transfer technique and LVA were offered. Finally, for those patients with amastia who wished to undergo breast reconstruction, they were offered a deep inferior epigastric artery perforator (DIEAP) flap and lymph node transfer in addition to LVA. The patients with ICG-L demonstrating nonfunctional lymphatic system were not included in this study and were offered a reductive technique such as liposuction.

See supplement 1 for details regarding the algorithm - supplement 1

All patients who accepted for lymphedema surgery had a BMI $<30\,kg/m^2$, demonstrated compliance with compression

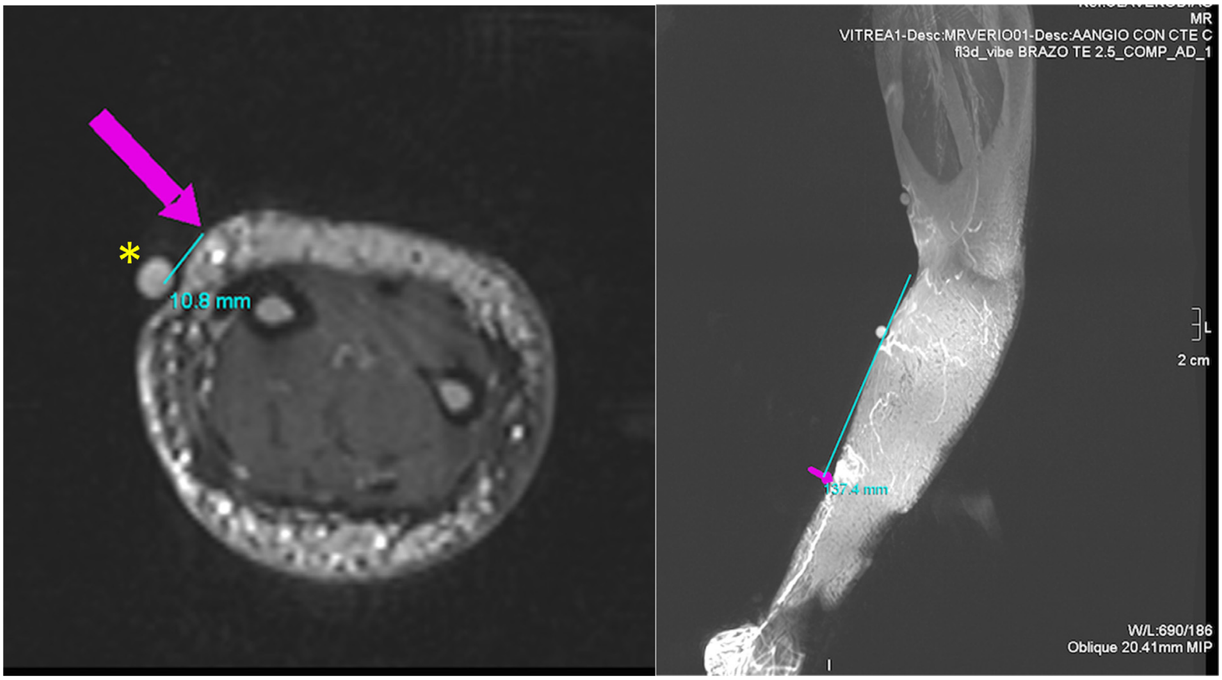

Figure 3 (a): MRL with axial multiplanar reconstruction for determining coordinates. The x-axis is defined as a line from the center of the antecubital fossa to the radial styloid. The lymphatic vessel is marked with a pink arrow, and the hyperdense marker (x-axis) is indicated with asterisks. This lymphatic is 10.8 mm from the hyperdense marker – the x-coordinate. A reticular pattern of the subcutaneous tissue and dermal thickening is also demonstrated. (b): MRL with sagittal multiplanar reconstruction for determining coordinates. The y-axis is defined as the center of the elbow. Again, the lymphatic vessel is marked with a pink arrow and measures 137.44 mm from the center of the elbow – the y-coordinate. Ultimately, this coordinate was the most proximal coordinate for this lymphatic and was determined to be suitable for LVA.

therapy, and received complex decongestive therapy preoperatively.

All data of the study were collected in accordance with institutional review board approval.

Imaging: indocyanine green lymphography

ICG-L was performed with the photodynamic eye (Hamamatsu Photonics K.K., Hamamatsu, Japan), which uses a charged coupled device camera and a diode that emits LED light of 760 nm. We injected 0.2–0.4 ml of the ICG dye solution (Diagnogreen 0.5%; Daiichi Sankyo Co., Tokyo, Japan) subcutaneously in the second and fourth interdigital spaces of the upper or lower limbs. The ICG dye was taken up and transported by functional lymphatic channels, which were visualized as fluorescent lines on a monitor. This first diagnostic study was performed to determine the lymphatic function and candidates for LVA.

Imaging: magnetic resonance lymphangiography and coordinate analysis

All candidate patients for LVA underwent MRL 1 to 4 weeks prior to surgery. MRL was completed with a 3T Magnetic Resonance system (MAGNETOM Verio, Siemens, Erlangen, Germany). Images were assessed with workstation type VITREA 4, version 4.1.14.0. The technique was based on sequences the three-dimensional gradient echo potentiated in T1 with fat suppression (matrix of 380 × 70, fov of 40 × 40 cm, repetition time of 5.7 ms, echo time of 2.5 ms, inclination angle of 70°, and acquisition time of 2 min). Three acquisitions were performed in different stations in lower limbs and two stations in upper limbs. Positioning of the extremities for image acquisition was the same as positioning for ICG imaging. The contrast injected was 0.8 ml of solution containing gadobenate dimeglumine (MultiHance ®, Bracco, Italy) and 0.2 ml of SCANDINIBSA (Braun Medical, SA) in the same interdigital spaces as the ICG-L. To process and interpret images, different stations were added and multiplanar reconstructions in maximum-intensity projection (MIP) were obtained.

The same plastic surgeon and radiologist evaluated all images jointly. Multiple coordinates were identified along the course of every lymphatic vessel. The coordinate values were defined based on hyperintense markers (vitamin A) placed along the extremity (Figure 3a and b) to define the x-axis along the medial antecubital fossa and radial styloid and the y-axis defined as the center of the elbow. When choosing the suitable coordinates for LVA, the most proximal coordinate along the length of each lymphatic vessel (which was distal to the obstruction) was the one selected for LVA. On axial view, we also measured lymphatic channel caliber and depth into subcutaneous tissue.

All data were stored on CD to allow for reviewing images in the immediate preoperative period.

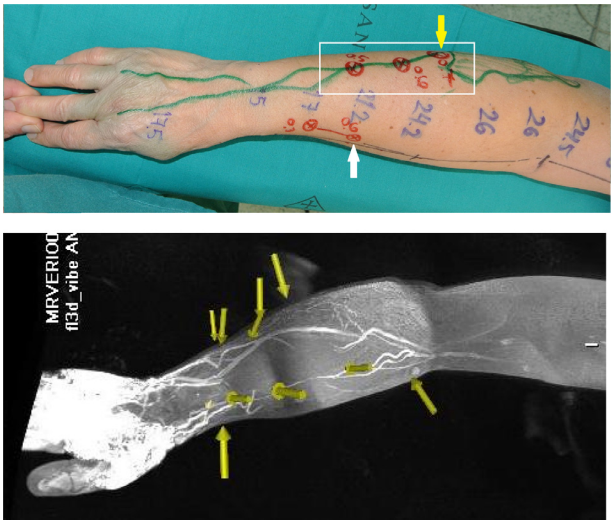

Figure 4 (a): Preoperative markings of upper extremity with Stage 2 lymphedema. Green lines indicate ICG-L information and red dots indicate MRL coordinate data. In this patient, there are multiple MRL coordinates along the same ICG-L identified lymphatic (box) - concordance between MRL and ICG. For our surgical strategy, the first selected site for LVA is the most *proximal* location of a functional lymphatic channel recognized by both ICG-L and MRL (yellow arrow). Second, proximal sites just distal to dermal backflow sites based on ICG data alone. Third, the most proximal locations of lymphatic channels depicted by only MRL (white arrow) are selected for LVA. Only one LVA per lymphatic channel is performed. (b): Upper limb MRL of the same patient in Figure 4a. This image shows multiple linear lymphatic channels that go proximally beyond the elbow and an area of dermal back flow in the proximal forearm (asterisks). Yellow arrows mark the locations of functional lymphatic channels. These coordinates are recorded and then used in the preoperative markings.

Lymphaticovenous anastomosis surgical technique

The day before surgery, ICG-L was repeated to map and mark the lymphatic system. Simultaneously, the information from MRL was transferred to the skin using a tape measure and x-y coordinates previously determined. The order of priority for performing LVA was as follows (Figure 4a and b):

1st. the most proximal locations where ICG-L and MRL data coincided (ICG-*L*+ MRL +)
2nd. the most proximal locations with ICG-L data only (ICG-*L*+ MRL -)
3rd. the most proximal locations with MRL data only (ICG-L- MRL+).

We performed LVA based on Koshima's technique[18] with patients under general anesthesia. We injected 0.1–0.2 ml of patent blue V dye (Bleu Patente V sodique GUERBET 2.5%, 2 ml, France) 2 cm distally to the planned incision to allow for the location and dissection of the lymphatic channel. Under the microscope, we performed a 2.5–3 cm skin incision at the exact points obtained in preoperative planning. We dissected the subcutaneous tissue until we identified a lymphatic vessel that we anastomosed end-to-end or end-to-side to a nearby vein. We used 11-0 nylon sutures in most cases (Figure 5). Patency was assessed with ICG-L intraoperatively. The incision was closed with 4-0 nylon sutures. In selected cases, lymph node transfer or DIEAP and lymph node transfer (DIEAP-LNT) were also performed.

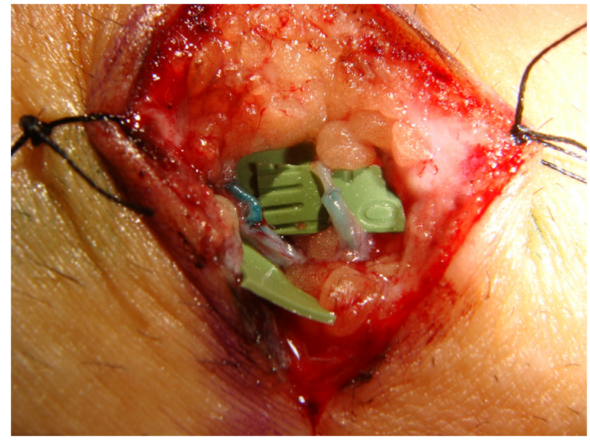

Figure 5 Intraoperative view of two LVAs performed using MRL and ICG-L data. The anastomosis on the left is an end-to-side, retrograde, while the anastomosis on the right is an end-to-end, antegrade. Patency, demonstrated as blue lymph, is being transported into the anastomosed veins.

Statistical analysis

Statistical analysis was first based on a descriptive study of the variables analyzed. We used chi-square test or Fisher's exact test to compare categorical variables and Studentś-t-test or ANOVA to compare continuous variables as a function of categorical variables. Values of $p<0.05$ were considered significant.

Results

Descriptive analysis of patient population

We performed LVA in 86 extremities (4 patients had bilateral surgery). We analyzed data from 82 patients with a mean age of 45.5 years and mean BMI of 23.8 kg/m^2. Most patients (74.3%) developed lymphedema secondary to an oncological procedure (Figure 6A). Lymphedema affected the upper limbs in 60.5% of cases and the lower limbs in 39.5% (Figure 6B). According to the International Society of Lymphology recommendations,[19] 9.8% of our patients had stage 1 lymphedema, 73.2% had stage 2, and 17.1% had stage 3 (Figure 6C)). The majority of the patients, 81.7%, demonstrated a linear pattern on preoperative ICG-L, which was associated with a splash or stardust pattern[7] (Table 2) (Figure 6D).

In 73.2% of our patients, LVA surgery alone was performed; in 17.1%, it was combined with LNT; and in 9.8% (women requiring simultaneous breast reconstruction), it was combined with DIEAP-LNT in a single procedure.[20]

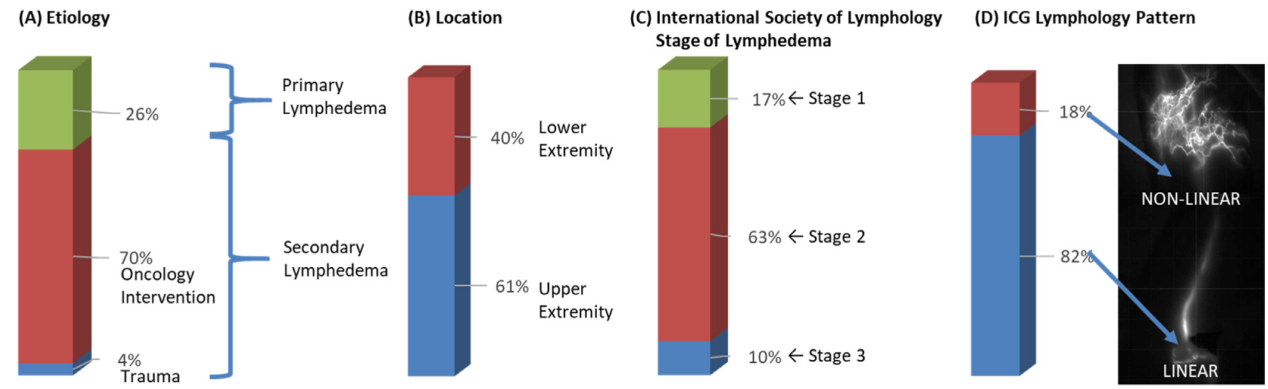

Figure 6 Descriptive analysis of patient population.

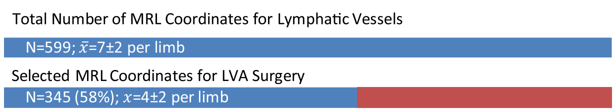

Figure 7 MRL coordinates selected as suitable coordinates for LVA surgery.

There was no significant association between the etiology of lymphedema and number of LVAs performed per extremity (Student's t-test, $p = 0.236$).

Analysis of ICG-L and MRL concordance

MRL provided a total of 599 coordinates among all limbs, with a mean of 6.87 MRL coordinates per limb. A total of 345 MRL coordinates (58% of all identified) were selected as a suitable location for LVA, a mean of 4.04 MRL coordinates per limb (Figure 7). For these selected MRL coordinates, the concordance between ICG-L and MRL occurred for 47%. Leaving a little over half, 53% of the selected MRL coordinates were based on MRL alone.

Analysis of execution of LVA

During all LVA surgeries, the lymphatic vessel was identified at 82.6% of the coordinate locations. A satisfactory LVA was performed in 73.3% of attempts. In attempts where an LVA was unable to be performed, the hindrance was a lack of vein (9.3%) or inability to locate the lymphatic vessel (17.4%).

There was a statistically significant relationship between concordance of MRL coordinates and ICG-L data and the ability to perform a successful LVA (Chi-square, $p = 0.0001$) (Figure 8). When concordance between the two imaging techniques existed, a lymphatic vessel was located in 96.9% of locations and a successful LVA performed in 91.4% of locations. In those locations where an LVA was not performed, the impediment was due to the lack of vein (5.5%) or inability to locate the lymphatic vessel (3.1%).

When the coordinates selected for LVA were based on MRL information only, the lymphatic vessels were located in 69.7% of locations and a successful LVA was performed at 57.1% of locations. The inability to perform LVA occurred at 30.2% of these locations because of the absence or poor quality of the lymphatic vessel for anastomosis.

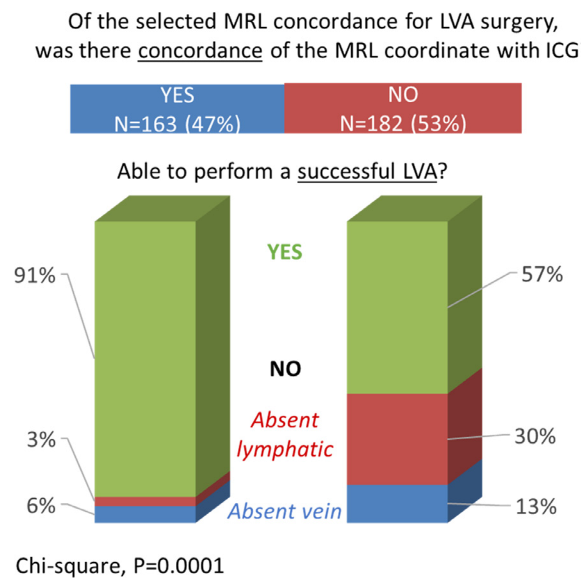

Figure 8 Relation between concordance of MRL and ICG data and the success of performing the LVA surgery.

The mean lymphatic channel caliber on MRL and the real intraoperative caliber were 2.16 and 0.5 mm, respectively. The mean depth of lymphatic channel into subcutaneous tissue was 0.64 cm.

Discussion

Locating functional lymphatic vessels is one of the most difficult and time-consuming challenges in LVA surgery. This dual-imaging (ICG-L and MRL) approach provides the surgeon with an improved understanding of each patient's lymphatic anatomy. Therefore, the surgeon can choose safe and functional locations for LVA while also improving efficiency and success of the operation.

To better understand the direction of LVA surgery, looking at the prior approach to LVA surgery is necessary. Today, it is well accepted that LVA surgery should only be performed in patients with functional lymphatic vessels. However, before ICG-L was widely available, beyond the information from LS, the functional status and anatomy of the lymphatic system for each patient were unknown, and incisions for LVA were planned randomly. Koshima et al. in 2003[21] reported planning incisions close to large veins in areas with thin cutaneous tissue. This technique had significant disadvantages: they performed multiple incisions with a low probability of finding functional lymphatics, and the same lymphatic vessel could be transected several times at different levels. This prior approach put intact functional lymphatic vessels at high risk of injury, which could, in fact, worsen lymphedema symptoms. With advancements in imaging and better understanding of lymphedema and lymphatic anatomy, all tools available should be used to refine our strategy.

Both ICG-L and MRL are complimentary yet entirely different imaging modalities. The complementary information obtained by them permits the selection of safe, efficient, and most effective locations for LVA. Again, ICG-L is the standard approach for preoperative and intraoperative planning for LVA, as it provides high reliability; however, the major disadvantage is that only the superficial lymphatics are detected. Adding MRL to preoperative planning provides an accurate individual evaluation of the entire limbś lymphatic system – both superficial and deep. This provides an important global guide for LVA strategy because it assists in determining exact locations to perform LVA.

As with any tool, understanding the benefits and limitations of the tool is crucial for proper implementation, and this should not stop one from applying the knowledge appropriately. When comparing ICG-L with MRL, MRL is clearly a more sensitive test. In our study, all functional lymphatic vessels identified by ICG-L were confirmed along their course by at least one coordinate determined by MRL. In contrast, several MRL-identified lymphatics were not visualized by the ICG-L. MRL identifies deeper lymphatics ($>$2 cm depth) not visible with IGC-L. Further demonstration of the greater sensitivity is that the image amplification resulted in reported lymphatic sizes of up to 200% to 300% greater than the actual size due to the manner of the study. MRL identified satisfactory LVA locations based on only MRL data for 53% of the attempts. It is important to recognize that these locations would not have otherwise been recognized using the standard ICG-L approach. When MRL located a lymphatic vessel but ICG-L could not detect a vessel, we found a lymphatic vessel in 71.4% of locations and performed LVA successfully in 60.4%. This demonstrates that preoperative planning with both techniques identifies more functional lymphatic channels, and consequently, more LVAs can be performed.

Evaluating and choosing the MRL coordinates is not a trivial process. When reviewing the MRL reconstructions for coordinates, the sheer number of coordinates obtained should not be misleading. Each lymphatic is traced along its course from distal to proximal along the limb, resulting in multiple coordinates for each functional lymphatic vessel. The critical point for choosing the locations for LVA based on MRL coordinates is that the selected coordinate for the bypass should be placed within the functional lymphatic vessel nearest to the lymphatic obstruction (in other words, the most proximal site along the functional lymphatic). Functional lymphatic vessels that demonstrated continuity from distal (hand or foot) to proximal (axillary or inguinal region) were preserved. These were not selected for LVA, as transection of these functional lymphatic vessels may worsen lymphedema.

The addition of MRL data helped select the optimal locations for LVA, thus (1) preserving intact lymphatic function, (2) maintaining the maximum function by placing the bypass within the functional lymphatic vessel nearest to lymphatic obstruction, (3) ensuring that the lymphatic chosen is only transected once along its course, and (4) potentially allowing for both anterograde and retrograde LVA to decompress both the proximal and distal lymphedema extremity (Figure 5). On the basis of this approach, LVA is performed only in specific locations to achieve maximum lymphedema decompression with minimum morbidity.

Currently, if pushed to choose only one diagnostic imaging technique, we would undoubtedly choose ICG-L. It is simple, reliable, and easy to interpret. We are mindful that adding MRL to preoperative planning can be costly and not economically sustainable, difficult for patients due to claustrophobia and time, and impossible due to noncompatible implants. Nonetheless, we have a strong feeling that MRL plays a role in our treatment algorithm for patients with lymphedema. MRL depicts a higher number of lymphatic vessels because it detects both the superficial and deep lymphatic system in more detail than ICG-L. For such a demanding surgical procedure, easing the challenge of locating functional and safe lymphatic vessels is essential. MRL is key to provide very valuable information to assist that endeavor, and therefore, it should be strongly considered.

As providers, our goal should be to offer each patient the correct surgery at the right time. An individualized assessment is paramount to clinical success among our patients with lymphedema. In the future, further developments in diagnostic imaging will likely trigger improvements in understanding lymphedema pathophysiology and lead to defining better definitive treatment options for our patients with lymphedema. Undoubtedly, additional cost analysis is needed to advocate for MRL for all lymphedema surgery centers.

Conclusion

Both ICG-L and MRL are reliable, minimally invasive diagnostic imaging techniques that provide critical anatomic and functional information about the patient's lymphatic system. We have demonstrated the complementary information obtained from ICG-L and MRL provided thorough LVA preoperative planning, which lead to safe, reliable, and rationale surgery.

Funding

None.

Conflicts of interest

None declared.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.bjps.2019.02.024.

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